



# A Dynamic Investigation to Analyzing Divorce Effects within Wolbachia Models

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## ABSTRACT

Dengue fever, a mosquito-borne viral disease, poses a significant global health burden with approximately 390 million infections reported in 2016. As insecticide resistance increases, novel vector control methods such as Wolbachia bacteria are being investigated. Wolbachia reduces dengue transmission by decreasing mosquito lifespan and inhibiting viral replication. The mathematical model has demonstrated Wolbachia's potential to eliminate local dengue transmission. Field trials in Australia and Indonesia have exhibited substantial reductions in dengue incidence following Wolbachia releases. However, concerns remain that these reductions may be transient. This report reviews a mathematical model of Wolbachia for dengue control, evaluating its assumptions and findings. The model indicates Wolbachia could potentially eliminate dengue locally, yet also permit endemic transmission. We propose further analysis of this model to assess the long-term impacts of Wolbachia deployment. Examining the duration of control measures and post-release effects will provide greater insight into Wolbachia's capacity for sustainable dengue mitigation. The reviewed model comprises a system of seven ordinary differential equations representing a dual Susceptible-Exposed-Infected-Recovered (SEIR) structure for human and mosquito populations. Key assumptions include only modeling female mosquitoes' post-aquatic life stages and complete cytoplasmic incompatibility of Wolbachia. The basic reproductive number was derived and equilibrium points were identified. This mathematical modeling approach enables the simulation of complex dengue transmission dynamics under various Wolbachia release scenarios. Further analysis can evaluate the potential for the "honeymoon effect" and "divorce effect" to undermine the initial successes of Wolbachia trials. This will facilitate a more robust assessment of Wolbachia's long-term viability as a dengue control strategy.

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## 1. Introduction

Dengue fever, an endemic ailment, stands as the foremost source of both sickness and mortality in tropical regions, as reported by [49, 30] in 2020. In the year 2016 alone, an estimated 390 million individuals fell victim to this disease, a disconcerting statistic that has exhibited a consistent upward trajectory in recent decades, as elucidated by [55] in 2020 and reiterated by Zhang et al. Dengue, characterized as a vector-borne disease, does not propagate directly from one human to another. Rather, it follows a circuitous path, transferring from humans to a vector (typically the *Aedes* mosquito), which then serves as the intermediary agent transmitting it back to humans. This intricate transmission cycle has fueled the persistence and spread of dengue, necessitating comprehensive measures for control and prevention to mitigate its widespread impact on public health [31].

To effectively combat the menace of dengue fever, we face a pivotal choice: whether to direct our efforts towards the human population through immunization or concentrate on strategies that target the vector, which do not rely on immunization [35]. The optimal approach, undoubtedly, lies in immunizing the human population. This multifaceted strategy not only thwarts the disease from seeking new vectors but also hinders the vector's ability to develop resistance against non-immunizing control measures. Regrettably, the pursuit of widespread immunization programs has encountered considerable challenges and limited success, prompting a shift in focus within the scientific community. This shift has led to an emphasis on non-immunizing control measures. These methods adopt a proactive stance by curbing the vector population and reducing its capacity to transmit the dengue virus to humans. By taking these alternative measures, we can create a formidable barrier against the spread of dengue, reducing its impact on public health and minimizing the risks associated with the disease [50, 40].

The *Aedes aegypti* (AE) mosquito stands as the relentless harbinger of dengue fever, challenging conventional control strategies due to its remarkable adaptability. These resilient creatures display an uncanny ability to deposit their eggs even in the tiniest pools of stagnant water, with the eggs demonstrating incredible resilience, remaining viable for several months until moisture triggers their swift hatching (Zhang et al., 2020). Compounding the challenge, the AE mosquito has developed resistance to numerous commonly used insecticides, as documented in studies by Lima et al. (2011) and Marcombe et al. (2012) [20, 22, 27]. This formidable resistance issue has forced researchers to explore innovative approaches in their quest to curtail the AE mosquito's impact on public health. Given the gravity of the dengue threat and the AE mosquito's elusive nature, scientists are now pursuing novel strategies to overcome these challenges. This includes the development of genetically modified mosquitoes, advanced surveillance and monitoring techniques, and the exploration of eco-friendly larvicides and repellents. These creative endeavors reflect the urgency and determination of the scientific community in combating this resilient vector and safeguarding public health [14].

