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WOLBACHIA METHOD AS A DENGUE CONTROL STRATEGY IN BRAZIL

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ABSTRACT

Dengue represents a significant public health challenge in Brazil, with thousands of cases reported annually. Effective control of this disease requires innovative and sustainable approaches. In this context, the *Wolbachia* method emerges as a promising strategy, harnessing the ability of this endosymbiotic bacterium to reduce the vector competence of the *Aedes aegypti* mosquito, the dengue virus transmitter. This integrative review assessed its effectiveness in Brazil, using scientific articles from PubMed, SciELO, and BVS databases from 2019 to 2024. Selected studies with the keywords "Brazil", "Dengue Virus", and "*Wolbachia* Method" demonstrated a significant reduction in disease incidence following its implementation in affected areas. Complementarity with socio-environmental measures, such as waste management, is essential to sustain these results. Despite its promise, technical challenges and the need for research investment to expand its implementation against additional arboviruses are crucial for its continued effectiveness.

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INTRODUCTION

Dengue, a viral disease transmitted by the *Aedes aegypti* mosquito, represents a serious public health issue in Brazil, being part of the group of diseases known as arboviruses. These are characterized by being caused by viruses transmitted by arthropod vectors. In Brazil, the vector for dengue is the female *Ae. aegypti* mosquito. Dengue viruses (DENV) belong to the Flaviviridae family and the Flavivirus genus, scientifically classified. So far, four serotypes are known - DENV-1, DENV-2, DENV-3, and DENV-4 - which have different genetic materials and distinct lineages. Evidence suggests that the mosquito was introduced to Brazil through ships carrying African slaves. The first clinically and laboratorially documented epidemic occurred in 1981-1982 in Boa Vista (RR), caused by serotypes 1 and 4. Four years later, in 1986, epidemics affected the state of Rio de Janeiro and some capitals in the Northeast region. Since then, dengue has occurred endemic, with epidemic episodes often associated with the introduction of new serotypes in previously unaffected areas and/or changes in the predominant serotype, accompanying the vector's expansion (Brazil, 2024). Factors such as urbanization, uncontrolled population growth, lack of basic sanitation, and climatic conditions contribute to the continuous presence of the vector, influencing the dynamics of arbovirus transmission. Dengue follows a seasonal pattern, with an increase in cases and the risk of epidemics, especially between October and May of the following year. Although with chronic conditions such as diabetes and hypertension are at higher risk of developing severe cases and complications that can lead to death (Brazil, 2024). In 2024, over a million people were infected, overwhelming hospitals (WHO, 2024). With the alarming increase in dengue cases in recent years, it becomes imperative to seek effective strategies to control this disease. In response to this urgency, Brazil has been exploring innovative methods to combat the virus's spread. In this context, the *Wolbachia* method stands out as a promising approach to significantly reduce dengue transmission (Brazil, 2024). *Wolbachia*, an intracellular endosymbiotic bacterium, is common in arthropods and nematodes, belonging to the order Rickettsiales and the family Anaplasmataceae. Despite its discovery in 1924, a detailed understanding of *Wolbachia* only occurred in the 1990s. This bacterium can live inside cells of insects and other invertebrates, evading detection by conventional culture methods, and is classified as gram-negative. *Wolbachia* infects a wide range of species and profoundly influences the biology of its hosts, including reproductive manipulations that affect the sex ratio in offspring and even male death. Its presence has significant implications for evolution and pest control (Tortora, Funke & Case, 2017, p. 292). *Wolbachia*, including in *Ae. aegypti*, has been the subject of studies indicating its ability to alter mosquito vector competence. This modification can lead to a reduction in DENV transmission. This approach, already implemented in various parts of the world including Brazil, has shown promising results. Commonly found in about 60% of insects, *Wolbachia* has been successfully introduced into *Ae. aegypti* eggs in introduction has resulted in significant inhibition of DENV, Zika, and

