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Optimal control of dengue epidemic outbreaks under limited resources

Lilian Sofia Sepulveda-Salcedo[1] | **Olga Vasilieva**[2] | **Mikhail Svinin**[3]

[1]Department of Mathematics and Statistics, Universidad Autónoma de Occidente, Cali, Colombia

[2]Department of Mathematics, Universidad del Valle, Cali, Colombia

[3]Department of Information Science and Engineering, Ritsumeikan University, Kusatsu, Japan

Correspondence
Lilian Sofia Sepulveda-Salcedo, Department of Mathematics and Statistics, Universidad Autónoma de Occidente, Cali, Colombia.
Email: lssepulveda@uao.edu.co

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Abstract

In this paper, we reflect upon control intervention practices habitually exerted by healthcare authorities in tropical areas that suffer from incidental outbreaks of dengue fever, in particular, the city of Cali, Colombia. Such control interventions, principally based on the insecticide spraying, are carried out sporadically in order to overcome an ongoing epidemic or at least to reduce its size. It is worth pointing out that control actions of this type do not usually account for sufficient budget because epidemic outbreaks are difficult to predict. In practical terms, these occasional control interventions are performed by spraying, as quickly as possible, all existing stock of insecticide (regardless of its lethality) and employing all available manpower. The goal of this paper is to design better strategies for insecticide-based control actions, which are capable of preventing more human infections at no additional cost, and to reveal the obsolescence of current vector eradication practices. Our approach relies on dynamic optimization, where the number of averted human infections is maximized under budget constraint and subject to a simple dengue transmission model amended with one control variable that stands for the insecticide spraying. As a result, we obtain structurally robust control intervention policies that demonstrate better performance and higher resilience to possible budget limitations than traditional *modus operandi*.

KEYWORDS

dengue outbreaks, insecticide-based vector control, isoperimetric constraint, optimal control, optimization, Ross-Macdonald model

1 | INTRODUCTION

Dengue fever has been ranked by the World Health Organization as the most frequent and persistent vector-borne viral disease in the world, and dengue morbidity is strongly correlated with the presence and abundance of *Aedes aegypti* mosquitoes,[1] which act as the principal transmitters of four serotypes of the dengue virus (DENV1-4). The recovery from an infection caused by one serotype grants a life-long immunity to this particular serotype. However, people recently recovered from primary dengue infection are more predisposed to secondary infections by other (heterologous) serotypes than people never infected with dengue virus, and secondary dengue infections may lead to more acute disease manifestations, such as severe dengue (also known as *dengue haemorrhagic fever*) and dengue shock syndrome.[2]

The pathogen of DENV is transmitted between mosquitoes and human hosts during the cycle of blood-feeding because the female mosquitoes need to ingest human blood in order to mature their eggs.

In recent decades, the incidence of dengue has increased dramatically worldwide, and this is attributed to various reasons, namely:

- Climate changes and global warming jointly provide more favorable conditions for mosquito reproduction and their expansion into new geographic areas.
- Ongoing urbanization processes in many tropical countries result in dense settlements with poor sanitation conditions in and around metropolitan areas; therefore, people are forced to store water for domestic needs and this increments the number of mosquito breeding sites.
- Increase of the people mobility facilitates the expansion of all four serotypes of DENV into new geographic areas.

In the absence of effective vaccine against all dengue serotypes,[3] the disease control efforts are usually centered on reduction of the local mosquito density. These control measures can be subdivided into two groups:

1. *Routinary control actions*, which are carried out repetitively by the public healthcare authorities in dengue-endemic areas and regardless of the presence (or absence) of the disease outbreaks. These actions are usually regarded as *preventive* and their respective (fixed) costs are fully covered by municipal government sources of public healthcare entities.
2. *Coercive control actions*, which are eventually applied in order to overcome an ongoing epidemic or at least to reduce its size when a disease outbreak is officially declared. The costs of such actions are not fully anticipated in the yearly budget of local healthcare entities. Therefore, the challenging issue here is related to optimizing the use of all available resources for averting as many human infections as possible.

In this paper, we address the second group of control intervention measures by applying a mathematical approach based on dynamic optimization. In Section 2, we present the general panorama of dengue morbidity and persistence in the city of Cali, Colombia and also describe the current practices of local healthcare authorities for implementation of coercive control measures aimed at reduction of vector population and eventual suppression of dengue outbreaks in the city.

The principle goal of this paper consists of showing that these practices are not the best, and to design better strategies for coercive control actions, which are capable of preventing more human infections than currently used policies without increasing the overall costs of control intervention measures. To reach this goal, we introduce in Section 3 a stylized dynamical model for dengue transmission amended with one control variable that models an external intervention aimed at reduction of mosquito population by means of insecticide spraying. Furthermore, we formulate an optimal control problem that aims at designing of optimal strategies for coercive control measures based on the insecticide spraying.

In Section 4, we provide numerical solution of the formulated optimal control problem under different scenarios, which combine three types of insecticide employed for control interventions (with low, medium, and high lethality) and various options of budget constraints, including their absence. For all scenarios, we also provide estimations for expected number of human infections, which can be avoided by applying optimal control policies instead of the policies habitually used in practice.

Finally, Section 5 discusses the results of this paper and provides solid arguments for revisal of existent vector control policies in the city of Cali, Colombia, as well as in other municipalities suffering from occasional outbreaks of vector-borne diseases.