Gene drive technology empowers scientists to strategically manipulate the genetic composition of a population by introducing alleles with a selective fitness disadvantage into the gene pool [37, 38]. This revolutionary genetic engineering tool, which harnesses the power of CRISPR-based gene editing, has far-reaching implications. It can be used to combat the spread of disease-carrying vectors like mosquitoes, potentially curbing the transmission of diseases such as malaria and Zika [29, 6]. Furthermore, gene drives offer a promising avenue

for addressing ecological challenges, such as the control of invasive species or the restoration of endangered ones. Nevertheless, the widespread application of gene drives also raises complex ethical, ecological, and regulatory concerns that necessitate careful consideration and responsible governance. Applied to mosquito populations, gene drive can either suppress the population or give the vector resistance to the virus. Suppression works by reducing the size of the population so that it becomes much harder for dengue to spread, in its most extreme form suppression can lead to eradication. Giving the vector resistance to the virus prevents the virus from using them as an effective host [43, 9, 17]. One of the drawbacks of these methods is that if the gene drive escapes the target population it could have unforeseen negative impacts on the ecosystem or spread to areas that the local human population has not consented to it being released [32, 4]. To avoid this, most gene drives are designed to be reversible. Even with reversibility, concerns about gene drives escaping, causing unforeseen effects, or simply because its "unnatural" has prevented any field test of a gene drives. Because of this resistance against gene drives, their potential to help people right now is limited [33, 28].

Alternatively, Wolbachia bacteria exhibit similarities to certain gene drive mechanisms, yet they possess a higher degree of versatility for deployment, making them a promising tool to address the pressing needs of communities [?]. This biological agent, with its intricate symbiotic relationship within insect populations, holds the power to revolutionize disease control strategies and ecological interventions. Wolbachia's capacity to induce reproductive alterations in insects, such as the inhibition of dengue virus transmission by *Aedes* mosquitoes, showcases its potential for vector-borne disease mitigation. Moreover, its non-toxic and self-limiting nature ensures that it poses minimal environmental risks [51, 53]. In the pursuit of improving global public health and ecosystem preservation, harnessing the potential of Wolbachia offers an innovative, sustainable, and community-oriented approach. Wolbachia are small bacteria that live naturally in the cytoplasm of cells in 16% of insect species [56, 52]. They are maternally inherited and spread in populations by taking advantage of cytoplasmic incompatibility (CI) [26]. CI works by increasing the probability (close to 100% in some cases) of death in the progeny of infected males mated with uninfected females [54, 36]. This change in the proportion of surviving infected to uninfected insects is enough that in some cases Wolbachia can spread in a population while carrying a small fitness cost [42, 10]. One of the common fitness costs associated with Wolbachia is a shortened lifespan. This inspired researchers to successfully implant them in AE. The rationale was that with a shortened lifespan, AE would not have time to bite an infected human and incubate long enough for the mosquito to be infectious [39, 8]. Furthermore, in addition to the intriguing findings mentioned, researchers have unveiled another remarkable facet of Wolbachia's impact on the natural world. It has been observed that Wolbachia inhibits the growth of certain viruses, with the dengue virus being a notable example [57, 19]. This discovery further fortifies the notion that Wolbachia could serve as a potent tool in the fight against dengue fever, a debilitating mosquito-borne disease [34].

In the past few years, this novel and advanced approach to disease control has gained momentum, which is leading to the release of Wolbachia-infected mosquitoes in various countries, also it including Australia and Indonesia. So, these pioneering releases have demonstrated promising and strong results, showcasing a substantial protective efficacy of approximately 77 percent in Indonesia [48, 5]. This success not only offers hope in the battle against dengue but also paves the way for innovative strategies in mosquito-borne disease prevention [7, 11]. We can able to use Wolbachia-infected mosquitoes that represent an exciting frontier in public health, as well as it leverage a naturally occurring bacterium to reduce the transmission

of harmful viruses. A testament to the ingenuity of the scientific research community and research as well, and also underscores the potential for bio-control methods to alleviate the burden of vector-borne diseases on global populations. This field continues to evolve, and the applications of Wolbachia and similar bio-control agents are likely to expand, offering new avenues for combating a range of infectious diseases [12, 13].

Mathematical models have demonstrated Wolbachia's potential to eliminate local dengue transmission [15]. Encouragingly, field trials in Australia and Indonesia have already shown significant reductions in dengue cases after releasing Wolbachia-infected mosquitoes. However, concerns remain that these initial successes could be temporary [15, 16, 18]. The "honeymoon effect" occurs when reductions are not sustained long-term after stopping releases. The "divorce effect" causes spikes in infections due to increased population susceptibility after cessation of the control measure [21, 23]. This comprehensive analysis will not only help identify the persistence of positive outcomes but also pinpoint any potential setbacks that may arise over time with Wolbachia deployment. We aim to offer a more robust evaluation, shedding light on the long-term sustainability and reliability of Wolbachia in the ongoing battle against dengue fever. The insights gained can inform guidelines for optimal Wolbachia release strategies, aiding public health authorities seeking to leverage this innovative tool [24, 3]. Furthermore, the model provides a framework to simulate localized rollouts, guiding context-specific implementations in dengue-endemic regions. By deepening our understanding of the complex dynamics at play, this study hopes to facilitate responsible Wolbachia deployment worldwide, harnessing its potential to create resilient communities less burdened by the threat of dengue [25, 47]. The stakes are high in the fight against this growing health threat, underscoring the need for nuanced mathematical modeling analyses to ensure novel control measures like Wolbachia can sustainably and effectively improve global public health [41, 46].

