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Mathematical Model for the Optimal Control of the Seasonal Dengue Transmission

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Abstract

The aim of this paper is to propose optimal strategies for dengue reduction and prevention in some community. For this purpose, we formulate a seasonal dengue transmission model, which is amended with two control variables. These variables express feasible control actions to be taken by an external decision-maker. First control variable stands for the insecticide spraying and thus targets to suppress the vector population. The second one expresses the protective measures (such as use of repellents, mosquito nets, and insecticide-treated clothes) that are destined to reduce the number of contacts (bites) between female mosquitoes (principal dengue transmitters) and human individuals. We apply the Pontryagin's maximum principle in order to derive the optimal strategies for dengue control and then numerical analysis of these strategies is performed in order to choose the most sustainable one in terms of cost–benefit.

Keywords: Dengue, *Aedes aegypti*, seasonality, deterministic periodic system, maximum principle, optimal control.

I. INTRODUCTION

Dengue fever (DENV) is the arthropod-transmitted disease with the highest morbi-mortality in the world, also one of the most frequent causes of hospitalization and significant interruption of income potential in endemic areas (an estimated 390 million people become infected every year, 500000 people suffering from severe dengue require hospitalization and 2.5% die), it affects the tropical and subtropical countries of Asia, the Pacific Islands, the Caribbean islands, Africa and Central and South America [1]. There are macrofactors to explain the increase of DENV on a global scale: climatics (global warming) and social, such as the increase in world population, the tendency to disorderly urbanization, international travel and poverty expressed in problems of housing, education, water supply, solid waste collection and others, as well as the lack of effective national and international programs against this disease and its vector; currently, vector control is the predominant strategy to prevent the spread of DENV because there are no effective, economical or tetravalent vaccine and treatment for disease [2].

DENV belongs to the family Flaviviridae and there are four serotypes formally recognized: DEN-1, DEN-2, DEN-3 and DEN-4 [3], but in October 2013 a possible fifth sylvatic serotype (DENV-5) has been detected during screening of viral samples taken from a 37 year old farmer admitted in hospital in Sarawak state of Malaysia in the year 2007 [4]; the infection by a serotype 1 to 4 confers permanent immunity against this serotype and only for a few months against the rest of the serotypes; if a person is infected by one of the four serotypes, they will never be infected by the same serotype (homologous immunity), but lose immunity to the other three serotypes (heterologous immunity) in approximately 12 weeks and then becomes more susceptible to developing dengue hemorrhagic fever [5]. The primary vector of DENV is *Aedes aegypti* and the secondary vector is *Aedes albopictus*, both can feed at any time during the day and acquires the virus through the bite to a sick person during his period of viremia, which goes from a day before the onset of fever to an average of 5 or 6 days after the start of the same, being able to reach up to 9-10 days exceptionally [6].

Climate variables such as temperature, humidity and rainfall significantly influence the mosquito development and several studies suggest that entomological parameters are temperature sensitive as the dengue fever normally occurs in tropical and subtropical regions [7]; the high temperature increases the lifespan of mosquitoes and shortens the extrinsic incubation period of the dengue virus, increasing the number of infected mosquitoes, the rainfall provides places for eggs and for larva development [8]. Many of these regions have shown seasonal patterns that directly influence the dynamics of dengue transmission, leading researchers to develop mathematical models with periodic transmission rates [9, 10] and periodic demographic rates due to mosquito life cycle [11, 12].

In Latin America, local health authorities prefer the use of chemicals (first option), directly targeting the reduction of mosquito populations, and thus they usually neglect the measures aimed at personal protection of human individuals from mosquito bites. On the other hand, WHO and PAHO experts call upon the implementation of Integrated Management Strategy for the Prevention and Control of Dengue [79], which is a genuine combination of the aforementioned options. Under this approach, the Integrated Vector Management (IVM) is defined by WHO as "A rational decision-making process for the optimal use of resources for vector control". However, optimization of IVM destined resources is not on the present-time agenda of Colombian decision-makers from public health authorities.

A natural and important problem associated with epidemic models is to estimate whether an infection can invade and persist in a population, and then determine a measure of the effort required to control it, a threshold value used for this is the basic reproduction number (BRN). Diekmann et al., van den Driessche and Watmough [13] – [15] presented a general approach for the calculus of the BRN for autonomous ordinary differential equations models with compartmental structure. In the past twenty years, many authors have extended the definition of the BRN to periodic environments, we highlight authors like Bacaër and Guernaoui (2006), Wang and Zhao (2008), Thiems (2009), Bacaër (2011), Inaba (2012), Bacaër and Ait Dads (2012), Wang and Zhao (2017) [16] – [22]. Bacaër and Guernaoui [16] published a paper proposing a method to calculate the BRN for a model of cutaneous leishmaniasis using an approach which extends the linear operator method first defined by Diekmann et al. on autonomous systems, by adapting the next-generation operator method of van den Driessche and Watmough to periodic systems. They proved this reproductive number held the same threshold behaviour for the model but did not lay out an explicit formula for calculating it. Wang and Zhao [17] presented a theory of the basic reproductive number for a large class of periodic compartmental models that parallels Bacaër's method by extending the work of van den Driessche and Watmough.

II. MODEL FORMULATION

We consider a model of a dengue serotype that circulates in some community due to the ecological interaction of humans and mosquitoes of the *Aedes aegypti* species, based on a system of nonlinear ordinary differential equations, whose assumptions are:

1. Preserving some resemblance regarding the symptomatology of the disease in the hosts (humans), we use the following nomenclature:

• susceptible population/non-carrier population, subscript S, comprising those individuals capable of catching the disease;

• non-infectious infected population/non-infectious carrier population, subscript E, comprising those mosquitoes temporarily unable of transmitting the disease;

• symptomatic population/infectious carrier population, subscript I, comprising those individuals capable of transmitting the disease; and

• recovered or immune population, subscript R, including those individuals who acquire permanent immunity against infection.

2. All vector population measures refer to densities of female mosquitoes.

3. Alternative dengue virus hosts are not considered as blood sources.

4. Dengue-induced mortality in humans or vectors is not considered.

5. Carrier vectors probably transmit the virus throughout the lifespan.

6. The total population of hosts is constant (births balance deaths).

7. The environment changes periodically (seasonal variations), these variations are modelled by including time-periodic parameters.

Dengue is principally vectored by the bite of the *Aedes aegypti* mosquito, the life cycle of which is influenced by seasonal variation in climatic variables: adult vector density is often higher during the wet season [25, 26], and ambient temperature is known to regulate dengue transmission through its effects on adult longevity, blood-feeding activity, and the incubation of the virus within the mosquito [27]. This seasonal component will be incorporated into the recruitment of adult vectors, daily mosquito bite and daily mortality through time-dependent periodic functions. On the other hand, it is plausible to assume that people experience the same rate of change in births and deaths not induced by dengue, given that the death rate from dengue is less than 1% under adequate medical care and the human population practically does not change on the time scale of several generations of mosquitoes [28, 29].