2 | DENGUE PANORAMA IN CALI, COLOMBIA

Cali (full name in Spanish: *Santiago de Cali*) is the capital of the *Valle del Cauca* department, and the most populous city in southwestern Colombia, with an estimated 2.370 000 of actual residents and strictly increasing population density.[4] The city spans 560.3 km^2 and it is located at elevation of about 1.000 m over sea level. All year around, the daily temperatures in Cali have very little seasonal variations (23-28°C) due to its closeness to the equator (Latitude: 3°26′13″ N, Longitude: 76°31′20″ W). The latter, combined with intermittent and abundant rainfalls, provides the ideal conditions for fast reproduction and persistence of *A. aegypti* mosquitoes in the region. On the other hand, the presence and abundance of *A. aegypti* mosquitoes is strongly correlated with dengue infections. Therefore, Cali is considered hyperendemic city with regard to dengue morbidity.[5,6]

Figure 1 clearly shows that dengue morbidity in Cali has endemo-epidemic patterns with epidemics repeated every 2-4 years. These patterns are explained by simultaneous circulation of four DENV serotypes during dengue outbreaks (see epidemic peaks, which occurred in 2010, 2013, and 2016 in Figure 1) and strong predominance of one particular DENV serotype during interepidemic (or endemic) periods.[5,7]

The public healthcare authorities are fully aware of the dengue presence and persistence in the city, and *routinary control actions* have never been suspended in Cali during the last decades. Namely, all rainwater catch basins located along the streets in residential and commercial areas are being routinely treated with larvicides in order to reduce the overall vector density in the city. It is worthwhile to note that these rainwater catch basins are the principal breeding sites of *A. aegypti* mosquitoes in Cali. These preventive control measures are carried out regardless of the number of dengue cases reported to the Municipal Secretariat of Public Health (MSPH) by all local healthcare institutions, and they are also (implicitly) reflected in the numbers of yearly dengue cases displayed in Figure 1. Without such measures, a much higher number of dengue infections would have been expected.

On the other hand, prediction of epidemic outbreaks is a challenging task, and public healthcare authorities must use certain criteria and underlying tools in order to determine whether the actual disease state should be regarded or not as (potentially) epidemic. The most comprehensive and detailed definition of epidemic disease state is provided in the official report of the American Public Health Association[8] and affirms the following.

"…An epidemic or outbreak is defined as the occurrence in a community or region of a group of illnesses of similar nature clearly in excess of normal expectancy, and derived from a common or from a propagated source. The number of cases indicating presence of an epidemic will vary according to

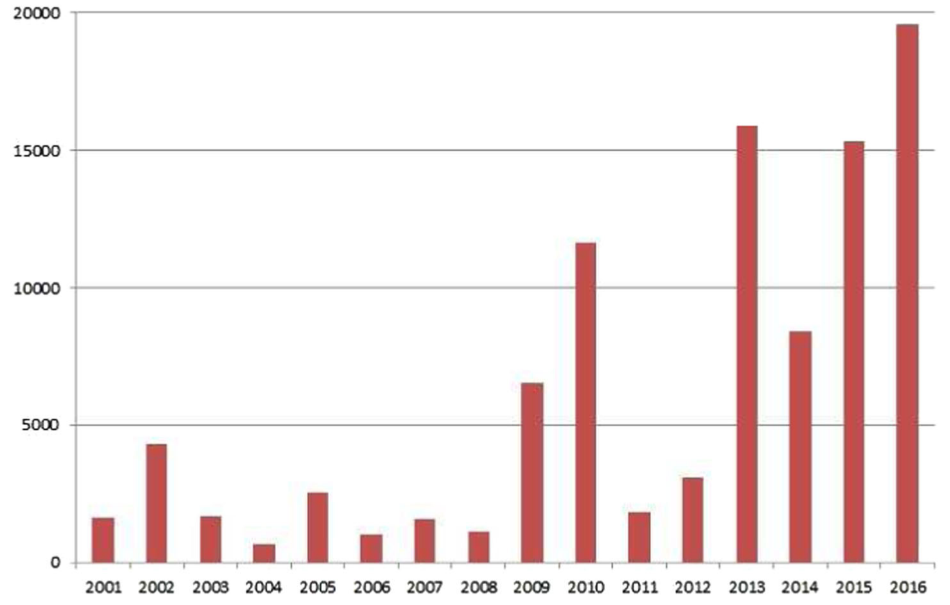

FIGURE 1 Annual dengue incidence in Cali, Colombia, during 2001–2016.
Source: SIVIGILA, Municipal Secretariat of Public Health (MSPH, Cali – Colombia)

the infectious agent, size and type of population exposed, previous experience or lack of exposure to the disease, and time and place of occurrence; epidemicity is thus relative to usual frequency of the disease in the same area, among the specified population, at the same season of year…"

According to the above definition, the number of historical cases of the disease registered in the same region during past years (or past disease frequencies viewed as time series) can be essentially helpful in classifying the present disease state as either epidemic or endemic. The difference between these two states is defined by the degree of the disease "expectancy." If the number of cases reported in present day (week, month) is close to its "expected value," the actual situation is categorized as endemic. Otherwise, when the number of cases reported in present day (week, month) is considerably higher than its "expected value," the actual situation is categorized as (potentially) epidemic. Thus, the key issue here is to estimate the so-called "expected values" for each forthcoming time step. These "expected values" can be calculated by means of standard statistical tools (such as calculating the rates of incidence, their means, standard deviations, confidence intervals, etc.) and using the information of historical disease cases registered in the same locality during the past 5-10 years.

