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Optimizing Dengue Control Strategies: A Two-Patch Mathematical Modelling Approach

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Abstract: This paper investigates the complex dynamics and control strategies of dengue virus transmission, particularly focusing on the case of India. With dengue infections on the rise globally, the study addresses the challenges posed by factors such as urbanization, tourism, and climate change. It emphasizes the need for a comprehensive understanding of the virus's evolution and prevalence in India, a country experiencing a significant burden of dengue cases. The research employs a two-patch model of dengue transmission, considering human mobility between patches, to simulate the spread of the virus. The study explores the immunological constraints, transmission limits, and the influence of previous serotype infections on dengue evolution. Additionally, it highlights the potential impact of dengue vaccines, emphasizing the importance of assessing their efficacy against prevalent strains in India.
The paper introduces an optimal control approach, focusing on corrective actions, such as insecticide spraying, to minimize the economic and health burdens associated with dengue outbreaks.
In conclusion, the paper contributes valuable insights into the dynamics of dengue virus transmission in India, offering a nuanced perspective on factors influencing its evolution and control. The optimal control strategies presented underscore the potential for cost-effective measures to mitigate the impact of dengue outbreaks, thereby providing a foundation for informed public health policies.

Keywords: Dengue, Mathematical Model, Optimal control, Health burden, cost effective, Transmission and Management.

1. Introduction

Over the past 20 years, dengue illnesses have skyrocketed and are predicted to continue rising as they expand to new areas thanks to urbanization and tourism [1]. Dengue infections could affect around half of the world's population [1,2]. Only 96 million instances of dengue infections were documented clinically in 2010, according to estimates from 2010 [3]. India was thought to be the source of about one-third of these infections [3], yet the majority of them go undetected [4]. Nearly every Indian state has an endemic case of dengue [5,6]. There have been reports from throughout the nation of all four antigenically different serotypes (DENV-1-DENV-4) of the virus that exhibit strong immunological cross-reactivity because of 65–70% homology [7-9]. Dengue evolution in the nation has been shaped in diverse and unanticipated ways, albeit this is still poorly understood. These factors have been combined with a complicated transmission cycle and high dengue seroprevalence [5].

Diagnosis Process

Immunological constraints and pathogen transmission limits influence the evolution of the dengue virus globally [10,11]. A rise in human mobility and globalization may contribute to the international spread of newly developing dengue virus strains. However, the virus's restricted travel range, acute nature, and confinement to tropical parts of the vector can limit its spread. Due to horizontal transmission, the dengue virus, like other vector-borne viral diseases, changes its environment and applies a strong purifying selection pressure [10,12,13]. Pre-existing immunity can aid in the formation of immunological escape variations in both the human host and the broader population. In addition, the degree of cross-reactive antibodies and the antigenic similarity between the infecting serotypes during primary and secondary infection can influence the co-evolution of dengue serotypes due to heterotypic immunity [11, 14]. Moreover, antigenically related serotypes may benefit selectively from antibody-dependent enhancement (ADE) when there are insufficient amounts of cross-reactive antibodies [15–17].

The dengue virus can also be controlled by complex community immunity, which can alter the annual infection and caseload rates. Every 2-4 years, there are cyclical dengue outbreaks in the endemic areas. These outbreaks are frequently linked to serotype/genotype replacement, in which the dominance of one serotype/genotype shifts throughout the ensuing outbreak [18–21]. This has been linked to a mix of short-term (up to two years) protection from the heterotypic secondary infection and long-term protection from homotypic dengue infection [22–24]. This makes it possible for the heterotypic serotype to cause an outbreak, depending on the population's immunity and serotype prevalence in the area [18]. Additionally, ADE may contribute to an increase in dengue occurrences after serotype replacement. Elevated dengue viremia levels noted during ADE [25–27] may be a factor in the virus's enhanced spread [28, 29]. As a result, ADE-related consequences may accentuate the outbreaks' cyclical nature. It is uncertain, nevertheless, if this benefit also contributes to the virus's evolution. Therefore, knowing the dengue virus's evolutionary history and forecasting future outbreaks can be aided by information of the virus's longitudinal prevalence, serotype distributions, and prior serotype of infection [30].