Most of the terms in the model can be understood by referring to the list below, where the meaning of the parameters is described.

• $m(t)$: natural mortality rate of adult mosquitoes.

• h: natural mortality rate of humans.

• $\hat{l}$: rate of humans who develop dengue symptoms.

• r: human recovery rate.

• b: per head contact rate of adult female mosquitoes on humans, namely, the average number of bites per mosquito per day.

• q: probability of transmission of an infectious carrier mosquito by bite on a susceptible human.

• p: probability of transmission from a symptomatic human to mosquito.

• c: transfer rate of mosquitoes from non-infectious carrier to infectious carrier.

• $\Delta(t)$: mosquito recruitment rate (by birth and immigration) at time t.

• $H(t)$: average number of people in the community at time t

The transmission dynamics is interpreted according to seven state compartments and the flows between classes, four compartments for the human population and three for the vector population.

III. OPTIMAL CONTROL PROBLEM

This section is devoted to formulating a control problem to mitigate dengue from a community, focusing on two main groups of control actions:

• Reduction of the transmissibility of the disease: This control action aims to reduce the number of bites taken by mosquitoes and received by human hosts, it includes educational campaigns that stimulate people's awareness of removal of breeding sites, the use of repellants, mosquito nets, insecticide-treated clothing at home level or in workplaces [81].

• Suppression of the mosquito population: This control action aims to reduce the density and longevity of mosquitoes, it consists of spraying mosquito habitats and peripheral surfaces in a neighborhood or commune with insecticide or spatial treatment, capable of destroy larval infestations in breeding sites and may eliminate adult mosquitoes in the process [82].

We introduce two piecewise continuous real functions into system (2), which are also called "control variables" or simply 'controls'. These time-dependent controls apply for t_f days, and are: $u_{\mathrm{H}}(t) \in [0,1]$ represents the level of effort to prevent contact between mosquitoes and humans (personal protection), in other words, the fraction of people who take preventive measures; $u_{\mathrm{M}}(t) \in [0,1]$ represents the level of adulticide/larvicide administered in vector breeding areas (spatial treatment/focal treatment), in other words, the proportion of adult/immature mosquitoes that die due to insecticide application. Therefore, the mosquito-human contact rates are reduced by a factor $(1-\varpi_1 u_{\mathrm{H}}(t))$, the factor $\left(1-\varpi_2 u_{\mathrm{M}}(t)\right)$ reduces the recruitment rate of the non-carrier mosquito population, and the natural mortality rate of mosquitoes increases additively with $\varpi_2 u_{\mathrm{M}}(t)$.

After incorporating the above-mentioned controls, the controlled system is:

$$\frac{d\mathrm{H_S}}{dt} = h\mathrm{H} - \left(1-\varpi_1 u_{\mathrm{H}}(t)\right) q b(t) \mathrm{M_I H_S}/H - h\mathrm{H_S}$$

$$\frac{d\mathrm{H_E}}{dt} = \left(1-\varpi_1 u_{\mathrm{H}}(t)\right) q b(t) \mathrm{M_I H_S}/H - (\hat{l}+h)\mathrm{H_E}$$

$$\frac{d\mathrm{H_I}}{dt} = \hat{l}\mathrm{H_E} - (h+r)\mathrm{H_I H_R} = r\mathrm{H_I} - h\mathrm{H_R} \qquad \textbf{(1)}$$

$$\frac{d\mathrm{M_S}}{dt} = \left(1-u_{\mathrm{M}}(t)\right)\Delta(t) - \left(1-\varpi_1 u_{\mathrm{H}}(t)\right) p b(t) \mathrm{H_I M_S}/H - \left(m(t)+\varpi_2 u_{\mathrm{M}}(t)\right)\mathrm{M_S}$$

$$\frac{d\mathrm{M_E}}{dt} = \left(1-\varpi_1 u_{\mathrm{H}}(t)\right) p b(t) \mathrm{H_I M_S}/H - \left(c+m(t)+\varpi_2 u_{\mathrm{M}}(t)\right)\mathrm{M_E}$$

$$\frac{d\mathrm{M_I}}{dt} = c\mathrm{M_E} - (m(t)+\varpi_2 u_{\mathrm{M}}(t))\mathrm{M_I}$$

subject to the initial conditions at $t = t_0 \geq 0 : \mathrm{H_S}(t_0) > 0, \mathrm{H_E}(t_0) > 0, \mathrm{H_I}(t_0) > 0, \mathrm{H_R}(t_0) > 0, \mathrm{M_S}(t_0) > 0, \mathrm{M_E}(t_0) > 0, \mathrm{M_I}(t_0) > 0$; the constant parameters verify that $h > 0, \hat{l} > 0, r > 0, c > 0$, and $(\varpi_1, \varpi_2, p, q) \in [0,1]^4$; the rates $\Delta(t), b(t)$ and $m(t)$ are continuously differentiable, positive, real-valued, $\omega-$periodic functions; $u_{\mathrm{H}}(t), u_{\mathrm{M}}(t): [0, t_{\mathrm{f}}] \mapsto [0,1]$.

The next set establishes a domain where the system is mathematically and epidemiologically reasonable, since it guarantees that the population trajectories are always positive, continuous and that they do not grow indefinitely over time:

$$\Pi = \left\{\mathbf{x} \in \mathrm{R}_+^7 : \mathrm{H_s} + \mathrm{H_E} + \mathrm{H_I} + \mathrm{H_R} = \mathrm{H} = \text{constant} \wedge 0 \leq \mathrm{M_S} + \mathrm{M_E} + \mathrm{M_I} \leq \frac{\Delta^u}{m^l}\right\}.$$

Where $\mathbf{x}_{\mathrm{H}} = [\mathrm{H_s} \quad \mathrm{H_E} \quad \mathrm{H_I} \quad \mathrm{H_R}]^\top$ and $\mathbf{x}_{\mathrm{H}} = [\mathrm{M_S} \quad \mathrm{M_E} \quad \mathrm{M_I}]^\top$.

The control analysis is certainly appropriate in the context of the persistence of the disease, therefore $\mathrm{R}_0 > 1$ is satisfied. Since we seek to minimize the number of exposed hosts, infected hosts, total number of mosquitoes and the cost of applying the controls, we consider the following objective cost functional:

$$\underset{\mathbf{u} \in \Gamma}{\text{Minimize}} \left\{ J(t, \mathbf{x}(t), \mathbf{u}(t)) = \int_0^{t_{\mathrm{f}}} \left(\rho_1 \mathrm{H_I}(t) + \rho_2 \mathrm{H_E}(t) + \rho_3 \mathrm{M_{EI}}(t) + \frac{\kappa_1}{2} u_{\mathrm{H}}^2(t) + \frac{\kappa_2}{2} u_{\mathrm{M}}^2(t) \right) dt \right\}, \qquad \textbf{(2)}$$

subject to the state system (1). The quantities ρ_i and κ_j (constant weights), $i \in \{1, 2, 3\}$ and $j \in \{1, 2\}$, reflect the importance given to the decrease in dengue cases and vector density. In order for the sum described in the integrand to make sense, it should be considered that the weights are not only related to the costs of the mitigation campaign but are also defined so that the units of the terms that are used coincide.