This technique is known as the establishing of *endemic corridor*[9,10] (or endemic range, or endemic channel), which is a graphic expression of a frequency band with upper/lower limits and expected values of disease cases given by the underlying time series. Figure 2 provides the time series of dengue cases registered in Cali, Colombia during 2009-2015 (dark blue line), drawn over the endemic corridor with upper and lower limits (marked by two red lines), and the expected values of dengue cases (plotted by the green line).

When the number of reported cases exceeds the upper limit of endemic corridor, the local healthcare authorities should declare an epidemics of dengue and request that the local government authorities provide resources for additional *coercive control actions*, which usually consist of the insecticide spraying around the neighborhoods with higher number of registered dengue cases. Local governments usually assign very limited resources (in terms of monetary funds or insecticide supplies) for such additional

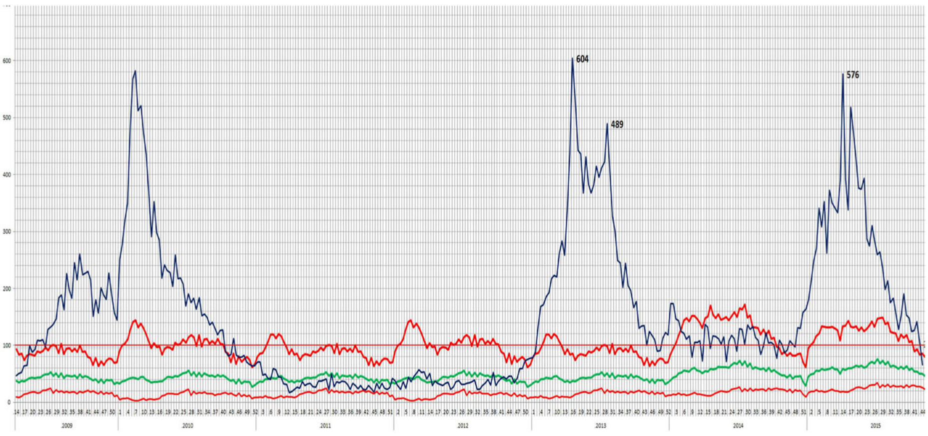

FIGURE 2 Registered cases of dengue in Cali, Colombia during 2009-2015 (dark blue line); two red lines mark the upper and lower limits of the endemic corridor, while the green line denotes an expected number of dengue cases. *Source*: SIVIGILA, Municipal Secretariat of Public Health (MSPH, Cali – Colombia)

control measures, and the lump amounts may vary from one epidemic outbreak to another. Therefore, the current practices in Cali, Colombia comprise the insecticide spraying at the maximal attainable capacity of manpower and until fully depleting all available stock of the insecticide.

The purpose of this paper is to show that these practices are not the best and to provide better intervention policies for coercive control actions based on the insecticide spraying. Our approach relies on the optimal control theory that allows to design different policies for control intervention aimed at suppressing the dengue outbreaks. To this purpose, we present in the following section a simple stylized model of dengue transmission, which is amended with control variable whose role consists of modeling the insecticide spraying.

3 | OPTIMAL CONTROL FOR ROSS-MACDONALD MODEL

In this section, we present the classical model that captures the core features related to indirect transmission of various vector-borne diseases, including dengue fever. However, our version of the model includes one exogenous variable that models an external intervention by mean of insecticide spraying (Subsection 3.1). This model, besides being rather simple, is quite plausible and expositive, because it allows to assess the number of human infections with and without control intervention. Further, this model is employed to formulate an optimal control problem that seeks to design new control policy with better performance than habitual vector control practices commonly used by local healthcare authorities. This optimal control problem is presented and formally solved in Subsection 3.2.

3.1 | Dengue transmission model with control variable

Ronald Ross and George Macdonald are fairly credited with developing the mathematical formalization of the theory that explains and describes the mechanism of vector-borne pathogen transmission between mosquitoes and human hosts. Nowadays, there exists a group of mathematical models under the common name of "Ross-Macdonald models" (see a comprehensive review accomplished by Smith et al[11]). Despite its simplicity, all models of Ross-Macdonald type include epidemiological and entomological concepts and metrics for measuring the pathogen transmission and, therefore, can capture the essentials of vector-borne disease propagation.

Our study is focused on the epidemic Ross-Macdonald model in canonical form initially proposed by Aron and May[12] and further amended with control variables.[13] It is worthwhile to note that this model includes the fractions of infected mosquitoes $0 \leq V(t) \leq 1$ and human hosts $0 \leq H(t) \leq 1$ and describes their dynamics during a short time-lapse $t \in [0, T]$ of the epidemic outbreak. In other words, the model application to interepidemic periods (characterized by endemic persistence of the disease at low levels) will not be considered in our study because no coercive control actions are actually needed during such periods. For the sake of simplicity, both populations (mosquitoes and human hosts) are normalized to unity and remain essentially invariant during $[0, T]$. Other principal assumptions of this model are:

- Both populations are homogeneous in terms of attraction, exposure, and susceptibility.
- Once infected, the mosquitoes do not recover and die being infectious.
- There is no mortality associated with the disease neither for humans nor for mosquitoes.
- The latency is ignored in both populations.
- Only susceptible (or fully recovered) individuals may get infected and the gradual acquisition of immunity by human hosts is ignored.