Therefore, further research is critically needed to assess the long-term impacts of Wolbachia deployment for dengue control. By using mathematical modeling, this study aims to simulate the complex dengue transmission dynamics over time under different Wolbachia release scenarios [44, 45]. The objective is to meticulously assess the potential for the honeymoon or divorce effects to erode the initial successes witnessed in experimental trials. By scrutinizing both the longevity of control measures and the enduring impact post-release, we aim to gain a more comprehensive understanding of the long-term viability of Wolbachia as a solution for dengue reduction [2, 1]. This comprehensive analysis will not only help identify the persistence of positive outcomes but also pinpoint any potential setbacks that may arise over time. We aim to offer a more robust evaluation, shedding light on the sustainability and reliability of Wolbachia in the ongoing battle against dengue fever.

Here are the descriptions for each of the sections included in this paper:

**Introduction:** Provides background on dengue and motivation to use modeling to assess the long-term impacts of Wolbachia deployment.

**Mathematical Modeling and Methods:** Outlines the Wolbachia transmission model structure, assumptions, equations, and parameters.

**Results and Discussion:** Discusses limitations of current trials and potential honeymoon and divorce effects post-Wolbachia release.

**Conclusion:** Summarizes key points and emphasizes using the model to evaluate the sustainability of Wolbachia for dengue control.

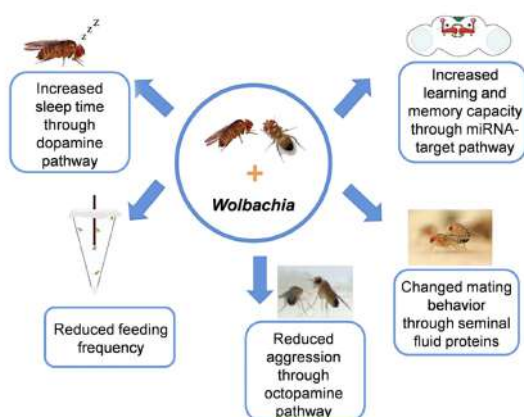
## 2. Mathematical Modeling and Methods

### 2.1. Model Overview:

Dengue fever constitutes a significant global public health challenge, with a staggering 390 million infections reported worldwide in the year 2016 alone. This alarming prevalence underscores the urgent need for heightened awareness and robust measures to combat this debilitating disease. The burden of dengue extends beyond the sheer numbers, as it not only affects the physical well-being of millions but also places a considerable strain on healthcare systems and economies.

These statistics emphasize the importance of continued research, vaccination programs, and effective mosquito control strategies to curtail the spread of dengue. Furthermore, education and community engagement are vital components of a comprehensive response to this mosquito-borne virus, raising public awareness and promoting preventive measures. Dengue's potentially severe symptoms, such as high fever, severe headaches, joint pain, and hemorrhagic manifestations, make it imperative to bolster healthcare infrastructure and preparedness in regions where it is endemic.

Dengue fever's global impact in 2016 serves as a stark reminder of the pressing need for international cooperation, research, and investment in public health initiatives to mitigate its devastating consequences. As insecticide resistance rises, new vector control methods like Wolbachia are being explored as alternatives. Wolbachia are bacteria that can reduce dengue transmission by shortening mosquito lifespan and inhibiting viral replication in mosquitoes. Mathematical models have demonstrated that Wolbachia could potentially eliminate dengue transmission. Field trials in Australia and Indonesia have also shown significant reductions in dengue incidence after Wolbachia releases. However, there are concerns that these reductions may be temporary. The "honeymoon effect" is when reductions reverse after controls cease, while the "divorce effect" causes spikes in infections from increased susceptibility post-control.

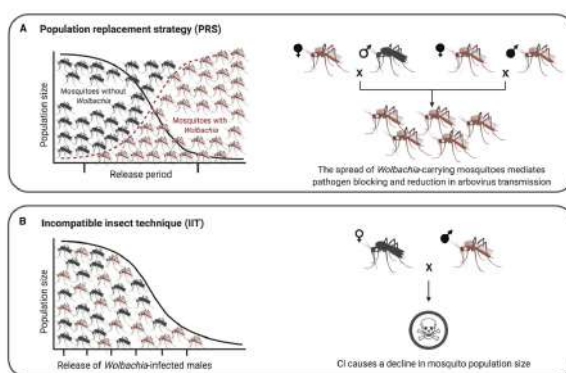


**Fig. 1.** An elementary framework delineating the impacts of Wolbachia infection on the behavioral patterns of insect hosts.

## 2.2. Model Assumptions:

This paper reviews a mathematical model of Wolbachia for dengue control to assess its assumptions and findings. The model shows Wolbachia could potentially eliminate dengue locally, but may also allow continued endemic transmission. The motivation for using this mathematical model is to further analyze the long-term impacts of Wolbachia releases, assessing whether the honeymoon or divorce effects could undermine initial success. Examining control duration and post-release effects using the model will better evaluate Wolbachia's potential for sustainable dengue reduction. Mathematical modeling provides a way to simulate these complex disease dynamics over time and evaluate different Wolbachia deployment strategies.