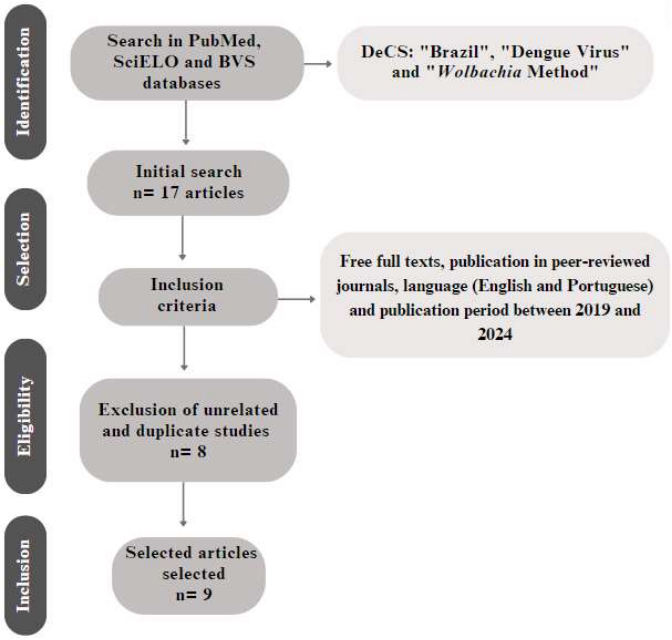
Chikungunya development within the mosquito, as confirmed by recent studies (Pereira *et al*., 2018; Santos *et al*., 2021; Fox *et al*., 2024). Since 2015, the *Wolbachia* method has been expanded in Rio de Janeiro and Niterói to cover an area with just over 1 million people. Mosquitoes infected with *Wolbachia* have covered an area with a population of over 3 million across five municipalities: Rio de Janeiro, Niterói, Belo Horizonte, Campo Grande, and Petrolina (Moreira *et al*., 2009; Hoffmann *et al*., 2011; Durovni *et al*., 2019). A study revealed an 86% reduction in hospitalizations in areas treated with *Wolbachia*, demonstrating that the method's effectiveness is consistent across all four dengue serotypes (Utarini *et al*., 2021).

The technique using *Wolbachia* involves releasing *Ae. aegypti* infected with wMel or wAlbB strains, derived from Drosophila melanogaster and Aedes albopictus (Aliota *et al*., 2016). *Wolbachia* establishes itself in the local mosquito population, resulting in a high prevalence of infection. This process is driven by maternal transmission and a reproductive advantage called cytoplasmic incompatibility. Additionally, infected mosquitoes are less susceptible to all four serotypes of the dengue virus and have a lower likelihood of transmitting the virus through saliva (Serbus *et al*., 2008; Carrington *et al*., 2018; Flores *et al*., 2020). One of the main benefits of the *Wolbachia* method is its self-sustaining nature. Once released into the environment, mosquitoes infected with *Wolbachia* are capable of transmitting the bacterium to their offspring, thereby maintaining a mosquito population with the desired trait. This characteristic makes *Wolbachia* a compelling option for dengue control, as it does not require constant interventions. Experimental studies and pilot programs have demonstrated the effectiveness of the *Wolbachia* method in reducing dengue transmission. These promising results have spurred the implementation of this strategy in other areas of the country (Pinto *et al*., 2021). In addition to dengue, the *Wolbachia* method also has the potential to control other diseases transmitted by *Ae. aegypti*, such as chikungunya fever and Zika virus. Studies have shown that the presence of *Wolbachia* in mosquitoes can also reduce the transmission of these viruses, thereby expanding the positive impact of this strategy on mosquito-borne disease control (Pereira *et al*., 2018).