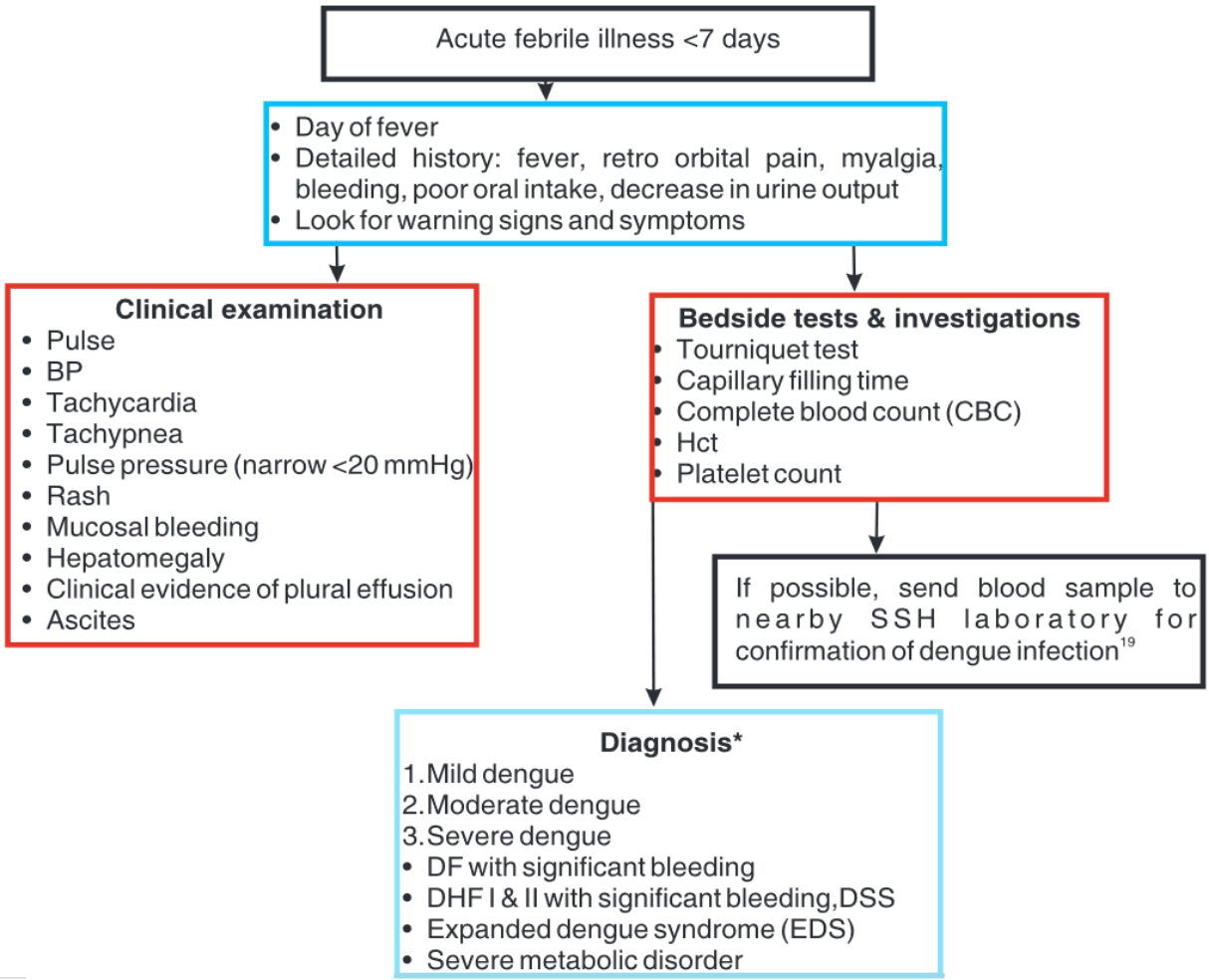


Figure 1. Diagnosis Process of Dengue

Despite India being a dengue hotspot, our knowledge of the evolution of the dengue virus has been hampered by the lack of dengue genomic data from this country. Due to the constraints of a brief collecting period, previous dengue studies conducted in India have concentrated on regional epidemics [7-9,31–33], which are dominated by a single or closely similar strain. At the city-scale, immunity-driven co-evolution of dengue virus strains has been demonstrated to be a result of all serotypes' persistence in a backdrop of high seroprevalence [11]. Whether these selection factors are influencing dengue virus divergence over the entire nation of India is unknown in the lack of longitudinal analysis of dengue viral diversity.