Numerous Wolbachia models exist, but we will focus on the groundbreaking model introduced in Zhang et al.'s 2020 paper. This remarkable model comprises a dynamic system governed by seven ordinary differential equations. It mimics the behavior of dual Susceptible-Exposed-Infected-Recovered (SEIR) models, characterizing both human and mosquito populations infected with dengue. The seventh equation within the system is exclusively dedicated to capturing the dynamics of Wolbachia-infected mosquitoes. This pioneering approach provides a comprehensive framework for understanding the complex interplay between dengue infection and the influence of Wolbachia, shedding light on potential strategies for disease control and vector management. By integrating these aspects, the model not only enhances our comprehension of the disease dynamics but also offers a valuable tool for devising more effective strategies to combat dengue fever, ultimately contributing to the global effort to mitigate the impact of this significant public health concern.



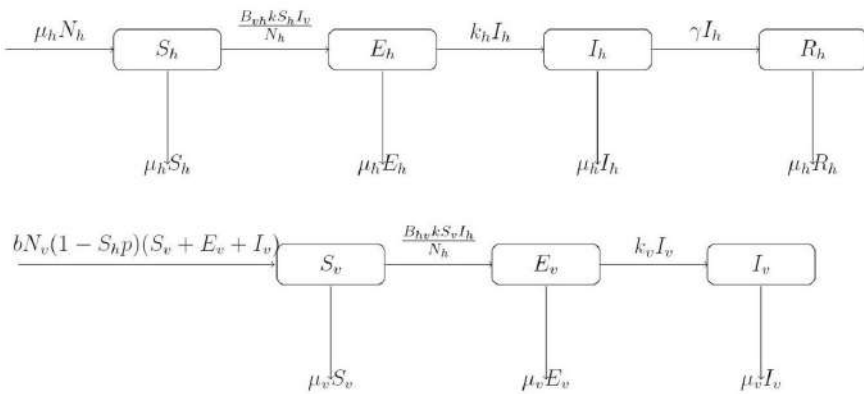
**Fig. 2.** Enhancing the Utilization of Wolbachia for Insect Vector Control.

Here the given model is employed in a comprehensive SEIR model, so distinguishes itself from a simpler SIR model because of the intricate nature of the dengue virus transmission. Dengue presents a unique and different challenge, as it possesses an incubation period in both humans and as well as mosquitoes. In humans, this incubation period spans a range of three to ten days approximately, making it crucial to account for this variability (Zhang et al, 2020). Furthermore, in mosquitoes, the incubation period extends even wider, around from two to fifteen days.

**2.3. Model Equations and Parameter Values:**

So, the augmentation of complexity within the SEIR model presents a heightened level of sophistication, it providing us with a finer-grained depiction of the intricate dynamics of the virus as well. The given enhanced model empowers us to gain deeper insights into the propagation patterns of dengue, which, in turn, equips us with the ability to make more accurate predictions about its spread. By incorporating additional parameters and variables, we can account for a broader spectrum of factors influencing disease transmission, such as population demographics, climatic conditions, and vector behavior. So we can see that enriched understanding facilitates the development of more effective public health strategies and interventions, ultimately it leads to aiding in the control and mitigation of dengue outbreaks. Also, this advanced SEIR model can be instrumental in guiding public health authorities and researchers in formulating targeted vaccination campaigns, optimizing resource allocation, and fostering a more resilient response to this challenging health issue. The incorporation of these incubation periods for both hosts is essential for capturing the intricate interplay of dengue transmission, thus aiding in the development of effective control and prevention strategies. By considering the full spectrum of incubation durations, this model offers a more holistic view of the disease, ultimately contributing to our ability to combat this significant public health concern. In female mosquitoes who have lifespans of only 8 to 48 days, this can take a large portion of their life. The seven equations model: susceptible humans ( $S_h$ ), exposed humans ( $E_h$ ), infected humans ( $I_h$ ), susceptible mosquitoes ( $S_v$ ), exposed mosquitoes ( $E_v$ ), infected mosquitoes ( $I_v$ ), and wolbachia infected mosquitoes ( $W$ ).

$$\begin{aligned} \dot{S}_h &= \mu_h N_h - \frac{B_{vh} k S_h I_v}{N_h} - \mu_h S_h, \\ \dot{E}_h &= \frac{B_{vh} k S_h I_v}{N_h} - \kappa_h E_h - \mu_h E_h, \\ \dot{I}_h &= \kappa_h E_h - \gamma I_h - \mu_h I_h, \\ \dot{S}_v &= b(N_v)(1 - s_h p)(S_v + E_v + I_v) - \frac{B_{hv} k S_v I_h}{N_h} - \mu_v S_v, \\ \dot{E}_v &= \frac{B_{hv} k S_v I_h}{N_h} - \kappa_v E_v - \mu_v E_v, \\ \dot{I}_v &= \kappa_v E_v - \mu_v I_v, \\ \dot{W} &= b(N_v)(1 - s_h p)W - (\mu_v + D)W + u(t) \end{aligned}$$



The model has several assumptions. It only takes into account female mosquitoes, assuming that the males will be at the same numbers. It does not consider the aquatic stages



of a mosquito's life, only modeling once it is past this stage and can become infected. It also assumes that there will be complete CI, meaning that 100% of the offspring of matings between a Wolbachia-infected male and an uninfected female will die. Additionally, the model only considers 1 strain of dengue when in reality there are 4 serotypes, where recovering from one does not always give immunity from the others. All seasonal effects are also ignored, using constant values for parameters that may vary over the year. Finally, the model assumes that Wolbachia completely blocks dengue, so there is no coinfection. These assumptions limit the model in some ways but also make it much more manageable to deal with it.