The objective is to find a function $\mathbf{u}^*(t) = [u_{\mathrm{H}}^*(t) \quad u_{\mathrm{M}}^*(t)]$ in a set of admissible controls:

$$\Gamma = \{\mathbf{u}(t) = [u_{\mathrm{H}}(t) \quad u_{\mathrm{M}}(t)] \mid u_{\mathrm{H}}(t), u_{\mathrm{M}}(t) : [0, t_{\mathrm{f}}] \mapsto [0,1] \text{ are piecewise continuous}\}$$

such that

$$J(\mathbf{u}^*(t)) \leq J(\mathbf{u}(t)), \forall \mathbf{u} \in \Gamma \Leftrightarrow J(\mathbf{u}^*(t)) = \min_{\mathbf{u}\in\Gamma} J(\mathbf{u}(t)).$$

III.1 Application of the Pontryagin Maximum Principle

To determine the optimal pair $[u_{\mathrm{H}}^*(t) \quad u_{\mathrm{M}}^*(t)]$ we apply the Pontryagin's maximum principle as described in [86], for this we define what is called the Hamiltonian function:

$$\mathcal{H}^\star(\mathbf{x},\mathbf{u},\gamma) =$$

$$\rho_1 \mathrm{H_I} + \rho_2 \mathrm{H_E} + \rho_3 \mathrm{M_{EI}} + \frac{\kappa_1}{2} u_{\mathrm{H}}^2 + \frac{\kappa_2}{2} u_{\mathrm{M}}^2 + \gamma_1 \Big(h\mathrm{H} - (1 - \varpi_1 u_{\mathrm{H}}) \frac{qb(t)\mathrm{M_I H_S}}{\mathrm{H}} - h\mathrm{H_S}\Big) + \gamma_2 \Big((1 - \varpi_1 u_{\mathrm{H}}) \frac{qb(t)\mathrm{M_I H_S}}{\mathrm{H}} - (\hat{l} + h)\mathrm{H_E}\Big) + \gamma_3(\hat{l}\mathrm{H_E} - (h + r)\mathrm{H_I}) + \gamma_4(r\mathrm{H_I} - h\mathrm{H_R}) + \gamma_5 \Big((1 - u_{\mathrm{M}})\Delta(t) - (1 - \varpi_1 u_{\mathrm{H}}) \frac{pb(t)}{\mathrm{H}} \mathrm{H_I M_S} - (m(t) + \varpi_2 u_{\mathrm{M}})\mathrm{M_S}\Big) + \gamma_6 \Big((1 - \varpi_1 u_{\mathrm{H}}) \frac{pb(t)}{\mathrm{H}} \mathrm{H_I M_S} - (c + m(t) + \varpi_2 u_{\mathrm{M}})\mathrm{M_E}\Big) + \gamma_7(c\mathrm{M_E} - (m(t) + \varpi_2 u_{\mathrm{M}})\mathrm{M_I})$$

The optimality condition is obtained by adding penalty terms:

$$J^{\star\star}(\mathbf{x},\mathbf{u}) = \mathcal{H}^*(\mathbf{x},\mathbf{u},\gamma) + \rho_1^\star u_{\mathrm{H}} + \rho_2^\star(1 - u_{\mathrm{H}}) + \rho_3^\star u_{\mathrm{M}} + \rho_4^\star(1 - u_{\mathrm{M}}), \quad \textbf{(3)}$$

to ensure that u_{H} and u_{M} are positive fractions, and must satisfy:

$$\rho_1^\star u_{\mathrm{H}} = 0, \rho_2^\star(1 - u_{\mathrm{H}}) = 0, \rho_3^\star u_{\mathrm{M}} = 0, \quad \textbf{(4)}$$

$$\rho_4^\star(1 - u_{\mathrm{M}}) = 0, \rho_j^\star \geq 0 \text{ for } j \in \{1, 2, 3, 4\}$$

We now derive the necessary conditions that an optimal control function and corresponding states must satisfy. In the following proposition, we present the adjoint system and the control characterization by applying the necessary conditions to the Hamiltonian.

Proposition 1. *Given an optimal control* $\boldsymbol{u}^\star(t) = [u_H^\star(t) \quad u_M^\star(t)] \in \Gamma$ *and a corresponding solution* $\boldsymbol{x}^\star(t) = [\mathrm{H_S^\star} \quad \mathrm{H_E^\star} \quad \mathrm{H_I^\star} \quad \mathrm{H_R^\star} \quad \mathrm{M_S^\star} \quad \mathrm{M_E^\star} \quad \mathrm{M_I^\star}]^\mathsf{T} \in \Pi$ *of the control system (1), then there are adjoint functions* $\gamma_j, j \in \{1, 2, \dots, 7\}$*, satisfying*

$$\begin{aligned}
\frac{d\gamma_1}{dt} &= \gamma_1 h + (\gamma_1 - \gamma_2)\Big((1 - \varpi_1 u_{\mathrm{H}}(t))qb(t)\mathrm{M_I^\star}/H\Big) \\
\frac{d\gamma_2}{dt} &= -\rho_2 + \gamma_2 h + (\gamma_2 - \gamma_3)\hat{l} \\
\frac{d\gamma_3}{dt} &= -\rho_1 + \gamma_3 h + (\gamma_3 - \gamma_4)r \\
&\quad + (\gamma_5 - \gamma_6)\Big((1 - \varpi_1 u_{\mathrm{H}}(t))pb(t)\mathrm{M_S^\star}/H\Big) \\
\frac{d\gamma_4}{dt} &= \gamma_4 h \\
\frac{d\gamma_5}{dt} &= \gamma_5(m(t) + \varpi_2 u_{\mathrm{M}}(t)) \\
&\quad + (\gamma_5 - \gamma_6)\Big((1 - \varpi_1 u_{\mathrm{H}}(t))pb(t)\mathrm{H_I^\star}/H\Big) \\
\frac{d\gamma_6}{dt} &= -\rho_3 + \gamma_6(m(t) + \varpi_2 u_{\mathrm{M}}(t)) + c(\gamma_6 - \gamma_7) \\
\frac{d\gamma_7}{dt} &= -\rho_3 + \gamma_7(m(t) + \varpi_2 u_{\mathrm{M}}(t)) \\
&\quad + (\gamma_1 - \gamma_2)\Big((1 - \varpi_1 u_{\mathrm{H}}(t))qb(t)\mathrm{H_S^\star}/H\Big)
\end{aligned} \quad \textbf{(5)}$$