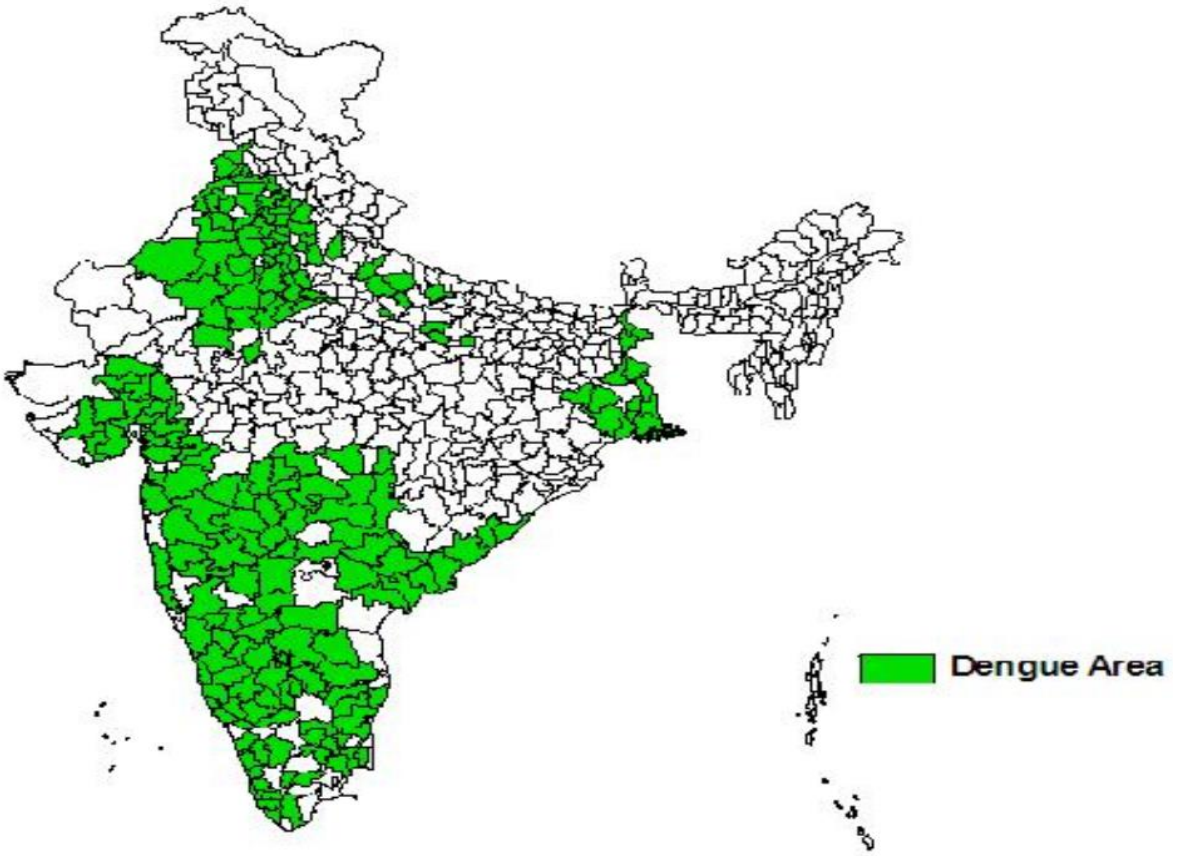


Figure 2. Situation of Dengue in India

The design and development of vaccines may be significantly impacted by the large divergence of common dengue genotypes [34, 35]. There are now several dengue vaccines in various phases of clinical testing that target all four serotypes [36]. The older dengue isolates from outside of South Asia served as the basis for these vaccinations. It is uncertain if they will produce the best amounts of neutralizing antibodies against the dengue viruses that are circulating in India because efficacy tests have not been conducted there. Not only may certain vaccine candidates not offer adequate defence against dengue infection, but they may further exacerbate the illness through adjuvant illness development (ADE) in the event of a second infection, as demonstrated by the CYD-TDV vaccine [37, 38]. However, to yet, no research has been done to compare the antigenic sites of vaccines and common strains of dengue fever in India.

Dengue diseases carried by Aedes aegypti and Aedes albopictus mosquitoes are becoming more common due to climate change. With an annual estimate of 100–400 million infections, [39] 96 million clinical symptoms, and 40 000 deaths, more than half of the world's population is at risk.[2]. An estimated 3·97 billion individuals (in 129 countries) are vulnerable to dengue illness, despite indications of 30- to 50-fold increases in incidence in tropical and subtropical regions over the past 50 years and the fastest growing risk of infection.[40, 41] Due to a number of causes, including as international trade and travel, urbanization, population growth, and climate fluctuation and change, which all create favorable circumstances for dengue vectors and viruses to proliferate, dengue disease has progressively increased over the past 50 years.[42, 43] Urbanization, temperature rise, vector suitability, vulnerability of populations, and climate change all pose threats to the spread of dengue.[44, 45]

The disease was contained to a few nations in southeast Asia in the 1950s and 1960s, but in the 1970s, regional and global dengue epidemics started, and during the next two decades, the disease spread. The incidence of dengue in India underwent a significant change by 2012–2013. In many places of southeast Asia, dengue has become an annual epidemic, and as the environment changes, the disease's dangers increase. Based on the latest available statistics, there were 110 473 cases of dengue recorded in India between January and October of 2022.

We should not undervalue the severity of the current COVID-19 pandemic, which has caused severe disruptions to health policy and priorities related to COVID-19. This has resulted in changes to the prevention, control, and management of infectious and vector-borne diseases, including dengue, and has caused havoc in terms of morbidity, mortality, and economic burden. The infrastructure supporting health care is under stress due to the

increasing incidence of COVID-19 and dengue, as well as the potential for co-infection. Treating dengue cases as soon as feasible and addressing the socioeconomic and environmental factors related to dengue and other vector-borne illnesses can help reduce transmission and fatality.