The recovered populations are not modeled here because once infected mosquitoes do not recover, the human population uses a fixed population size, so the recovered population can be found by taking the totals in each human population and subtracting that from the fixed total human population. Each parameter is defined in Table 1 by Zhang et al 2020. The table presented illustrates the spectrum of parameter values and their corresponding interpretations as employed in Equation 2.1. These values are integral to our forthcoming numerical simulations, which will be extensively covered in Sections four and five of our study.

**Table 1.** Range of the parameter values and their meanings used in numerical simulations.

Parameter (unit)	Range	Meaning
$B_{vh}$	(0.10, 0.75)	Probability of infection from infected mosquito to human
$B_{hv}$	(0.10, 0.75)	Infection likelihood from infected human to susceptible mosquito
$k$	(0.33, 1)	Biting rate
$K/N_h$	(1, 5)	Ratio of mosquito population to human population
$\mu_h$ (1/years)	(1/76, 1/60)	Human death-rate
$\mu_v$ (1/days)	(1/42, 1/8)	Mosquito death-rate
$\gamma$ (1/days)	(1/12, 1/4)	Human recovery rate
$\kappa_h$ (days)	(1/10, 1/3)	IIP for humans
$K_v$ (days)	(1/15, 1/2)	EIP for mosquitoes at 30° C
$b_0$ (1/days)	(0.5, 1)	Intrinsic growth rate of mosquitoes
$s_f$	(0, 0.25)	Reduction in birth-rate for Wolbachia-infected mosquitoes
$s_h$	(0.75, 1)	Reduction in birth-rate due to CI
$D$ (1/days)	(1/20, 1/10)	Death-rate of Wolbachia-infected mosquitoes
$a$	(0.01, 0.10)	Rate of release of Wolbachia in fraction of $K$

Unlike the constant human population size the model has a variable mosquito population size. The mosquitoes growth rate is given by the following logistic growth equation. Taking a close look at the equation modeling the susceptible population of mosquitoes,  $S_v$ , we can see that the cytoplasmic incompatibility comes from  $(1 - s_h * p)$  where  $p$  is the proportion of mosquitoes infected with wolbachia ( $W/N_v$ ), and  $s_v$  is the fraction of eggs that survive when a wolbachia infected male mates with a female with no wolbachia (Zhang et al 2020, Hughes et al 2013). Fitness costs of the wolbachia infection are built into the  $W$  equation and come in the form of females laying  $1 - s_f$  eggs and having an increased mortality rate,  $D$ .

#### 2.4. Non-dimensionalization:

The nondimensionalization process readies the model for simulating releases of different proportions of Wolbachia-infected mosquitoes as a vector control intervention against dengue. It allows adjusting the crucial  $W$  population representing the introduced Wolbachia-infected mosquitoes to assess the impacts on disease transmission. This is a key step in utilizing the model to evaluate long-term sustainability of Wolbachia as a vector control method.



To nondimensionalize these functions the authors first divide the three human sub-populations by the total human population ( $N_h$ ), and the four mosquito populations by the carrying capacity ( $K$ ). The authors also combined some parameters by letting  $\beta_1 = B_{vh}kK/N_h$ ,  $\beta_2 = B_{hv}k$  and  $b(N_v) = -$  with  $b_1(N_v) = b_0(1 - N_v) + \mu_v N_v$ . This yields the following system of differential equations. As in Zhang et al, normally there would be a bar to denote the no dimensionalized equations, but we omit it for simplicity. This yields the non-dimensionalized system:

$$\begin{aligned}\dot{S}_h &= \mu_h - \beta_1 S_h I_v - \mu_h S_h, \\ \dot{E}_h &= \beta_1 S_h I_v - k_h E_h - \mu_h E_h, \\ \dot{I}_h &= k_h E_h - \gamma I_h - \mu_h I_h, \\ \dot{S}_v &= b(N_v)(1 - s_{hp})(S_v + E_v + I_v) - \beta_2 S_v I_h - \mu_v S_v, \\ \dot{E}_v &= \beta_2 S_v I_h - \kappa_v E_v - \mu_v E_v, \\ \dot{I}_v &= \kappa_v E_v - \mu_v I_v, \\ \dot{W} &= b(N_v)(1 - s_f)W - (\mu_v + D)W + u(t)\end{aligned}$$