First four assumptions are customary for simplified models that describe the dengue dynamics during the disease outbreaks and within interepidemic periods. However, the fifth assumption is consonant only with dengue epidemic outbursts where all four DENV serotypes circulate simultaneously in the environment, that are rather typical for Colombia.[14]

The controlled Ross-Macdonald model is then described by the system of two differential equations:

$$\frac{dV}{dt} = \alpha\, p_V\, H(1 - V) - [\delta + u(t)]\, V, \quad V(0) = V_0 > 0, \tag{1a}$$

$$\frac{dH}{dt} = \alpha\, p_H\, \xi\, V(1 - H) - \gamma\, H, \quad H(0) = H_0 > 0, \tag{1b}$$

and all its entries are described in Table 1.

Equation (1a) basically states that the fraction of infected mosquitoes, $V(t)$, increases at each day $t \in [0, T]$ by the average number of effective contacts between susceptible mosquitoes, $(1 - V(t))$, and infected human individuals, $H(t)$ (ie, infectious bites taken by mosquitoes on infected people), and decreases daily with natural and insecticide-induced mortality.

Equation (1b) reveals that the fraction of infected humans, $H(t)$, increases at each day $t \in [0, T]$ by the average number of effective contacts between susceptible human hosts, $(1 - H(t))$, and infected mosquitoes, $V(t)$, (ie, infectious mosquito bites received by people) and decreases with recovery of human individuals.

Epidemic models of Ross-Macdonald type (1) implicitly assume the simplest population dynamics of female mosquitoes, both susceptible, $1 - V(t)$, and infected with DENV pathogen, $V(t)$. Thus, the total population of female mosquitoes or vectors (normalized to unity) is assumed essentially invariant, with recruitment rate matching the mortality rate (both denoted by δ, see Figure 3). By keeping this assumption, we consider the "worst" scenario and suppose that mosquito population is capable of recovering quickly to its original size after coercive control measures.

TABLE 1 Entries of the model (1)

Notation	Description	Role
$0 \leq V(t) \leq 1$	Fraction of infected mosquitos at the moment t	State variable
$0 \leq H(t) \leq 1$	Fraction of infected human hosts at the moment t	State variable
$0 \leq u(t) \leq u_{\max}$	Mosquito mortality rate due to insecticide spraying at the moment t	Control variable
$0 < u_{\max} < 1$	Maximum efficiency (% of lethality) of insecticide	Constant
$\xi > 0$	average number of female mosquitoes per one human host	Constant
$\alpha > 0$	The human blood feeding rate, the proportion of mosquitoes that feed on humans each day (the number of bites on a human, per mosquito and per day)	Constant
$0 < p_V < 1$	The proportion of infected human hosts that are infectious (or a probability for a mosquito to become infected after biting an infected human)	Constant
$0 < p_H < 1$	The proportion of infected mosquitoes that are infectious (or a probability for a human to become infected when bitten by an infected mosquito)	Constant
$0 < \delta < 1$	Rate of mosquito natural mortality (an average mosquito lifespan is $1/\delta$ days)	Constant
$0 < \gamma < 1$	Rate of human recovery from the disease (in average, a person remains infected during $1/\gamma$ days)	Constant

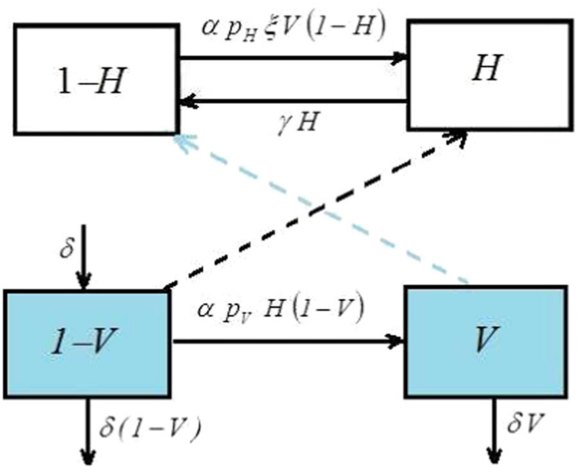

FIGURE 3 Block diagram of the Ross-Macdonald model in canonical form with $u(t) = 0$

In the absence of external intervention (ie, when $u(t) = 0$), the disease dynamics is illustrated in Figure 3. According to the description given in Table 1, $u(t)$ is an external control action aimed at suppressing the mosquito population. In mathematical terminology, this control action is a piecewise continuous real function

$$u(\cdot) \in PC[0, T] \quad \text{and} \quad u(t) \in U = [0, u_{\max}] \quad \text{for all} \quad t \in [0, T], \tag{2}$$

where $U = [0, u_{\max}]$ determines the *set of admissible controls*, which is compact in $\mathbb{R}_+$.

For better understanding of the control action $u(t)$, let $v(t) \in [0,1], t \in [0,T]$ be the share of the amount of insecticide available per day. Thus, $v(\hat{t}) = 0.5$ means that, on the day $\hat{t}$, only a half of daily available insecticides should be used. On the other hand, let $u(t) = u_{\max} v(t)$, where $0 < u_{\max} < 1$ denotes the insecticide lethality, so we have $0 \leq u(t) \leq u_{\max}$. Under such setting, $u(\hat{t})/u_{\max} = 0.5$ expresses that, on the day $\hat{t}$, only the half of daily available insecticides should be used.