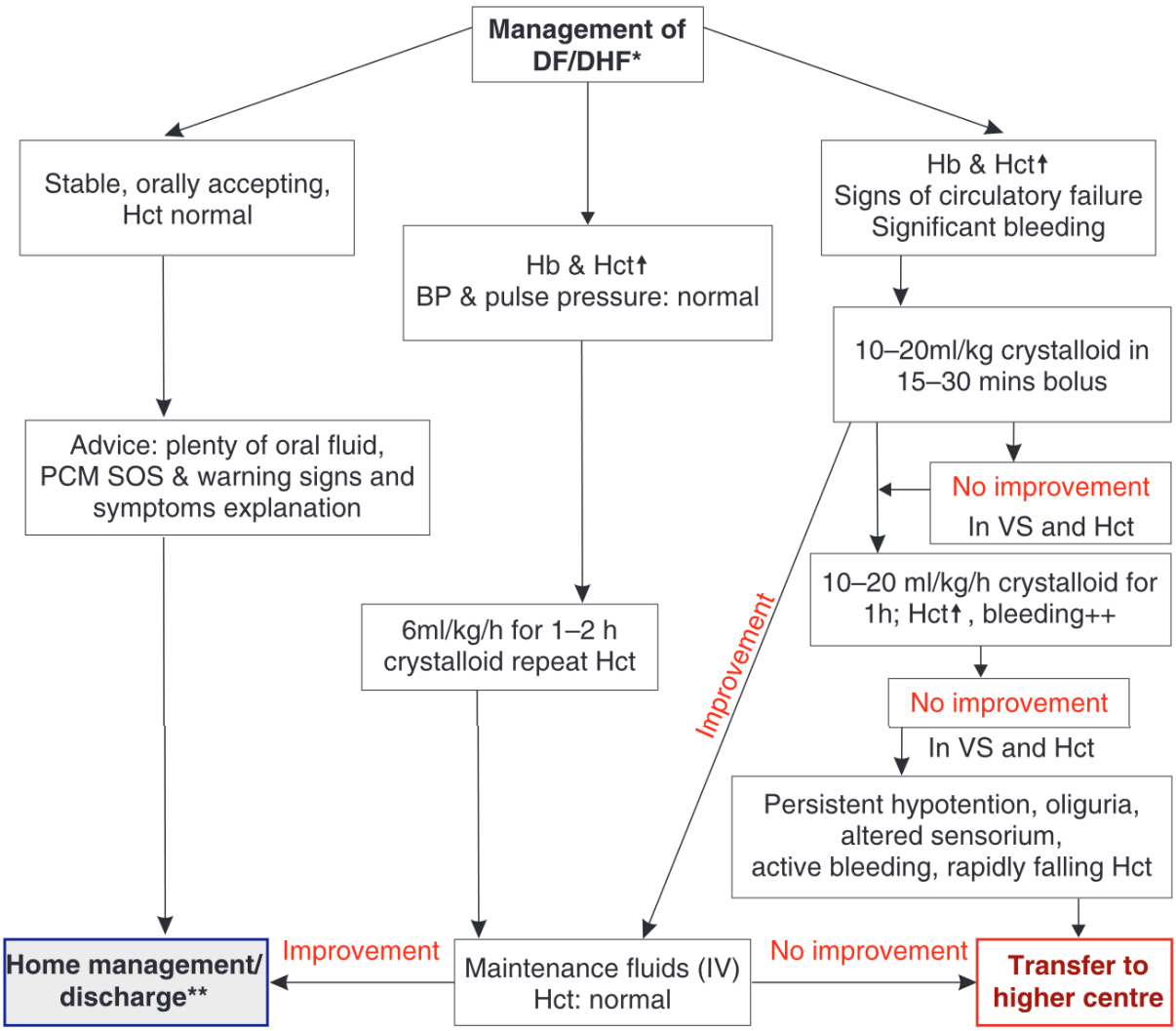


Figure 3. Control Dengue Management System

Two-Patch Model of Dengue Transmission

Let us start by going over the initial presentation of the SEIR(S)-SEI type two-patch dengue transmission model in [46]. The standard assumptions that guided the development of this model were as follows:

The human resident populations in both patches, $Nh1$ and $Nh2$, along with the vector resident populations in both patches, $Nv1$ and $Nv2$, remain pretty much unchanged over time.

Regarding susceptibility, exposure, and attraction, all populations Nhi,,=1,2} are homogeneous.

It is not possible for dengue to cause death in humans or vectors alike.

The mosquitoes carry the DENV infection for the whole of their lives and never fully recover.

Since there is no vertical DENV transmission, both human and vector babies are DENV-free.

Although mosquitoes spend their entire lives in a single patch, humans are able to migrate between the patches.

There are four distinct classes of human individuals living in each patch: susceptible individuals (those who do not have the virus), exposed individuals (those who have the virus but are not yet infectious), infectious individuals (those who have the virus and can infect female mosquitoes during a bite), and individuals who have recovered from the illness. For each patch, the fractions of the appropriate human groups with respect to the total populations Nhi,=1,2 are indicated by the symbols Shi, Ehi, $\boldsymbol{U}hi$, and Rhi, respectively. Likewise, the entire populations of vectors Nvi,=1,2 that live in each patch are separated into three disjoint classes: susceptible (female mosquitoes that do not carry the virus), exposed (female mosquitoes that carry the virus but are not yet infectious), and infectious (female mosquitoes that carry the virus and have the potential to bite humans). The fractions of the matching groups of vectors with respect to the total populations Nvi,=1,2 residing in each patch are shown by the symbols Svi, Evi, and Ivi, respectively. Remarkably, every population fraction or proportion presented above varies with time and satisfies the following relationships, which hold true for any $t\geq0$:

$$S*i+Ehi+\boldsymbol{U}hi=1,+Evi=1,i=1,2.$$

First (1)

A multitude of investigations has verified that dengue sickness, resulting from any of the four dengue serotypes DENV1-DENV4, can induce asymptomatic infection or vary from mild feverish illness resembling the flu to severe dengue or dengue shock syndrome (DSS). Though their percentage of total dengue morbidity is unknown, estimates of silent infections suggest that they may even outnumber symptomatic cases [47]. Thus, we can presume that certain infectious human beings from the groups Ihi,=1,2} might not show any symptoms and be unaware that they are contagious. These individuals might go between the two patches, which would aid in the disease's spread.

We assume that both the human population (Nhi,i=1,2) and the vector population (Nvi,i=1,2) have similar birth and death rates in order to mimic the demographic changes while maintaining the populations of humans and vectors essentially unchanged across time. Specifically, the symbol for the birth and death rate of humans is μh, whereas the symbol for the birth and death rate of mosquitoes is μv. [48]

The study focuses on the spread of dengue virus between two patches, assuming that the incubation periods of intrinsic and extrinsic viruses are $1/\kappa h$ and $1/\kappa v$ days, respectively. Recovery from the sickness takes $1/\gamma$ days, and after $1/\tau$ days, recovered people become vulnerable to heterologous DENV serotypes.