with the transversality conditions *(or boundary conditions):* $\gamma_j(t_{\mathrm{f}}) = 0, j \in \{1, 2, \dots, 7\}$. *Furthermore, the optimal control is given by*

$$\mathbf{u}^\star(t) = \begin{bmatrix} \min\left\{\max\left\{0, \dfrac{\varpi_1(\gamma_2 - \gamma_1)\left(\frac{qb(t)\mathrm{M_I^\star H_S^\star}}{\mathrm{H}}\right) + \varpi_1(\gamma_6 - \gamma_5)\left(\frac{pb(t)\mathrm{H_I^\star M_S^\star}}{\mathrm{H}}\right)}{\kappa_1}\right\}, 1\right\} \\ \min\left\{\max\left\{0, \dfrac{\gamma_5(\Delta(t) + \varpi_2 \mathrm{M_S^\star}) + \gamma_6(\varpi_2 \mathrm{M_E^\star}) + \gamma_7(\varpi_2 \mathrm{M_I^\star})}{\kappa_2}\right\}, 1\right\} \end{bmatrix} \quad \textbf{(6)}$$

Proof. Let $\mathbf{e}_i$ be the i-th canonical vector. The adjoint equations and the transversality conditions result from

$$\frac{d\gamma}{dt} = -\mathsf{D}_{\mathbf{x}}\mathcal{H}^\star(\mathbf{x}^\star,\mathbf{u}^\star,\gamma) = \sum_{i=1}^{7} \left(\frac{\partial \mathcal{H}^\star(\mathbf{x}^\star,\mathbf{u}^\star,\gamma)}{\partial(\mathbf{x} \cdot\cdot\, \mathbf{e}_i)}\right)\mathbf{e}_i, \gamma(t_{\mathrm{f}}) = 0.$$

To get the characterization of the optimal control we solve $\mathrm{D}_{\mathbf{u}}J^{\star\star}(\mathbf{x}^\star, \mathbf{u}^\star) = 0$ with (3) on the interior of the control set. Solving the equations (7) allows to characterize the optimal vector of the form (6).

$$\begin{bmatrix} \kappa_1 u_{\mathrm{H}} + \varpi_1(\gamma_1 - \gamma_2)\left(\dfrac{qb(t)\mathrm{M}_{\mathrm{I}}^\star \mathrm{H}_{\mathrm{S}}^\star}{\mathrm{H}}\right) + \varpi_1(\gamma_5 - \gamma_6)\left(\dfrac{pb(t)\mathrm{H}_{\mathrm{I}}^\star \mathrm{M}_{\mathrm{S}}^\star}{\mathrm{H}}\right) + \rho_1^\star - \rho_2^\star \\ \kappa_2 u_{\mathrm{M}}(t) - \gamma_5(\Delta(t) + \varpi_2 \mathrm{M}_{\mathrm{S}}^\star) - \gamma_6(\varpi_2 \mathrm{M}_{\mathrm{E}}^\star) - \gamma_7(\varpi_2 \mathrm{M}_{\mathrm{I}}^\star) + \rho_3^\star - \rho_4^\star \end{bmatrix} = \begin{bmatrix} 0 \\ 0 \end{bmatrix} \quad \textbf{(7)}$$

IV. NUMERICAL RESULTS AND DISCUSSION

IV.1 Optimality System. The optimal controls and states are found by solving the optimality system, which consists of the state system (1), the adjoint system (6), initial conditions, boundary conditions and the characterization of the optimal control.

IV.2 Data search and algorithm implementation. Given the characteristics of the optimization system, it is not possible to find analytical solutions, and it is decided to study the solutions numerically. We start by defining the constants ρ_1 and ρ_2 in (2), for this we proceeded to a review of the literature about the costs generated by dengue in Colombia:

- Research about the socioeconomic burden of dengue fever determined that in Colombia, the average cost of treatment per dengue event in 2010 was USD 292 for an outpatient case, USD 600 per hospitalized case and USD 1975 for each case of severe dengue [88].
- Research about the economic impact of dengue in Colombia in the period 2000-2010, estimated that the average cost of patients with dengue was USD 599; outpatient care had an average cost of USD 87.9, the cost of inpatient care ranged between USD 670.8 and USD 6531.5, and the average cost of the patient with severe dengue was USD 2361 [89].
- Research about the multinational economic burden of the year 2014, found that the total cost per episode of dengue varies from USD 141 to USD 385 for hospitalized patients and from USD 40 to USD 158 in the cases of outpatients, Colombia with the economic burden highest and Thailand with the lowest [90].

These investigations included two main elements: the costs of medical treatment and the social cost of temporary disability leave of an infected person. Therefore, the total average cost for a dengue patient is assumed equal to USD 600 and the average daily cost (in U.S. dollars) of an infected person is set as $\rho_1 = \rho_2 = 48$ (USD 600 divided by $1/(r + \hat{l}) = 12.5$ days of sickness). To fix the maximum mortality rate due to insecticide spraying, ϖ_2, a review of the literature about studies of the effect of insecticides on mosquitoes was also carried out and it was found that the range of the lethality rate of an insecticide is rather wide, between 15% and 98% [91, 92]. Therefore, it would be useful to consider two types of insecticide: relatively cheap insecticide with low lethality of 20% and twice expensive insecticide with high lethality of 80%. In other words, there will be two alternative values for ϖ_2: $\varpi_2 = 0.20$ and $\varpi_2 = 0.80$.

According to [93], the most common repellants can reduce the number of mosquito bites by up to 95% when applied with the appropriate frequency, also mosquito bed nets and insecticide-treated clothing reduce the biting rate [94]. Therefore, two options are considered for controlling the biting rate: (1) $\varpi_1 = 0.30$, which means that all measures aimed at personal protection are capable of reducing the biting rate by 30%; (2) $\varpi_1 = 0.70$, which means that such measures can reduce the biting rate by 70%. We suppose that unit cost of the first option is twice less than that of the second option; in practical terms, this cost should express unit expenditure for educational campaigns that target to motivate human population for taking measure of personal protection (use of repellents, mosquito bed nets, insecticide-treated clothes, removal of mosquito breeding places within and around households, among others). According to [95], the high-efficiency unit expenditure for educational campaigns that aim to motivate the human population to take personal protection measures (use of repellents, mosquito nets, insecticide-treated clothing, elimination of mosquito breeding sites in and around households, among others) is approximately 50 times less than the total medical and social unit cost of having an infected individual, that is, $\kappa_1 = \rho_1/50$.

In the absence of precise information about the unit cost of the high-lethality insecticide, we assume that it is 10 times less than total medical and societal unit cost of having one infected individual, *i.e.*, $\kappa_2 = \rho_1/10$. There is also no plausible information regarding the average daily cost of having one carrier mosquito expressed by the weight coefficient ρ_3 and, on the other hand, the number of infected people is effectively correlated with the number of carrier mosquitoes [96, 97, 98]. then $\rho_3 = 0$ is established. The model represented by the equations (2) that includes the demographic dynamics in each population is suitable for modeling endemic situations characterized by the persistence of the disease at low levels. Therefore, the end time was set $t_f = 365$ days (equivalent to one calendar year).