The next step for the authors was to set  $u(t)$ , the amount of new Wolbachia mosquitoes being introduced to the system, to 0. And solve for the basic reproductive number of:

$$R_0 = \sqrt{\frac{\beta_1 \beta_2 \kappa_h \kappa_v}{\mu_v (\mu_h + \kappa_h) (\mu_v + \kappa_v) (\gamma + \mu_h)}}$$

After conducting a rigorous analysis, we delved deeper into the system's behavior and identified a series of steady states that exhibited a surprising level of complexity. These equilibrium points unveiled a rich tapestry of interactions and dependencies within the system, reflecting the intricate web of factors at play. Each steady-state revealed a unique set of conditions and variables that dictated the system's behavior, adding depth to our understanding. This complexity challenged our initial assumptions, highlighting the need for a more nuanced approach to address the intricacies of the system. As we continued our investigation, we realized that unraveling the secrets of these multifaceted steady states would be a rewarding endeavor, leading to valuable insights and potentially transformative outcomes. The first, trivial case was when all of both populations were in the susceptible group. So no disease could spread. The second, also relatively trivial case was when there was no dengue, but Wolbachia infected all of the mosquitoes. The third still has no dengue in the system, but has some Wolbachia endemic in the mosquito population. The final two steady states represent when dengue is endemic with no Wolbachia and when it is endemic with Wolbachia [24, 3, 25, 47].

The stability and existence of these steady states are intricately contingent upon the specific parameter values employed in the system. In dynamic systems, small changes in these parameters can lead to significant alterations in the system's behavior. Therefore, understanding the sensitivity of a system to parameter variations is essential for predicting its long-term behavior and making informed decisions in various fields, such as physics, engineering, and ecology. The study of bifurcation theory, for instance, explores how systems transition between different steady states as parameters change, shedding light on critical phenomena and phase transitions. Parameter values are essentially the controls that govern the intricate dynamics of a system, highlighting their significant influence on its behavior. Bipolarity, in which the

system can concurrently exist in two different and stable states, can be caused by a variety of parameter combinations. This phenomenon draws attention to the intricate interplay of variables that affect the resilience and behavior of the system. Predicting and managing the dynamics of the system requires an understanding of how these parameters interact. The complex link that exists between system behavior and parameter values emphasizes the necessity of accurate calibration in scientific and engineering applications.

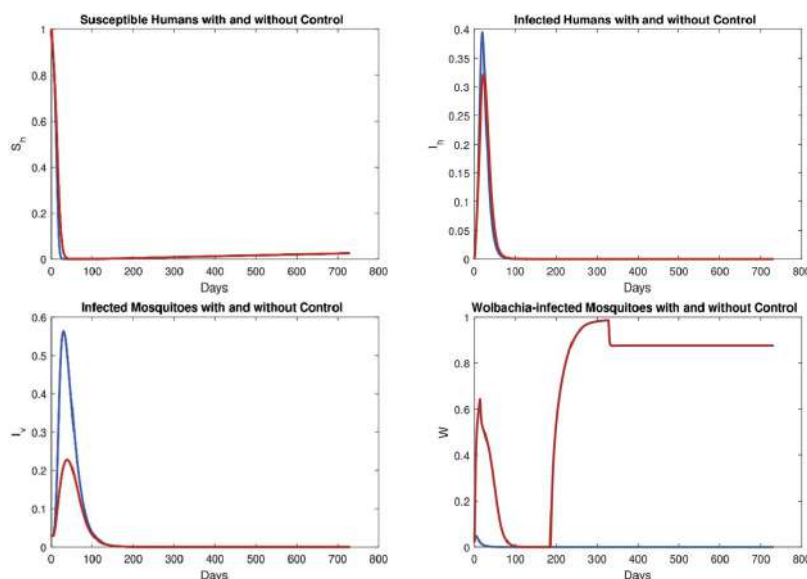
By carefully fine-tuning these parameters, researchers can harness bi-stability for innovative solutions or mitigate its effects to achieve desired outcomes. In summary, the stability and existence of steady states in complex systems are profoundly influenced by the nuanced interdependence of parameter values, offering a rich field for exploration and manipulation. The authors found that if  $R_0 > 1$ ,  $\beta_1 < 0$ , and  $\beta_2 < 0$  then the system is bi-stable with the stable fixed points when the Wolbachia fix in the mosquito population and dengue dies out, or where the dengue is endemic and the Wolbachia fix in the population.

### 3. Calculations

Harnessing Wolbachia to combat dengue emerges as a highly promising avenue within the sphere of non-immunizing control strategies. This innovative approach, though theoretically robust and showcasing initial success in early trials, necessitates a thorough examination of its inherent constraints. In reality, the application of Wolbachia faces challenges in scalability and long-term sustainability. The cost-effectiveness of large-scale implementation remains a pertinent concern, and the logistical hurdles involved in introducing Wolbachia-carrying mosquitoes into wild populations require careful planning and assessment.