Susceptible vectors living in Patch 1 (resp. Patch 2) can get the virus from biting an infectious human resident from Class $Ih1$ (resp. Class $Ih2$) or an asymptomatic visitor from Class $Ih2$ (resp. Class $Ih1$) who is a resident of Patch 1 (resp. Patch 2). Human hosts in Patch 1 (resp. Patch 2) who are susceptible to contracting the virus may do so through bites from infectious vectors originating from their home patch or from infectious vectors from Patch 2 (resp. Patch 1) that they encounter while visiting Patch 2 (resp. Patch 1).

The Lagrangian technique is used to describe the commuting of individuals between two patches, modeling the movement of individuals between patches in terms of their residence periods, or the shares of time spent at each patch. The "vector-to-human" virus transmission rate βh depends not only on the mosquito bite rate α and the probability of virus transmission but also on the so-called vectorial density, i.e., the average number of female mosquitoes per one human individual. [49].

Table 1. Description of virus transmission

Parameter	Description	Units	Assumed Value
κ_v	Latent-to-infectious conversion rate in vectors	day^{-1}	$1/8$
κ_h	Latent-to-infectious conversion rate in humans	day^{-1}	$1/4$
γ	Rate of human recovery	day^{-1}	$1/6$
μ_v	Per capita vector birth/death rate	day^{-1}	$1/30$
μ_h	Per capita of human births/deaths	day^{-1}	$1/(75 \times 365)$
α	Mosquito biting rate	day^{-1}	0.4517
τ	Reinfection rate for human individuals	day^{-1}	0.0262
p_v	Human-to-vector transmission probability of the pathogen	–	0.2378
p_h	Vector-to-human transmission probability of the pathogen	–	0.219

Ideal Control Method

Dengue fever control is a global effort involving entities, societies, health care systems, and authorities of government to reduce mosquito density. Vetor control actions in dengue-pendemic zones can be broadly categorized into two sorts of actions: corrective, which involves using pesticides as part of an emergency reaction to stop disease outbreaks or clusters of cases that have been discovered in a specific area, and preventive, which involves eliminating mosquito breeding grounds. [49]

The second set of control actions is examined in this study from the perspectives of dynamic optimization and taking into consideration individuals who commute between two patches. The present corrective management measures being implemented by the local healthcare officials aim to eventually suppress dengue cases within the city. The adaptability and resilience of remedial measures in the face of financial restrictions are discussed.[51]

Two exogenous variables were used to model the corrective control effects of insecticide spraying in both patches are introduced.

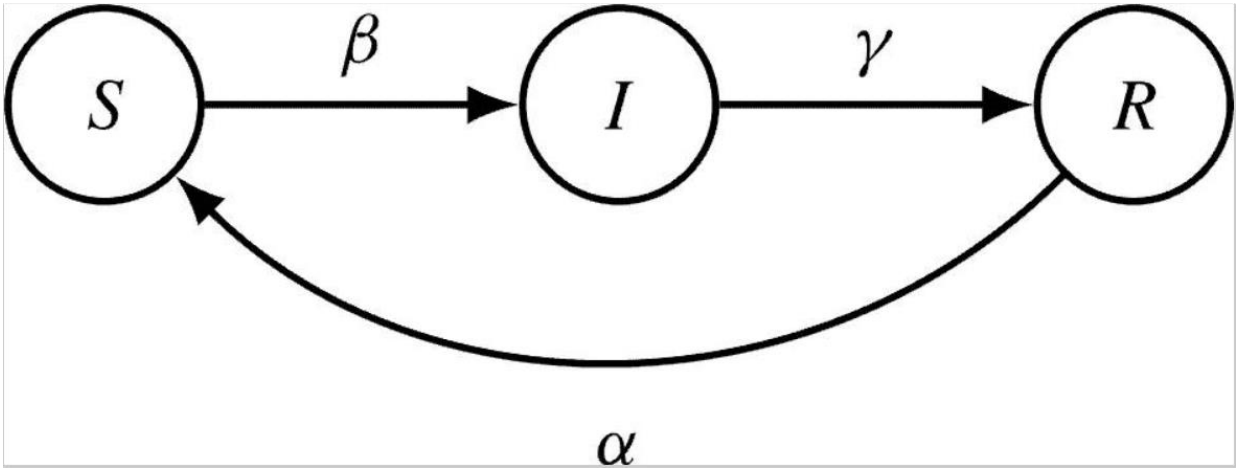
$$(t)\in[0,1],\ i=1,2,\ t\in[0,T].$$

The mosquito is directly impacted by these factors mortality rate, μv,in both patches

Depending on the insecticide's concentration and dilution, the maximum volume that can be applied daily over a unit area (shown by D) may change. [50]

Healthcare authorities worldwide are faced with the challenge of selecting the best insecticide spraying plan for both patches in a way that lowers the overall expenses of human infections during the dengue outbreak while yet satisfying any budgetary restrictions that may be placed in place. The numerical solutions to optimum control problems (8) and (9) derived with the GPOPS-II software package—created by PR Optimization Research LLC for the MATLAB platform—are presented in this work. The GPOPS-II solver transforms the continuous-time optimum control issue into a large sparse nonlinear programming problem by applying the Legendre–Gauss–Radau quadrature orthogonal collocation approach. The model is based on the dengue outbreak in Cali, Colombia, and the surrounding areas. The model makes the assumption that the overall numbers of humans and vectors are the same as in [49], and that the city has a lower average mosquito density than the outskirts. The study also considers four other significant factors: the large open spaces found in the suburbs, the tall apartment buildings seen in the city, and the issues with inconsistent water supply and sanitation that exist in the suburbs. The sequel takes into consideration several scenarios that further define the temporal residence matrix Q. The length of the period under consideration (T>0), the medical and social expenses of one human illness, and the average expense of one dengue infection are used to define the objective functional. The initial two elements of the desired outcome functional represent the entire accumulated cost for every dengue illness in both patches for T=30 days. Models of host-to-host transmission. [34]