As final data, numerous theoretical studies have modeled seasonality utilizing periodic forcings to describe vital processes and the transmission of parasites or viruses [9, 99]. The population of adult mosquitoes, fluctuates on a temporary scale at the rate of an average large number of eggs hatched per unit of time, survivors of development through the intermediate aquatic stages (larvae and pupae), so we suppose a birth function in the form [100]:

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$$\Delta(t) = \delta\left(1 - \varepsilon_2 \sin\left(\frac{2\pi t}{365} + \psi_2\right)\right).$$

It is assumed that the contact rate undergoes a simple harmonic oscillation [101]:

$$b(t) = \overline{b}\left(1 + \varepsilon_1 \cos\left(\frac{2\pi t}{365} + \psi_1\right)\right).$$

Here, Δ and b rates are periodic functions of time with a common period $\omega = 365$ days, or 1 year. The phase shifts $\psi_1, \psi_2 \in [-2\pi, 2\pi]$ play no dynamical role, they are included to align Δ and b when comparing model time series with data [74]. The coefficients $\overline{b}$ and δ represent the base transmission rate and the average vector recruitment rate, respectively. The parameters $\varepsilon_1, \varepsilon_2 \in (0,1)$ measure the degree of seasonality of the rates [75]. The variation of the mosquito mortality rate is assumed constant, $m(t) \equiv \overline{m}$ over $\mathbb{R}_+$ (baseline mortality mosquito rate), in order to reduce the computational effort, also $\psi_1 < 0$ and $\psi_2 = 0$ are assumed so that at the beginning of the year the contact rate is always at a local minimum and recruitment rate is always at a local maximum.

To numerically compute the BRN, it was necessary to rewrite the integral operator of the following infection in the form of (3) in [56], where an algorithm is proposed for the R_0 computation of periodic systems of ordinary differential equations. This algorithm was implemented in MATLAB with the data in Table 1 from which R_0 had a reasonable approximation. In Figure 3, we plot R_0 when the parameter $\overline{m}$ varies and the other parameters remain fixed. Consistent with the biological interpretation of R_0, R_0 is inversely proportional to m, the graph is seen as the branch of an equilateral hyperbola in the first quadrant passing through the points R_0 =0.9088 if $\overline{m}$ = 1/10, $R_0 = 1$ if $\overline{m}$ = 1/10.75 and $R_0 = 1.5409$ if $\overline{m}$ = 1=15. Thus, whenever the vector mortality rate is greater than 1/10.75 mosquitoes per day, dengue persists in the community.

Numerical solutions to the optimality system (30) have been carried out by running a code implemented in MATLAB of the *forward-backward sweep method* developed by Lenhart and Workman [102, 104], using the constant parameters tabulated in Table 1.

Table 1: Parameters and initial data described in the model and their ranges of possible values.

Parameter	Value(s)	Range	Source(s)	Dimensions	Parameter	Value(s)	Range	Source(s)	Dimensions
$\overline{m}$	1/15	1/20 - 1/4	[61, 62]	day^{-1}	H	$\frac{1}{75.6 \times 365}$		[71]	day^{-1}
r	1 - 7	1/7 - 1/2	[63, 64]	day^{-1}	$\hat{l}$	1- 5.5	1/11 - 1	[72, 70]	day^{-1}
b	1 - 3	0.3- 1	[65, 66]	day^{-1}	δ	35000		Assumed	Dimensionless
p	0.51	0.5 - 1	[67, 68]	Dimensionless	$(\varepsilon_1, \varepsilon_2)$	(0.6, 0.2)	0 - 1	Assumed	Dimensionless.
q	0.42	0.1 - 1	[67?]	Dimensionless	(ψ_1, ψ_2)	(-3, 0)		Assumed	Dimensionless
c	0.10	0.08 - 0.13	[63, 70, 90]	day^{-1}	H	304218		[73]	Dimensionless
ϖ_1	0.20, 0.80	0.15 - 0.98	[91, 92]	day^{-1}	$\rho_1 = \rho_2$	48	47.9 - 76.5	[88, 89]	U.S. Dollar
ϖ_2	0.30, 0.70	0 - 0.95	[93, 94]	Dimensionless	κ_1	$0.02\rho_1$		[108]	U.S. Dollar
t_f	365		Assumed	day^{-1}	κ_1	$0.1\rho_1$		Assumed	U.S. Dollar

Initial condition #	H_{S0}	H_{E0}	H_{I0}	H_{R0}	M_{S0}	M_{E0}	M_{I0}
IC3	92263	5	3	211947	419969	0	31
IC4	92266	6	4	211942	419970	30	0

IV.3 Control strategies for dengue reduction and prevention. Utilizing different upper bounds for $\boldsymbol{u}^{\star}(t)\ [u_H^{\star}(t)\ \ u_M^{\star}(t)]$ together with their respective unit costs, we can suggest eight control strategies whose descriptions are given in Table 2. Under these strategies the numerical solution of the optimal control problem is presented.

Table 2: Description of control strategies for model (1).

Strategy #	Description	ϖ_2	κ_2	ϖ_1	κ_1
S1	Low-lethality cheap insecticide only	0.2	2.4	0	0
S2	High-lethality expensive insecticide only	0.8	4.8	0	0
S3	High-efficiency expensive protective measures only	0	0	0.7	0.96
S4	Low-efficiency cheap protective measures only	0	0	0.3	0.48
S5	High-lethality expensive insecticide combined with high-efficiency expensive protective measures	0.8	4.8	0.7	0.96
S6	High-lethality expensive insecticide combined with low-efficiency cheap protective measures	0.8	4.8	0.3	0.48
S7	Low-lethality cheap insecticide combined with high-efficiency expensive protective measures	0.2	2.4	0.7	0.96
S8	Low-lethality cheap insecticide combined with low-efficiency cheap protective measures	0.2	2.4	0.3	0.48

Figures 1-(S1 and S2) and 2- A display the optimal state paths and controls when strategy 1 (or S1) and strategy 2 (or S2) are applied. As expected, the use of highly lethal insecticides guaranteed a more pronounced decline in the latent population, the symptomatic population, and the carrier populations during the first trimester, but thereafter these state trajectories have a similar behavior of the type of insecticide applied. Both optimal controls guarantee a remarkable reduction in the average number of dengue events at the end of the calendar year compared to the integral curves of the uncontrolled system (Figure 1-Uncontrolled), although their profiles are not that different. The high lethality insecticide (S2, dotted line and dashed line) requires an application with all its capacity which varies from 0.134 to 0.534, apparently periodically, with cycles close to 3 days during an estimated initial 35 days due to its high cost, but in the period of 35 to 68 days of the process, the amount of this type of insecticide will be damped above 0.534, and from now on it falls oscillatingly below 0.534; while the low lethality insecticide (S1, solid line and dash-dot line) requires a percentage of fumigation fluctuating cyclically every 3 days approximately within the maximum interval [0.134, 0.534] during 100 initial estimated days (because it is a fordable both in the sense economic and ecological), but in the period of 100 to 141 days of the process, the amount of this type of insecticide will be damped above 0.534, and from now on it falls oscillatingly below 0.534. Furthermore, the implementation of S1 will require more insecticide, while the total cost of insecticide spraying will be cheaper for S1 than for S2.