Further, let $C_1 > 0$ be the average daily societal cost of having one infected human individual (eg, treatment, temporary disability, etc.) and let $C_2 > 0$ be the average daily cost of control intervention $u(t)$ (eg, insecticide and spraying supplies, manpower costs, etc.). Suppose that $C_2 < C_1$ and there is a limited amount of external resources $0 < B < C_2 \, u_{\max} \, T$ available to implement this control action $u(t)$ within a time interval $[0,T]$; in other words, we have the so-called *isoperimetric constraint*

$$\int_0^T C_2 \, u(t) dt = B \tag{3}$$

imposed upon $u(t)$. Thus, the core problem of a decision maker (who acts outside of the model (1)) consists of choosing an optimal control strategy $u^*(t) \in U, t \in [0,T]$ that satisfies the budget constraint (3) in order to minimize the total costs associated with human infections during an ongoing dengue outbreak, as well as the overall costs of control intervention measures. This goal can be expressed mathematically by the following objective:

$$\mathcal{J}(u) = \int_0^T \left[C_1 H(t) + \frac{C_2}{2} u^2(t) \right] dt \to \min . \tag{4}$$

It is worth pointing out that the optimal control problem of minimizing the objective (4) subject to dengue transmission dynamics (1) without budgetary constraint (3) has been previously analyzed and solved numerically for two options of insecticides bearing either low or high lethality.[13] However, the presence of constraint (3) requires to make some essential adjustments in its solution that are further provided in Subsection 3.2.

In the objective (4), we assume that there is no linear relationship between the coverage of control action and its respective costs, while the total cost related to the treatment and temporary disability coverage of infected people is additive. Therefore, the integrand function in (4) is linear with respect to state variable $H(t)$ and is quadratic with respect to control variable $u(t)$. This approach is rather conventional in epidemiological modeling where optimal control methods are applied. In particular, it has been justified for models where control functions expressed optimal treatment and/or vaccination policies, as well as their combinations with vector control efforts.[13,15-18]

Previous studies[11,12] established that stability of the initial value system (1) without control intervention (ie, with $u(t) \equiv 0$ for all $t \in [0,T]$) depends on the threshold value

$$\mathcal{R}_0 = \frac{\alpha^2 p_H p_V \xi}{\gamma \delta} \tag{5}$$

(which is also called *basic reproductive number*) in the following sense:

- If $\mathcal{R}_0 < 1$, then system (1) has a unique disease-free equilibrium $(V_{\text{free}}, H_{\text{free}}) = (0,0)$, which is globally asymptotically stable for all non-negative initial conditions (V_0, H_0).

- If $\mathscr{R}_0 > 1$, then system (1) has an additional endemic equilibrium

$$(V_{\text{end}}, H_{\text{end}}) = \left(\frac{\mathscr{R}_0 - 1}{\mathscr{R}_0\left(1 + \frac{\delta}{\alpha p_V}\right)}, \frac{\mathscr{R}_0 - 1}{\mathscr{R}_0\left(1 + \frac{\gamma}{\alpha p_H \xi}\right)} \right) \tag{6}$$

  with strictly positive components, which is globally asymptotically stable for all initial conditions $(V_0, H_0) \neq (0, 0)$, while $(V_{\text{free}}, H_{\text{free}}) = (0, 0)$ becomes unstable.

The first condition ($\mathscr{R}_0 < 1$) guarantees the disease extinction as $t \to \infty$, while the second one ($\mathscr{R}_0 > 1$) characterizes the persistence of the disease and compels for external actions aimed at the disease control. Because the optimal control problem (1)-(4) is considered appealing only in the context of disease persistence, we will assume further on that

$$\mathscr{R}_0 = \frac{\alpha^2 p_H p_V \xi}{\gamma \delta} > 1$$

is held for all constant parameters of the system (1) given in Table 1.

It is worthwhile to note that $\mathscr{R}_0$ is decreasing with respect to the mosquito mortality rate δ (cf. formula (5)). Therefore, the value of $\mathscr{R}_0$ is reduced when the mosquito's natural mortality δ grows to $\delta + u(t), u(t) \geq 0$ on the cause of insecticide spraying. However, an eventual suspension of coercive control measures will bring the value of $\mathscr{R}_0$ to its original level detected at $t = 0$. Notwithstanding, coercive control actions $u(t)$ are capable of reducing a considerable number of human infections during the course of epidemics. This issue is addressed in Section 4.

3.2 | Solution of the optimal control problem

In our setting, the control variable $u(t), t \in [0, T]$ expressed the enhancement of the mosquito's natural mortality δ due to the insecticide spraying. This type of control intervention is viewed as a coercive control measure of short-term action aimed at reducing the size of an ongoing epidemics. Therefore, formal solutions to the optimal control problem of minimizing the objective (4) subject to (1) and (3) will be sought for the periods of the disease outbreaks, thus leaving aside the periods of endemic persistence of the disease that do not require this type of control intervention.

Using the property of *quasimonotonicity* of the system (1) and by applying the *comparison theorem*,[19] it was shown previously by Sepulveda and Vasilieva[13] that the set of all possible solutions to ODE system (1) is positively invariant with respect to initial conditions $(V_0, H_0) \in [0, 1] \times [0, 1]$, nonempty and bounded for all admissible controls (2), that is, piecewise continuous real functions with domain $[0, T]$ and range $[0, u_{\max}]$. Therefore, this set has the same properties for all admissible control functions $u(t)$, which additionally satisfy the budget constraint (3).