Dengue remains an urgent concern in Brazil, affecting millions of people and straining healthcare systems. This article aims to analyze the *Wolbachia* method as an innovative and effective approach to combating dengue in the country, focusing on its implementation, community acceptance, expansion, and efficacy (Collins *et al*., 2022). However, despite promising results, the effective implementation of the *Wolbachia* method as a dengue control strategy in Brazil faces challenges. Issues related to public acceptance, logistics of releasing infected mosquitoes, and long-term monitoring of effects are some aspects that must be considered to ensure the success of this method (Wikan & Smith, 2016). Additionally, it is important to emphasize that the *Wolbachia* method should not be viewed as a singular solution for dengue control. Integrated measures such as proper solid waste management, improvements in basic sanitation, and health education are also crucial for effectively combating this disease (Vasconcelos & Monath, 2016). Given the challenges faced in dengue control, the guiding question of this integrative review arises: "How can the *Wolbachia* method be effectively implemented and optimized as a dengue control strategy in Brazil?" This question directs our study to explore not only the method's efficacy but also its potential applications and implementation challenges. The *Wolbachia* method emerges as a promising strategy complementary to traditional *Ae. aegypti* control measures. Therefore, it is crucial to continue investing in research to enhance this approach and expand its implementation, aiming to reduce dengue incidence in Brazil.

MATERIALS AND METHODS

This is an integrative literature review, using scientific articles from the US National Library of Medicine (PubMed), Scientific Electronic Library Online (SciELO), and the Virtual Health Library (BVS). To identify relevant studies, DeCS (Health Sciences Descriptors) including the terms "Brazil," "Dengue Virus," and "*Wolbachia* Method." Initially, 17 articles were found. However, after applying inclusion and exclusion criteria, only 9 articles were selected for the study. Selection criteria included availability of free full texts, publication in peer-reviewed journals, language (English and Portuguese), and publication period between 2019 and 2024. Studies not directly related to the proposed theme were excluded from the analysis, ensuring the relevance and accuracy of the results obtained. The selection process is illustrated in Figure 1.



Source: Literature search process - developed by the authors.

Figure 1. Flowchart of the scientific articles search process

RESULTS AND DISCUSSIONS

Initially, 17 relevant articles were identified. However, after applying inclusion and exclusion criteria, only 9 were selected to integrate the study. The included studies are detailed in Table 1. These nine articles, as presented in Table 1, investigate the use of the *Wolbachia* method as a strategy to combat dengue. They provide insights into the potential of this method in controlling not only dengue but also other diseases transmitted by *Ae. aegypti*. They highlight its effectiveness in reducing the transmission of these diseases, pointing to the promise that this approach holds in addressing these public health challenges. Dengue continues to pose a significant challenge to public health in Brazil, with over 1.6 million cases reported in the first ten weeks of this year, surpassing the total case rate of 2023. These numbers set a new record, being the second highest since the beginning of the historical series in 2000, with the absolute record set in 2015. This high incidence underscores the urgency of finding effective solutions for disease control, with the *Wolbachia* method emerging as a promising approach to reduce virus transmission by the *Ae. aegypti* mosquito (Brazil, 2024). Arboviruses are viral diseases transmitted by arthropods such as mosquitoes and ticks. Dengue, in particular, is primarily transmitted by the *Ae. aegypti* mosquito, recognized for its efficiency in virus dissemination (Rocha *et al*., 2019; Petersen *et al*., 2023). It breeds in stagnant water sources and feeds on human blood. Infection with multiple serotypes over a lifetime increases the risk of severe forms of the disease, making dengue control a significant challenge (Malavige *et al*., 2023). The endemic nature of the disease is evidenced by episodic outbreaks that occur at regular intervals. Characterized by a significant increase in the number of dengue cases in a specific region during a defined period, these epidemics can overwhelm the healthcare system and have a significant impact on the population (Ribeiro *et al*., 2022; Araf *et al*., 2024).