Figures 1-(S1 and S2) and 2-B display the optimal state trajectories and controls when strategy 3 (or S3) (solid line and dash-dot line) and strategy 4 (or S4) (dotted line and dashed line) are applied. The pro les of the controls are similar to each other and require that proportions of susceptible people in the range of 0.134 to 0.534 and in a pattern that is repeated every 3 days, take all the protective measures throughout, at least, 138 days. However, the total cost of implementation of S3 will be higher than that of S4, S4 requires sustaining a fluctuating level of personal protection in the interval [0.134, 0.534] almost all year round, while S3 requires this same mode of full force operation one month in advance. When the protective control leaves the maximum efficiency range, it begins to oscillate to decreasing values that progressively approach zero at t = 365. The difference in the latent population, the symptomatic population and the carrier populations in terms of average numbers of individuals refers, comparing figures 1-(S3 and S4) and 1-Uncontrolled, could not justify an increase in costs, regardless of whether the time period of higher demand for S3 exceeds that of S4.

The figures 3-(S5 and S6) and 4-A help to visualize the results of the application of strategy 5 (or S5) and strategy 6 (or S6). Both strategies require that from the beginning the controls are exercised with full force for up to 31 days, periodically in their maximum efficiency range 0.134-0.534 and at the same intensity. When $u_H(t)$ and $u_M(t)$ leave the range of maximum efficiency, they experience ripples that are progressively dampened until that the control ceases to apply, although the application of the S5 requires raising the values of $u_H(t)$ more than when applying S6 and conversely the application of S5 requires reducing the values of $u_M(t)$ less than when applying S6. Strategies 5 and 6 produce almost the same effect in terms of reducing carrier mosquitoes and infected humans. Finally, the figures 3-(S7 and S8) and 4- B help to visualize the results of the application of strategy 7 (or S7) and strategy 8 (or S8). Both strategies require that from the beginning the spatial-focal treatment and personal protection be exercised with full-force for 86 days, in amounts that change 'periodically' in their maximum efficiency range 0.134-0.534 and are almost the same for both controls. When $u_H(t)$ y $u_M(t)$ leave the maximum efficiency range, they begin to oscillate to decreasing values that are progressively approaching zero, although for the S8 it will be necessary to carry out more spraying and greater citizen discipline with the protective measures unlike the S7. Optimal states do not undergo perceptible changes with strategies 7 and 8.

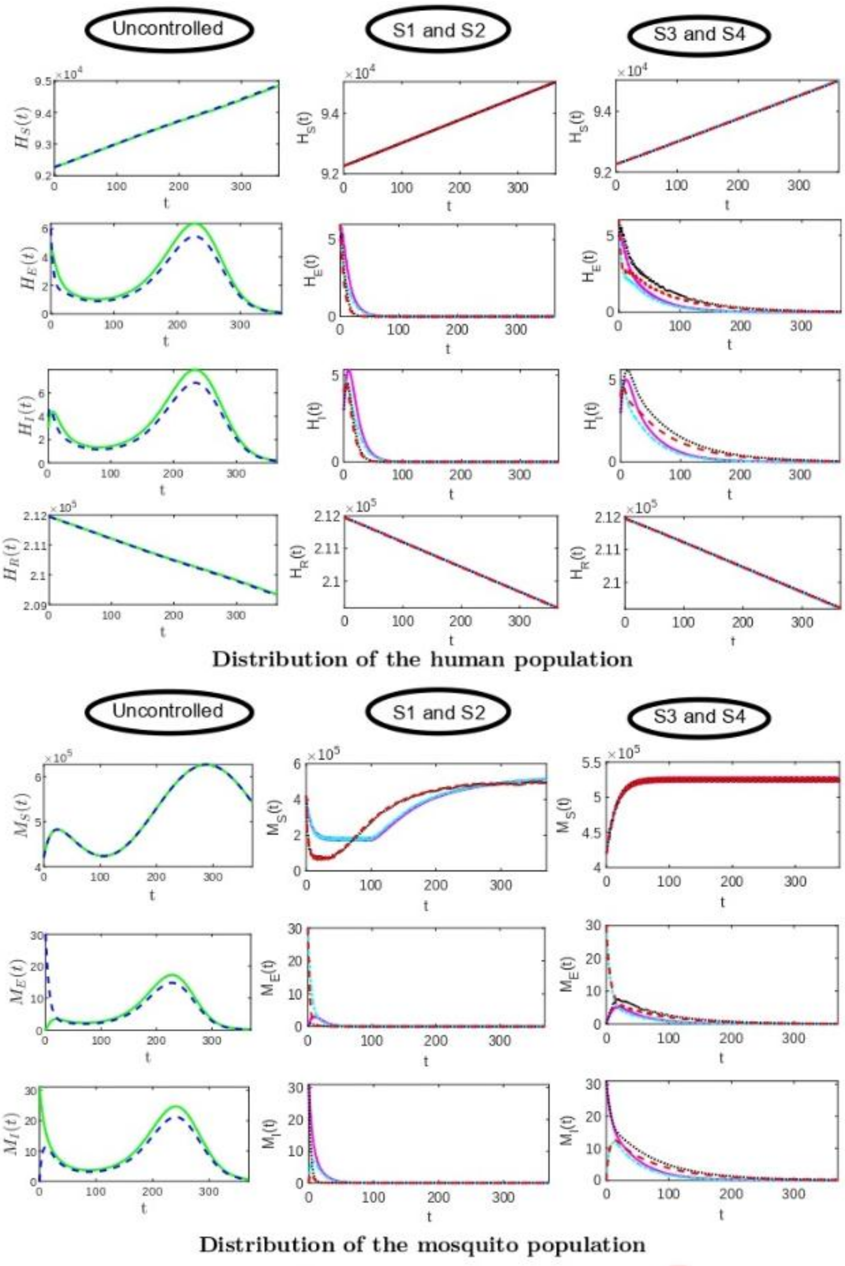

Fig. 1. Optimal state solutions of system (30) under strategies 1 to 4 in Table 2 grouped in pairs, blocks (S1 and S2) and (S3 and S4) in the same Cartesian plane. The specification *strategy*(*line style−initial condition*) for the subpopulations is: Uncontrolled(– – CI3; – – CI4), S5(– – CI3; – ● CI4), S6(– – CI3; ●● CI4), S7(– – CI3; – ● CI4), S8(– – CI3; ●● CI4). Consult CI3, CI4 and the other parameters in Table 1.