Using the standard technique generally adopted in the optimal control theory,[20] isoperimetric constraint (3) can be transformed into an additional state variable with endpoint conditions. Let $Z(t) \geq 0, t \in [0, T]$ be an increasing function defined by

$$Z(t) = \int_0^t C_2 u(s) ds.$$

Then

$$\frac{dZ}{dt} = C_2 u(t) \quad \text{with} \quad Z(0) = 0, \quad Z(T) = B$$

and the optimal control problem (1)-(4) can be formulated as:

$$\min_{0 \le u \le u_{\max}} \mathcal{J}(u) = \min_{0 \le u \le u_{\max}} \int_0^T \left[C_1 H(t) + \frac{C_2}{2} u^2(t) \right] dt, \tag{7}$$

subject to

$$\frac{dV}{dt} = \alpha\, p_V\, H(1-V) - [\delta + u(t)]\, V, \quad V(0) = V_0 > 0, \tag{8a}$$

$$\frac{dH}{dt} = \alpha\, p_H\, \xi\, V(1-H) - \gamma\, H, \quad H(0) = H_0 > 0, \tag{8b}$$

$$\frac{dZ}{dt} = C_2 u(t), \quad Z(0) = 0, \quad Z(T) = B. \tag{8c}$$

In consonance with the arguments given above, the controlled system (1) has a unique and bounded solution on $[0, T]$ for each admissible control function (2) and the following proposition establishes the existence of solution of the optimal control problem (7) subject to (8) and (2).

Proposition 1. *Given that the set of all solutions to system (8) is nonempty and bounded for all admissible control functions* (2)*, there exists an optimal control* $u^*(t)$ *satisfying* (2) *and its corresponding solution* $(V^*(t), H^*(t), Z^*(t))$ *to the ODE system (8) that minimizes the objective* (7).

Proof. The proof is based on the standard existence result[21] (see Theorem 4.1 and Corollary 4.1 at pp. 68-69). In this context, it is worthwhile to note that:

1. The control set $U = [0, u_{\max}]$ is closed and convex in $\mathbb{R}_+$.
2. The set of initial conditions $(V_0, H_0, 0)$ and the set of terminal states $(V(T), H(T), B)$ are both compact in $\mathbb{R}^3_+$.
3. The state system (8) is linear with respect to control variable.
4. The integrand in (7) is convex (quadratic) with respect to $u(t)$.

Conditions 1-4 plainly indicate that hypotheses (a), (b), and (c) of Theorem 4.1 and hypotheses (d') and (e') of Corollary 4.1[21] are satisfied and this is sufficient for existence of an optimal control $u^*(t)$. However, uniqueness of optimal control cannot be formally assured here due to the lack of strict convexity of the objective functional $J(u)$ with respect to state variable H.[21] ■

Proposition 1 provides sufficient conditions under which there exists an optimal control. Furthermore, we can apply Theorem 2 borrowed from the book by Seierstad and Sydsaeter[22] (see p. 85) and enunciate the following statement.

Proposition 2. *If* $u^*(t)$ *and* $(V^*(t), H^*(t), Z^*(t))$ *are optimal for problem* (7)*-(8), then there exists a piecewise differentiable adjoint vector-function* $\lambda(t) : [0, T] \mapsto \mathbb{R}^3$ *and a constant* λ_0*, equal to either 0 or 1, such that*

$$\mathcal{H}\big(V^*, H^*, Z^*, u^*, \lambda_1, \lambda_2, \lambda_3\big) \le \mathcal{H}\big(V^*, H^*, Z^*, u, \lambda_1, \lambda_2, \lambda_3\big) \tag{9}$$

for all admissible controls u *at each time* $t \in [0, T]$, *where the Hamiltonian* $\mathcal{H}$ *is*

$$\mathcal{H}(V, H, Z, u, \lambda_1, \lambda_2, \lambda_3) = \lambda_0 \left[C_1 H + \frac{C_2}{2} u^2 \right] + \lambda_1 [\alpha p_V H(1 - V) - (u + \delta)V] + \lambda_2 [\alpha p_H \xi V(1 - H) - \gamma H] + \lambda_3 [C_2 u] \tag{10}$$

and $\lambda(t) = (\lambda_1(t), \lambda_2(t), \lambda_3(t))$ *satisfies the adjoint ODE system*

$$\frac{d\lambda_1}{dt} = -\frac{\partial \mathcal{H}}{\partial V} = \left[\alpha p_V H^*(t) + \delta + u^*(t)\right] \lambda_1(t) - \alpha p_H \xi (1 - H^*(t)) \lambda_2(t), \tag{11a}$$

$$\frac{d\lambda_2}{dt} = -\frac{\partial \mathcal{H}}{\partial H} = -\lambda_0 C_1 - \alpha p_V (1 - V^*(t)) \lambda_1(t) + \left[\alpha p_H \xi V^*(t) + \gamma\right] \lambda_2(t), \tag{11b}$$

$$\frac{d\lambda_3}{dt} = -\frac{\partial \mathcal{H}}{\partial Z} = 0. \tag{11c}$$

with two *transversality conditions*

$$\lambda_1(T) = 0, \qquad \lambda_2(T) = 0. \tag{12}$$

There is no endpoint condition for $\lambda_3(t)$ because its corresponding state variable, $Z(t)$, has two endpoint conditions assigned (see Equation 8c). Generally speaking, the components of $\lambda(t)$ stand for so-called *shadow prices* associated with respective state variables and represent the change in the objective value calculated on optimal solutions when the constraints are relaxed by one unit.[20] From Equation (11c), we have immediately that $\lambda_3(t) \equiv C$ with $C \in \mathbb{R}$; in other words, a constant gain is expected in the value of the objective when (3) is relaxed by one unit.