Tabela 1. Presentation of the articles included in the review

Title of paper	Authors	Year of Publication	Journal Title
Pluripotency of *Wolbachia* against Arboviruses: the case of yellow fever	Rocha *et al.*	2019	Gates Open Res.
Pathogen blocking in *Wolbachia*-infected *Aedes aegypti* is not affected by Zika and dengue virus co-infection	Caragata *et al*.	2019	PLoS Negl Trop Dis
The impact of large-scale deployment of *Wolbachia* mosquitoes on dengue and other Aedes-borne diseases in Rio de Janeiro and Niterói, Brazil: study protocol for a controlled interrupted time series analysis using routine disease surveillance data	Durovni *et al.*	2019	F1000Res
Effectiveness of *Wolbachia*-infected mosquito deployments in reducing the incidence of dengue and other Aedes-borne diseases in Niterói, Brazil: A quasi-experimental study	Pinto *et al.*	2021	PLoS Negl Trop Dis
Reduced competence to arboviruses following the sustainable invasion of *Wolbachia* into native *Aedes aegypti* from Southeastern Brazil	Gesto *et al.*	2021	Sci Rep
High throughput estimates of *Wolbachia*, Zika and Chikungunya infection in *Aedes aegypti* by near-infrared spectroscopy to improve arbovirus surveillance	Santos *et al.*	2021	Commun Biol
Estimating the effect of the *w*Mel release programme on the incidence of dengue and chikungunya in Rio de Janeiro, Brazil: a spatiotemporal modeling study	Ribeiro *et al.*	2022	Lancet Infect Dis
EVITA Dengue: a cluster-randomized controlled trial to EValuate the efficacy of *Wolbachia*-InfecTed *Aedes aegypti* mosquitoes in reducing the incidence of Arboviral infection in Brazil	Collins *et al.*	2022	Trials
Dengue Exposure and *Wolbachia w*Mel Strain Affects the Fertility of Quiescent Eggs of *Aedes aegypti*	Petersen *et al.*	2023	Viruses

Source: Literature research process - prepared by the authors.

Furthermore, it is important to highlight the shift in dengue serotype prevalence over time. Studies have revealed that different serotypes have circulated in Brazil, with changes in predominance over the years. This implies that the population may be exposed to different serotypes at different times, increasing the risk of developing severe forms of the disease (Santos *et al*., 2024). The spread of dengue is influenced by various factors, including unplanned urbanization, population growth, lack of basic sanitation, and climatic conditions favorable to the vector. Uncontrolled urbanization promotes the formation of breeding sites for *Ae. aegypti*, increasing vector availability and the risk of disease transmission. Population growth contributes to the spread, particularly in densely populated urban areas where there is greater interaction between people and mosquitoes. Human mobility, both domestic and international, can also facilitate the spread of dengue serotypes between different regions (Costa *et al*., 2021). Another important factor is the lack of basic sanitation, which promotes the proliferation of *Ae. aegypti*. The absence of adequate water supply systems, sewage treatment, and garbage collection creates favorable conditions for mosquito breeding sites. The presence of stagnant water in containers, and open sewers, and the accumulation of solid waste increases the availability of breeding sites for the vector, thereby amplifying dengue transmission (Silva *et al*., 2022). Finally, climatic conditions play a significant role in the spread of dengue. The tropical and subtropical climate provides a conducive environment for the reproduction of *Ae. aegypti*, which thrives more rapidly in higher temperatures. Periods of heavy rainfall followed by periods of heat and humidity create ideal conditions for mosquito proliferation and disease transmission (Costa *et al*., 2021). It is relevant to highlight that all age groups are vulnerable to dengue, but certain groups, such as the elderly and people with chronic diseases, face a higher risk of severe complications. Natural aging compromises the immune system, hindering an effective response to the virus. Conditions like diabetes and hypertension further increase the risk. Studies indicate that advanced age is an independent factor for severe cases. Patients with chronic diseases have compromised immune systems, making them more susceptible to infections, including dengue. These conditions can impair the body's ability to fight the virus, raising the risk of serious complications (Silva *et al*., 2022). The *Wolbachia* method emerges as a promising strategy in combating dengue. Unlike wild-type species, these mosquitoes do not naturally carry this bacterium. Through infection, *Wolbachia* spreads across generations, altering the vector competence of mosquitoes and reducing their ability to transmit the virus. By interfering with viral replication and dissemination processes within the mosquito, this approach contributes to reducing dengue transmission (Popovici *et al*., 2010; Frentiu *et al*., 2014). The effective implementation of the *Wolbachia* method, both globally and in Brazil, has resulted in a notable reduction in dengue virus transmission (Caragata *et al*., 2019), with studies showing up to a 70% decrease in vector where the bacterium has been introduced. Its self-sustainability is one of its main advantages, as infected mosquitoes can pass the bacterium to their offspring, eliminating the need for constant interventions and making it more efficient and cost-effective in the long term (Gesto *et al*., 2021; Santos *et al*., 2022). *Wolbachia* has demonstrated stable transmission to subsequent generations of infected Aedes aegypti mosquitoes. Once introduced into the mosquito population, *Wolbachia* can be maintained self-sustainably, eliminating the need for continuous releases. Despite promising results, the effective implementation of this method faces challenges such as public acceptance (Gesto *et al*., 2021). Raising awareness is essential to ensure that communities understand the benefits and safety of this control strategy. The logistics of releasing infected mosquitoes are also challenging and require careful planning and monitoring to ensure adequate coverage of the target area. Furthermore, long-term monitoring of the effects of *Wolbachia* on the mosquito population and the environment is crucial (Dutra *et al*., 2015). The *Wolbachia* method should not be viewed as a standalone solution, but rather as complementary to traditional *Ae. aegypti* control measures. Integrated actions such as solid waste management and health education are essential to prevent mosquito breeding. Combining the *Wolbachia* method with other strategies, such as insecticide use, has been shown to enhance control efforts. The combination of these approaches has led to a significant reduction in the number of *Ae. aegypti* mosquitoes, combining *Wolbachia* with the release of sterile mosquitoes (Hoffmann *et al*., 2011). The *Wolbachia* method is a promising strategy in dengue control, but challenges such as public acceptance and release logistics need to be overcome. Continuous investment in research is necessary to refine the method and expand its implementation, not only for dengue but also for other arboviruses transmitted by *Ae. aegypti*, such as Zika virus and Chikungunya.