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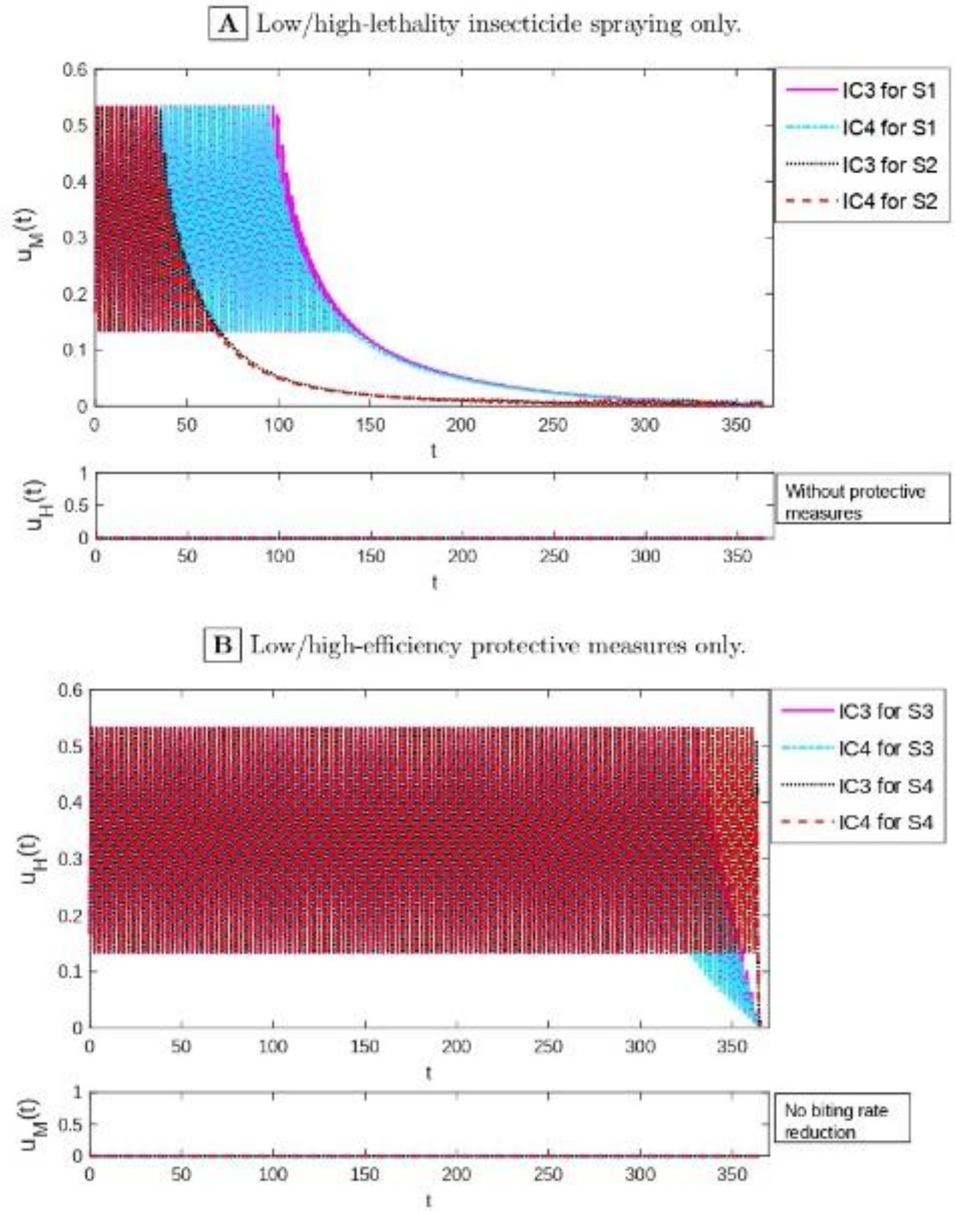

Fig. 2: Numerical solutions of the optimal controls under strategies 1 to 4 in Table 2, with the values of the parameters in Table 1. Each subfigure contains four control curves distributed in two strategies by two initial conditions:

A S1 (CI3; CI4), S2 (--CI3; CI4) and B S3 (CI3; CI4), S4 (CI3; CI4).