As shown in Fig. 4, various extensions of the traditional susceptible-infected-recovered (SIR) models have been used to model multi-serotype host-to-host dengue dynamics. [52]



The state-flow diagram for a basic SIR-type epidemiological model focuses on the multi-strain aspect of the disease and its effects on the host population, accounting for vector dynamics through effective parameters like seasonality in the infection rate. This approach is helpful because existing vector management strategies for dengue have little effect on their own and are difficult to implement and maintain on a large scale.

Mathematical models explaining the transmission of dengue viruses have concentrated on multi-strain characteristics, ADE, and Temporary Cross-Immunity (TCI) to explain the irregular behavior of dengue epidemics. A multi-strain mathematical model published by Ferguson et al. revealed deterministically chaotic dynamics, which led to co-infection. Billings et al. described chaotic desynchronization in a multi-serotype dengue model with ADE, but cross-infection was impossible as long as a person had a primary infection.[52]

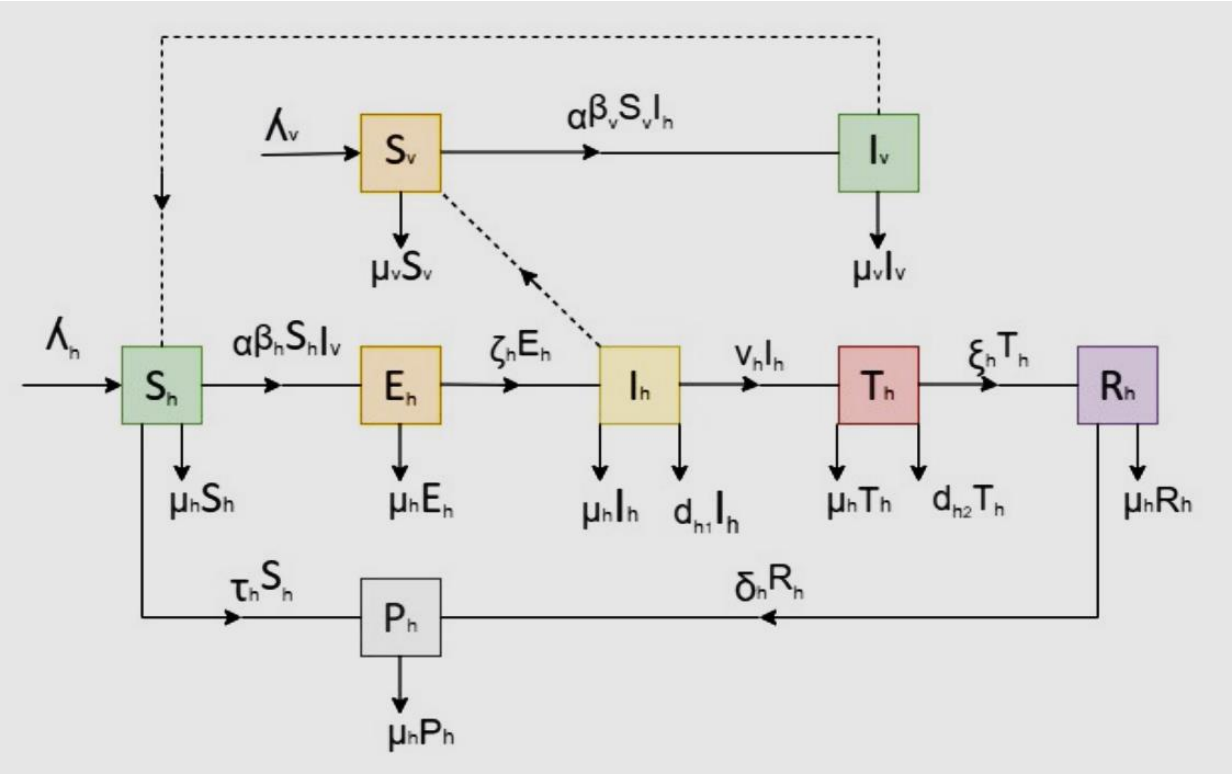
Aguiar and colleagues examined a simplified two-infection dengue model, which introduced Temporary Cross-Immunity (TCI) through additional compartments for persons healing from a primary infection, becoming sensitive again after a brief period of cross-immunity. This result suggested that deterministic chaos played a far larger role in multi-strain models than previously believed, providing new avenues for the examination of available data sets. [52]

Seasonality was added to the basic two-infection dengue model in 2011 to replicate the impact of vector dynamics. The epidemiological correlation showing a higher risk of serious illness in subsequent infections supported this idea. However, stochasticity had to be introduced to account for variations seen in some dengue data sets, exposing a situation in which complicated deterministic skeleton and noise interacted powerfully.[51, 52]

Several models have been developed to integrate the ADE effect with cross-protection assumptions, which raise transmissibility in secondary infections. Reich and colleagues proposed a model with an enhancement factor acting on individual susceptibility, assuming individuals with immunity to one serotype are more likely to acquire a second infection. Woodall and Adams assumed partial cross-protection following a primary dengue infection. Aguiar et al. supported the assumption that a secondary infection contributes less to the force of infection than a primary infection, combining a brief period of temporary cross-immunity between primary and secondary infections. The combination of TCI period and ADE effect is the most important feature driving complex dynamics in the system, more than the precise number of dengue serotypes to be added in the model.