Remark 1. The role of $\lambda_0 \in \{0, 1\}$ in (10) is essential and can be explained in the following way. When $\lambda_0 = 1$, we have the standard form of Hamiltonian function, which is customary in the optimal control theory. In this case, minimization of $J(u)$ subject to (8) is replaced by minimization of $\mathcal{H}$ with respect to u at (almost) each $t \in [0, T]$ along the optimal path. The latter is not always possible due to the fact that ODE system (8) is overdetermined (effectively, there are four endpoint conditions assigned to three differential equations). In other words, the optimization problem may become infeasible. In its turn, $\lambda_0 = 0$ allows to cope with such "infeasibility" by putting the sole priority of decision making on choosing an admissible control $u^*(t)$ that meets the constraint (3) (or satisfies Equation 8c) while disregarding the value of the objective functional (7).

In the context of our problem, it is essential to find a feasible minimizer of the objective functional (7). Therefore, we should suppose further on that $\lambda_0 = 1$ in (10) and try to find a feasible solution of the optimal control problem (7)-(8). Otherwise and in consonance with Remark 1, $\lambda_0 = 0$ would simply make the integrand of (7) vanish from the Hamiltonian and the resulting control trajectory $u^*(t)$ would acquire a *bang-bang* structure in order to satisfy the minimum condition (9), because in that case the Hamiltonian would become linear in u.

For $\lambda_0 = 1$, we have $\lambda_3(t) \equiv C$ and the optimal control $u^*(t)$ can be characterized by

$$u^*(t) = \min \left\{ \max \left\{ \frac{1}{C_2} \lambda_1(t) V^*(t) - C,\ 0 \right\},\ u_{\max} \right\}, \tag{13}$$

where $C \in \mathbb{R}$ is chosen to satisfy the endpoint condition $Z(T) = B$. The closed form (13) is obtained by rewriting the necessary condition (9) as

$$\frac{\partial \mathcal{H}}{\partial u} = C_2\, u - \lambda_1\, V + C\, C_2 = 0 \quad \Leftrightarrow \quad u = \frac{1}{C_2}\lambda_1(t)V^*(t) - C \tag{14}$$

and taking into account that $0 \le u(t) \le u_{\max}$ for all $t \in [0, T]$, that is,

$$\begin{cases} u^*(t) = 0 & \text{if} \quad \frac{\partial \mathcal{H}}{\partial u} > 0, \\ 0 < u^*(t) = \frac{1}{C_2}\lambda_1(t)V^*(t) - C < u_{\max} & \text{if} \quad \frac{\partial \mathcal{H}}{\partial u} = 0, \\ u^*(t) = u_{\max} & \text{if} \quad \frac{\partial \mathcal{H}}{\partial u} < 0. \end{cases} \tag{15}$$

It is worthwhile to note that (13) is a minimizer because $\frac{\partial^2 \mathcal{H}}{\partial u^2} = C_2 > 0$. Furthermore, to fulfill the transversality conditions (12), it is necessary that $u^*(T) = 0$; in other words, optimal control action $u^*(t)$ must be suspended by the end of observation period.

Remark 2. From the economics standpoint, the left-hand side condition in (14) implies that, under optimal strategy u^* and at each $t \in [0, T]$, the marginal cost of control action (expressed by the term $C_2\, u$) should be equal to its marginal benefit (given by the term $\lambda_1\, V - C\, C_2$). Additionally, if the marginal cost of u^* is higher than its marginal benefit (ie, $\frac{\partial \mathcal{H}}{\partial u} < 0$ in (15)), then it is optimal not to employ this strategy at all, that is, $u^*(t) = 0$. Alternatively, if the marginal cost of u^* is lower than its marginal benefit (ie, $\frac{\partial \mathcal{H}}{\partial u} > 0$ in (15)), then it is optimal to use all available resources, that is, $u^*(t) = u_{\max}$.

Remark 3. Application of Pontryagin maximum principle (Proposition 2) allows to reduce the optimal control problem (7)-(8) to solution of two-point boundary value problem that is usually referred to as *optimality system*. The latter is composed of six differential equations with six boundary conditions specified at the endpoints $t = 0$ and $t = T$. In our case, the optimality system is given by (8), (11), and (12) where $u(t)$ is replaced by its characterization (13). Existence of optimal control $u^*(t)$ (proved in Proposition 1) implies solvability of the optimality system, because $u^*(t)$ must satisfy the necessary condition of optimality. Additionally, the uniqueness of solution of the optimality system can be formally demonstrated for sufficiently small time intervals using conventional techniques.[23,24] Similar techniques are applicable to our problem because the right-hand sides of optimality system are Lipschitz-continuous in all state and adjoint variables. The formal proofs are omitted here because we deal with (sufficiently) short periods of time where the optimally system should be well posed. Therefore, it is safe to assume that the optimality system has a unique solution and the optimal control characterized by (13) is unique (its existence is proved by Proposition 1).