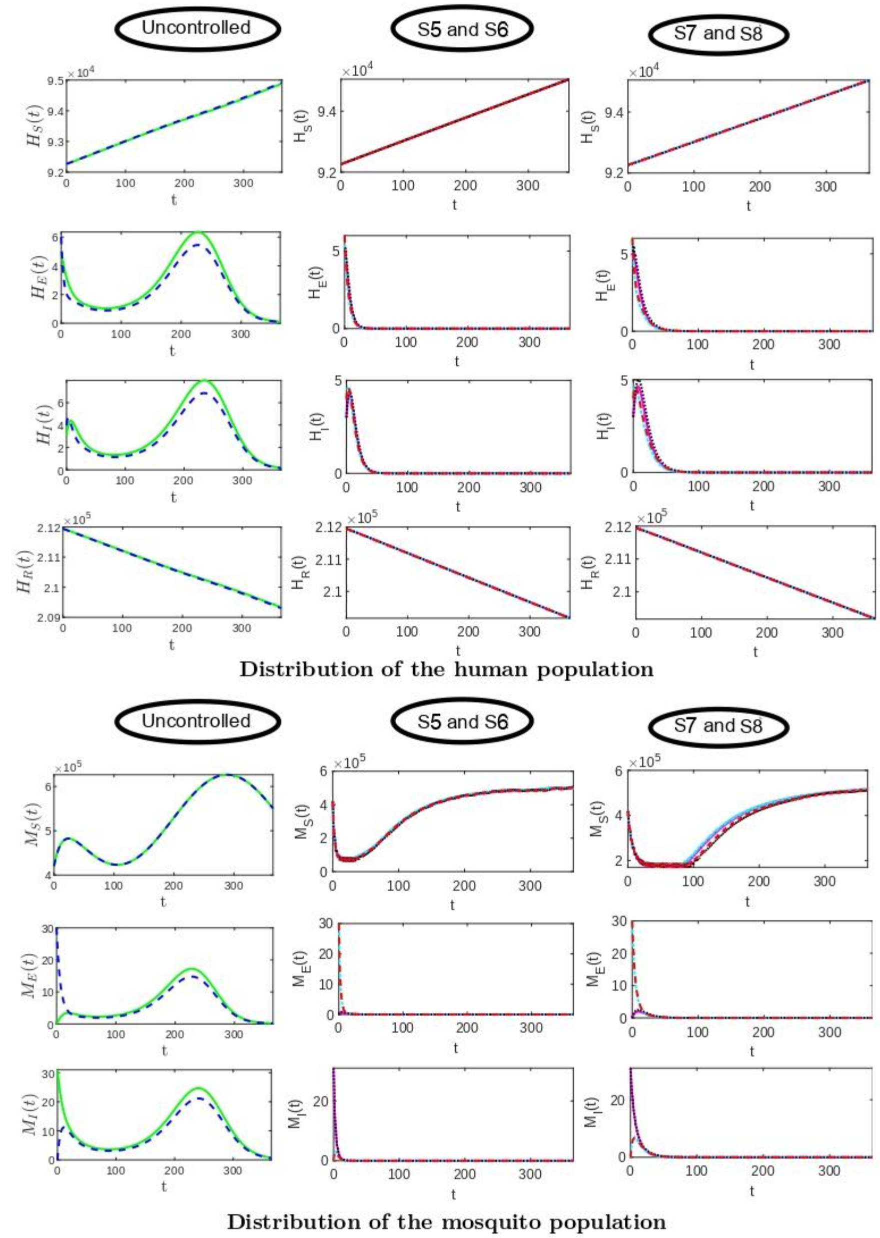

Fig. 3. Optimal state solutions of (30) under strategies 5 to 8 in Table 2 grouped in pairs, blocks (S5 and S6) and (S7 and S8) in the same Cartesian plane. The specification *strategy*(*line style−initial condition*) for the subpopulations is: Uncontrolled(CI3; CI4), S5(CI3; CI4), S6(CI3; CI4), S7(CI3; CI4), S8(CI3; CI4). Consult CI3, CI4 and the other parameters in Table 1.

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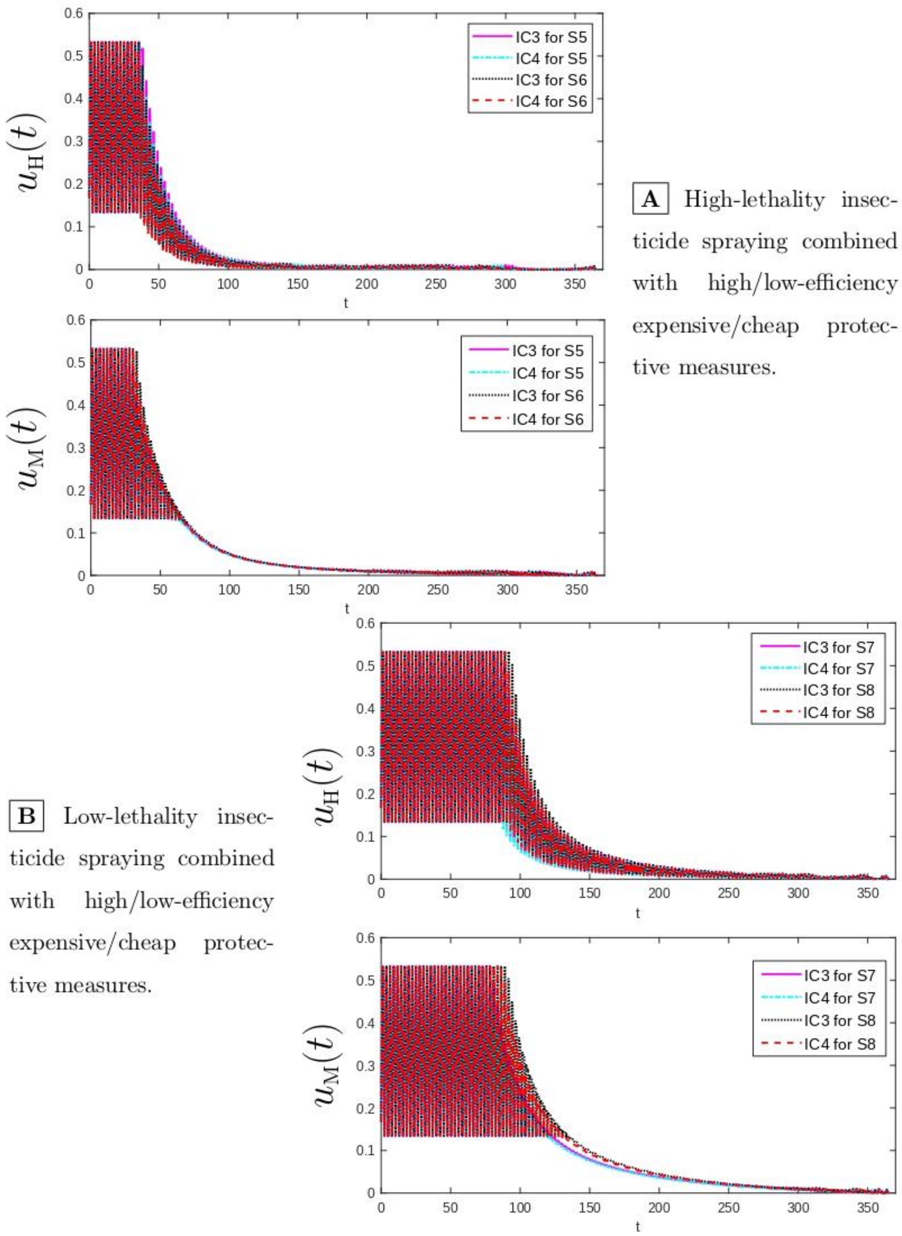

Fig. 4. Numerical solutions of the optimal controls under strategies 5 to 8 in Table 2, with the values of the parameters Table 1. Each subfigure contains four control curves distributed in two strategies by two initial conditions: A S5 (▬▬ CI3; ▬● CI4), S6 (--CI3; ●●CI4) and B S7 (▬▬CI3; ▬●CI4), S8 (- CI3; ●●CI4).

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CONCLUSION

A set of strategies were derived, and each strategy was obtained under different vector and disease control actions (fumigation with insecticides of high and low lethality and cost, personal protection against mosquito bites with high and low efficiency and costs, and their respective combinations). The numerical analysis of the model allows forecasting and evaluating the impact of each optimal strategy and graphically determining the appropriate or outstanding intervention program to face the dengue epidemic (short-term actions) and the persistence of dengue during inter-epidemic periods (long-term actions).

The educational campaign (use of repellants, mosquito nets and adequate clothing) only reduces the number of dengue patients not as well as the fumigation campaign alone, and of all the strategies stood out the intervention policy that consists of combining: (i) fumigation of an expensive insecticide with high lethality and (ii) deciding between applying low-efficiency or high-efficiency personal protection measures (use of repellents, mosquito nets, insecticide-treated clothing, among others), that is, people can moderate the effectiveness of its protective environment from mosquitoes.

Another aspect of the "best strategy" to highlight was that its efficiencies varied periodically in a fixed interval and in a shorter maximum term than the other strategies, passing as an oscillatory decrease throughout the rest of the year. This type of strategy is consistent with the guidelines established by WHO and PAHO [88], that is, all people residing in dengue endemic areas should not fully rely on the use of insecticides on a large scale, it is equally It is important to be more aware of the presence of the disease and to take adequate measures for personal protection against mosquito bites.

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