It also looks at how regular commutes affect the spread of infectious diseases. The study takes into account varying intensities of population flow from the suburbs to the city and concentrates on the more realistic scenario of suburban inhabitants commuting between the two areas. The outcomes are contrasted with the uncoupled example, comprising three fundamental scenarios: strong coupling, no commuting, and commuting. [52]

By giving the problem parameters and assuming that there are no restrictions on the use of pesticides, the optimal control problems (8) and (9) can be solved. Decisions made by healthcare authorities are typically made without taking into account the directions and intensities of persons moving between two patches. Figure 1a shows the outcomes of the GPOPS-II solver's numerical solution of optimum control problems (8) and (9). With the action of $u*1(t)$ reduced by up to 0.2 of a day and the action of $u*2(t)$ extended by a corresponding amount of time, both optimal controls, $u*1(t)$ and $u*2(t)$, are of the bang-bang type. [53].



The robustness and resilience shown for additional commuting scenarios make the most effective limits derived using the uncoupled case 𝕊0 suitable for implementation as a corrective tool for dengue reduction. By comparing the total number of new human infections that occur throughout the observation period [0,] with control intervention to the baseline case, the impact of the optimal controls may be evaluated. By employing the optimal control strategies $u*1,*2$, it is possible to cut the dengue-related public spending from US$2,207,106 to US$856,761, meaning more than a 2.5-fold reduction compared to the no-intervention case. However, this favorable result can only be guaranteed if the healthcare authorities have solvency for implementing the insecticide spraying in both patches.[53]

The study focuses on the optimal control strategy for dengue in two patches, with a budget of US$337,740. Local healthcare authorities face budget constraints and can either reduce uniformly by -sharing the budgets or keep the budget despite drastic reductions. Three principal options can be formulated: uniform or unbiased budget cuts in both patches, keeping the budget despite budget cuts, or vice versa.[54]

Numerical solutions are solved under various residency time arrangements and with further restrictions. The findings demonstrate that, in every instance, the duration of insecticide spraying is lowered in proportion to budget cuts. There is no difference in $Ch(T;u*1,u*2)$ between Cases 1, 2, and 3 with a 10% budget cut. However, Case 1 (a uniform or unbiased distribution of the budget decrease) performs better than the two biased distributions when budget cuts reach higher levels (20% or 30%).