Furthermore, the potential ecological impact of introducing modified mosquitoes must not be understated. Long-term effects on local ecosystems and unintended consequences demand vigilant scrutiny. Additionally, public acceptance and regulatory approval must be secured to navigate potential ethical and societal concerns. To unlock the full potential of Wolbachia as a dengue control strategy, a holistic approach is vital, addressing not only the technical and scientific aspects but also the economic, ecological, and ethical dimensions of its implementation. This promising solution, while exciting, should be explored with diligence, transparency, and an awareness of its limitations to ensure its success in the fight against dengue.

To date, the trial outcomes may seem more compelling than their actual impact, especially in light of the initial Australian trial which commenced in an area with a relatively low incidence of dengue. The effectiveness of this method might vary when applied in regions with higher disease prevalence. Additionally, the relatively short trial periods of these studies may not provide a comprehensive understanding of long-term implications, which are crucial in assessing its viability as a long-term solution. To fully evaluate the potential of Wolbachia-based control, further research and extended trials, conducted across a range of epidemiological contexts, are imperative. Only then can we confidently determine the effectiveness and practicality of this innovative approach in the fight against dengue?



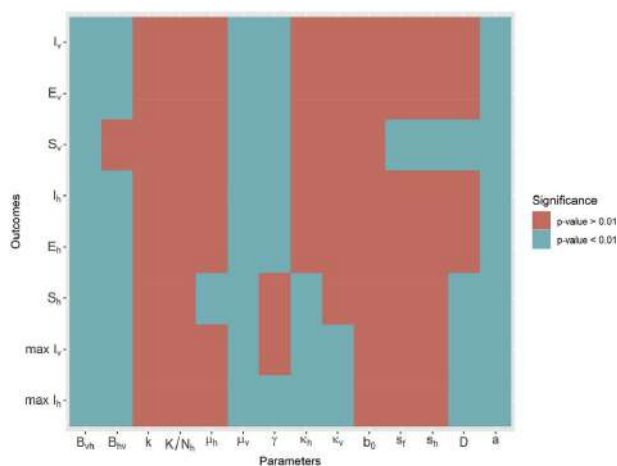
**Fig. 3.** Illustration depicting solution trajectories, where the ones guided by the optimal control  $u_s^*$  are highlighted in red, while those without optimal control are represented in blue. Parameter values are given in Table. Maximum values of infected humans,  $I_h$ , are 0.3943 and 0.3200 and occur on days 21 and 24 for the cases with and without control, respectively. Maximum values of infected mosquitoes,  $I_v$ , are 0.5637 and 0.2281 and occur on days 31 and 40 for the cases with and without control, respectively.

The honeymoon effect, a captivating phenomenon first elucidated by McLean and Anderson, offers a compelling window into the consequences of employing ineffective control measures in the context of an endemic disease. This intriguing concept sheds light on the intricate dynamics between pathogens and the interventions designed to curb their spread. Essentially, it underscores how, in the initial stages of implementing control strategies, there can be a deceptive period of apparent success. During this "honeymoon" phase, it might seem that the disease is under control, giving rise to a sense of optimism and complacency among public health officials and the general population. However, this illusory lull in the disease's impact is often short-lived. As time progresses, the pathogens can adapt and evolve, rendering the once-effective measures less potent.

Other than that the honeymoon impact serves as a poignant reminder of the importance of ongoing vigilance and adaptability in our technique for combating diseases. This underscores the requirement for long-term, sustainable control strategies that can withstand the test of time and also the ever-changing nature of infectious agents. Within the domain of public health, comprehension and addressing the intricacies of this phenomenon are crucial to making sure our efforts remain effective and beneficial in the fight against endemic diseases.

This term emphasizes the significance at the commencement, the disease's spread may appear to slow down or even also halt, creating a deceptive sense of success. Also, this false impression is short-lived, as the disease often rebounds with increased virulence, necessitating a more robust and sustainable approach to containment. Enlightenment of the honeymoon effect

is crucial for designing effective public health strategies against endemic diseases. Initially, there will be a steep drop in infections, but after a delay, the build-up of susceptibility to the disease will cause periodic spikes of infections. In the case of dengue the high numbers seen in the trial Wolbachia releases could represent this initial drop in number and the control could still be ineffective. Hollingsworth et al. were able to build on this idea and show that even an effective and efficient transient control can lead to spikes so high that the cumulative incidence, which is the total number of cases that occur since the start of the control, would be higher than if no control were employed. In this particular situation, when the trial ended the Wolbachia were not fixed in the population.



**Fig. 4.** The heat-map illustrating the statistical significance of Partial Rank Correlation Coefficients (PRCC) between input variables and their impact on the model's outcomes.