CONCLUSION

The increasing incidence of dengue in Brazil, as evidenced by recent record case numbers, underscores the urgency of finding effective solutions for controlling this disease. The introduction of the *Wolbachia* method emerges as a promising approach, offering the potential to significantly reduce the transmission of the virus by the Ae. aegypti mosquito, the primary vector of the disease. However, in addition to the technical challenges associated with implementing the method, such as release logistics and long-term monitoring, it is crucial to address the socio-environmental factors that contribute to dengue spread. Unplanned urbanization, population growth, lack of basic sanitation, and favorable climatic conditions for the mosquito vector are some of these factors affecting the transmission dynamics of arboviruses. The complementarity of the *Wolbachia* method with

other control measures, such as solid waste management and health education, underscores the importance of integrated approaches to prevent mosquito reproduction and proliferation. While the *Wolbachia* method shows promise in dengue control, a concerted and continuous effort is needed to overcome challenges and expand its implementation. Investments in research are essential to refine this approach and adapt it not only for dengue but also for other arboviruses transmitted by Ae. aegypti, such as Zika virus and Chikungunya. With a growing body of evidence showing that *Wolbachia*-infected Ae. aegypti mosquitoes can significantly reduce dengue incidence in endemic areas, and a substantial expansion in the application of this technology is anticipated in the coming years. The goal is to achieve lasting control or local elimination of pathogenic arboviruses for humans. Achieving long-term suppression in the field will depend on the evolutionary stability of *Wolbachia*, Ae. aegypti, and their interaction with DENV. *Wolbachia* and Ae. aegypti evolve more slowly compared to DENV, and mosquitoes infected with *Wolbachia*, collected years after their release, have maintained their antiviral profile so far. However, due to the high mutation rate of RNA viruses, likely, viruses like DENV will likely eventually adapt to Wolbachia-induced selective pressure, potentially developing resistance to the intervention.

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