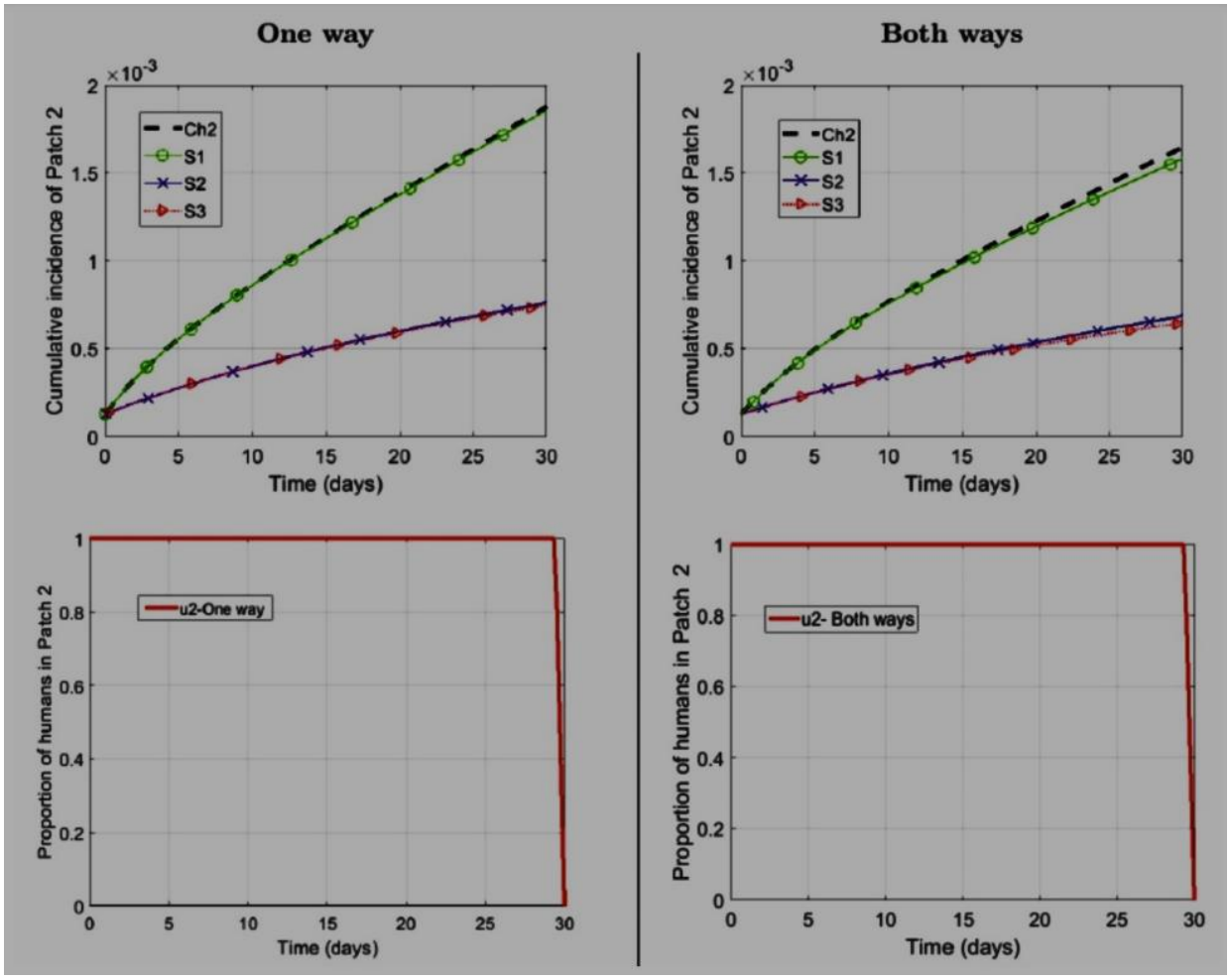


Figure 5. The upper row represents the cumulative incidence in Patch 2 ($C\mathbf{O}h2(tt)$, while the lower row represents the optimal control profiles ($uu2 * (tt)$) for situations 2 (left column) and 5 (right column) for the various situations. [53]

The worst option for controlling dengue fever is the most widely used method of handling budget cuts in real life. The paper also discusses the costs associated with applying pesticides and the costs of treating infections in humans that may recur even after corrective action is taken. [53]

Costs associated with dengue, both direct and indirect, differ with nations, areas, and socioeconomic situations. Indirect costs include lost productivity, absenteeism from work, and social repercussions including stress and emotional anguish for affected individuals and their family. Direct costs include the deployment of vector control measures and medical costs for local public health departments. The objective of this study is to calculate the direct costs under various budget cuts and for the three commuter scenarios that are outlined in Cases 1, 2, and 3. The cost of treating infected patients medically and spraying insecticides is included in the total direct cost associated with the dengue outbreak. Reducing the money needed for corrective control measures is not the ideal course of action because doing so will always result in a discernible increase in the overall cost. At least in cases where funding for corrective actions is completely accessible and no budget cuts take place, the volume of persons commuting has no discernible effect on the spread of the disease.[55 56]

Transmission models convert the evolution of an epidemic into mathematical form by describing the mechanical spread of infected individuals. The goal of this work is to create a mathematical model of dengue fever that includes two new classes: protected travelers class Ph and treatment class Th. The susceptible human population, exposed people, sick people, people receiving treatment, people who have recovered or been removed, and protected travelers are the different sections of the model. The probabilities of contact between susceptible individuals and infectious mosquitoes are represented by βh and βv, respectively, while the human population recruitment rate is represented by λh. [54 55]

The goal of the study is to reduce the number of human infections in order to control the disease. At disease-free and endemic equilibrium points, the suggested fractional-order dengue fever model fulfils both local and global stability features and is well-posed. By figuring out the best treatment rates for different fractional orders that minimize the cost functional and drastically lower the number of exposed and infected persons, the major goal is to limit the number of infected humans. According to numerical study, the rate of therapy and the memory index can both significantly reduce the effects of the condition. According to the study's findings, time-dependent control is more economical than time-independent control. [56]

2. Conclusion

In conclusion, this research delves into the complex dynamics of dengue virus transmission, with a specific focus on the case of India. By employing a two-patch mathematical model that considers human mobility between patches, the study provides valuable insights into the evolution and control of dengue in a country facing a significant burden of the disease. The investigation highlights the challenges posed by urbanization, tourism, and climate change in the context of rising dengue infections globally.
The study explores the immunological constraints, transmission limits, and the impact of previous serotype infections on the evolution of the dengue virus in India. It emphasizes the need for a nuanced understanding of the virus's prevalence, considering factors such as population mobility and serotype distribution. Additionally, the potential impact of dengue vaccines is addressed, stressing the importance of assessing their efficacy against prevalent strains in the Indian population.

The introduction of an optimal control approach, focusing on corrective actions like insecticide spraying, adds a practical dimension to the research. The study aims to minimize the economic and health burdens associated with dengue outbreaks. The optimal control strategies presented in the research underscore the potential for cost-effective measures to mitigate the impact of dengue, providing a foundation for informed public health policies.

Moreover, the paper emphasizes the global challenge of dengue control, considering factors such as climate change, urbanization, and international travel. The impact of daily commuting on disease propagation is explored, highlighting the importance of accounting for human movement in control strategies.

The optimal control approach introduced in the research, focusing on insecticide spraying, is particularly noteworthy. By employing numerical solutions and considering budget constraints, the study demonstrates the potential for substantial reductions in dengue-related public spending. The findings suggest that strategic insecticide spraying, when implemented optimally, can significantly reduce the economic burden of dengue outbreaks.

As the study acknowledges the severity of the ongoing COVID-19 pandemic and its impact on health policy priorities, it underscores the importance of addressing both infectious and vector-borne diseases concurrently. The paper concludes by emphasizing the significance of timely treatment for dengue cases and addressing socioeconomic and environmental factors to reduce transmission and fatality.

In summary, this research contributes valuable knowledge to the field of dengue control in India, offering a comprehensive understanding of the virus's dynamics and proposing practical and cost-effective measures for mitigating its impact. The insights provided lay a foundation for evidence-based decision-making in public health, particularly in regions grappling with the challenges of dengue transmission.

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