So, when the releases of Wolbachia cease, the potential consequence is the gradual decline of this beneficial bacterium within the population. This diminishment of Wolbachia opens the door for dengue, a mosquito-borne virus, to re surge. As a result, the human population once again becomes more susceptible to dengue infections, creating an environment conducive to the resurgence of this disease. The consequences are not limited to the immediate spike in infections; they can trigger a domino effect. This resurgence can lead to a rise in dengue cases, which, in turn, may lead to a greater strain on healthcare systems and resources. This strain is often referred to as the "divorce effect," where healthcare resources become increasingly divided between treating dengue cases and other medical needs. As a result, there exists a substantial risk of a widespread surge in the number of infections, which presents a daunting public health dilemma demanding meticulous and continuous attention. This escalating threat underscores the critical need for vigilant monitoring and proactive measures to contain the outbreak and protect the well-being of the population. The possibility of a rise in overall infections puts a burden on healthcare systems and has far-reaching economic and societal ramifications. For this reason, comprehensive strategies that balance public health protection with broader socioeconomic support are necessary.

Given this, communities, governments, and healthcare authorities must work together to develop effective preventive strategies, improve healthcare systems, and provide the public

with accurate information. To stop the spread of illnesses and keep our healthcare systems robust, such coordinated measures are essential. Furthermore, this situation serves as a stark reminder of the importance of global solidarity and preparedness to tackle emerging health challenges. The lessons learned from this experience should serve as a foundation for building a more resilient and responsive public health infrastructure that can effectively address not only the current crisis but also future ones, ensuring the safety and well-being of individuals worldwide.

#### 4. Results and Discussion

Leveraging Wolbachia to counteract dengue is an exciting non-immunizing approach that holds immense promise in theory and has demonstrated promising results in preliminary trials. Nevertheless, this innovative technique does come with certain limitations that warrant consideration. Up to this juncture, while the initial trials, particularly the one in Australia, appear compelling, it's essential to acknowledge that the baseline dengue prevalence was already low in the region. Furthermore, it's conceivable that the duration of the trial periods in these studies may have been somewhat inadequate. To harness Wolbachia's full potential in dengue control, we must delve deeper into these nuances and refine our approach for more comprehensive and reliable results.

The honeymoon effect, discovered by McLean and Anderson, describes what happens when an endemic disease is subjected to ineffective control. Initially, there will be a steep drop in infections, but after a delay, the build-up of susceptibility to the disease will cause periodic spikes of infections (McLean et al. 1988). In the case of dengue the high numbers seen in the trial Wolbachia releases could represent this initial drop in number and the control could still be ineffective. Hollingsworth et al. were able to build on this idea and show that even an effective transient control can lead to spikes so high that the cumulative incidence, which is the total number of cases that occur since the start of the control, would be higher than if no control were employed. In this case, when the trial ended the Wolbachia were not fixed in the population.

There could be severe repercussions if Wolbachia is no longer released. The Wolbachia bacteria, which is well-known for preventing the spread of the dengue virus, is vulnerable to population decline. Dengue's reappearance is therefore a serious threat. This resurgence could spell trouble for a human population that, over time, has gained a higher susceptibility to the virus due to reduced exposure. The repercussions are profound, potentially unleashing a devastating spike in dengue infections. This scenario sets the stage for a cascading effect, akin to a "divorce" between the protective barrier of Wolbachia and the human hosts. In this disconnection, dengue gains a foothold, causing a significant upswing in the number of infections. The collective impact of this resurgence could lead to a surge in the overall burden of dengue, affecting public health on a broader scale. In essence, the abrupt withdrawal of Wolbachia leaves the population vulnerable, and the dengue virus seizes the opportunity to resurface with a vengeance. As a result, the potential for a severe and widespread outbreak becomes a reality, demanding vigilant and ongoing efforts to maintain the equilibrium established by Wolbachia.

## 5. Future Research Directions

The mathematical modeling framework that this paper presents can be expanded upon in several ways, offering intriguing prospects for further investigation and use in applications. Here are some guidelines to take into account:

- Expand the model to include seasonal variations in parameters. This would allow assessing how Wolbachia impacts on dengue transmission may fluctuate at different times of year.
- Incorporate multiple dengue serotypes into the model to evaluate how Wolbachia may affect the complex immunological interplay between serotypes.
- Run the model across a wider range of parameters to further analyze its sensitivity and robustness. This could shed light on how generalizable the findings are.
- Use the model to optimize Wolbachia release strategies for long-term suppression of dengue transmission. This could identify ideal release sizes, frequencies, and durations.
- Adapt the model to represent specific dengue-endemic areas to simulate localized Wolbachia deployment. This could provide tailored insights to guide field implementation.
- Expand the model into a spatial framework to analyze how Wolbachia may spread geographically and affect heterogeneous transmission.
- Perform cost-effectiveness analyses using the model results to assess the economic viability of Wolbachia implementation.
- Use the model as a foundation for statistical and uncertainty analyses to further evaluate the reliability of predictions.
- Validate the model predictions against additional empirical data as it emerges from ongoing Wolbachia trials.
- Collaborate with public health officials to apply the model findings in shaping dengue control policies and Wolbachia release guidelines.

The next phase of this research will involve selecting one or more of these directions to develop the mathematical modeling approach into a practical tool that informs sustainable Wolbachia deployment worldwide.

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