Remark 4. Traditional *modus operandi* of the healthcare authorities disregards the minimization of the objective criterion (7) and merely seeks a feasible control strategy $u(t)$ that allows to fulfill the constraint (3), that is, to spend all available stock of the insecticide by spraying it at maximal capacity u_{max}. In mathematical terms, this situation can be modeled by the application of the so-called *baseline control strategy*:

$$\bar{u}(t) = \begin{cases} u_{\max}, & \text{if} \quad t \in [0, T^*] \\ 0, & \text{if} \quad t \in [T^*, T] \end{cases} \quad \text{where} \quad 0 < T^* = \frac{B}{C_2 u_{\max}} < T \tag{16}$$

TABLE 2 Values of parameters of the Ross-Macdonald model (1), (8)

Parameter	Description	Estimated value
α	The human blood feeding rate	0.3365
p_V	Probability for a mosquito to become infected after biting an infected human host	0.1532
p_H	Probability for a human host to become infected when bitten by an infected mosquito	0.2287
ξ	Average number of female mosquitoes per one human host (or average vectorial density)	1.0359
δ_V	Rate of mosquito natural mortality	0.0333
γ	Rate of human recovery from the disease	0.1
H_0	Fraction of infected human hosts at $t = 0$	1.82×10^{-4}
V_0	Fraction of infected mosquitoes at $t = 0$	5.46×10^{-4}

that ensures spending of all available insecticide stock exactly by the moment $T^* \in (0, T)$. This strategy is feasible in the sense that it reduces the population of infectious mosquitoes (the right-hand side of Equation 8a is decreasing in u) and causes a reduction in the number of infectious human hosts (due to quasimonotonicity of the Ross-Macdonald model). Baseline strategy (16) has the so-called "bang-bang" structure (all or nothing) and satisfies Equation (8c) with boundary conditions. This control strategy can be accepted as a solution if the optimality system becomes unsolvable. In such a case, optimization criterion is omitted by setting $\lambda_0 = 0$ in the Hamiltonian (10) (see Remark 1 above).

4 | NUMERICAL RESULTS

Numerical solutions of all optimal control problems (with and without budget constraint (3)) presented in this section have been carried out using GPOPS-II Next-Generation Optimal Control Software[25,26] (note that GPOPS-II Manual with basic descriptions can be downloaded from http://www.gpops2.com/) and the underlying program codes are available from the authors. GPOPS-II is a MATLAB-based software toolbox for solving different kinds of optimal control problems using variable-order Gaussian quadrature collocation methods. The software employs the Legendre-Gauss-Radau quadrature orthogonal collocation technique, where the continuous-time optimal control problem is transcribed to a large sparse nonlinear programming problem.

4.1 | Parameter values and initial data

Our numerical simulations are done for the observation period of 60 days, that is, $T = 60$ and $t \in [0, T] = [0, 60]$. In fact, dengue outbreaks can be controlled by insecticide spraying within 1-2 months because the epidemics becomes declared,[13,14,27] and the standard length of manpower contracts for performing the insecticide spraying is 2 months (information provided by the MSPH, Cali, Colombia).

For all numerical experiments, the values of parameters $(\alpha, p_V, p_H, \xi, \delta_V, \gamma)$ as well as initial conditions $V(0) = V_0, H(0) = H_0$ have been borrowed from previous studies conducted in Cali, Colombia,[13] where they were fitted to the observation data reported to the MSPH (Cali, Colombia) during the 2010 dengue outbreak—see Table 2. Although we suppose (for simplicity) that all parameters$(\alpha, p_V, p_H, \xi, \delta_V, \gamma)$ remain constant during the observation period $[0, T]$, in reality they may exhibit slight variations. In particular, α and δ are entomological parameters and their values are

FIGURE 4 Daily cases of dengue reported to the Municipal Secretariat of Public Health (Cali, Colombia) during the 2010 dengue outbreak

affected by the temperature and humidity variations.[28-30] Parameters p_V and p_H related to the disease transmission may vary with the virulence of circulating DENV strains.[31,32] Finally, the average vectorial density ξ depends on the total size of the vector population (assuming that the total number of human residents remain invariable), and its value is affected not only by the climatic changes,[28-30] but also by the efficiency of routinary control actions, such as periodical treatment of mosquito breeding sites with larvicides, and by inflow and outflow of daily commuters.[31,33]

Furthermore, it is worthwhile to note that the values of parameters $(\alpha, p_V, p_H, \xi, \delta_V, \gamma)$ given in Table 2 bear little difference with other estimations obtained from the incidence datasets collected in Cali, Colombia during different years.[28,31,34,35] Figure 4 displays the daily incidence (new dengue cases registered on a daily basis) reported to the MSPH (Cali, Colombia) during the whole year 2010, and our observation period corresponds to the epidemics peak.

It is essential to point out that during the period of observed data (January 30 and March 1 of 2010) no coercive control measures (such as the insecticide spraying) were used by the public healthcare authorities of Cali. However, the routinary control of mosquito breeding sites has never been suspended in Cali during the last two decades. In particular, the rainwater catch basins located along the streets in residential and commercial areas are being periodically treated with larvicides.

The objective functional (7) expresses a tradeoff between two major goals. On the one hand, the control intervention seeks to minimize the fraction of infected human hosts along the observation period $[0, T]$ (cf. first summand $C_1 H(t)$ in the integrand of (7)). On the other hand, the decision makers wish to avoid extra spendings on the policy implementation by minimizing the marginal cost of control intervention (cf. second summand $C_2 u^2(t)$ in the integrand of (7)). Thus, two positive weight coefficients, C_1 and C_2, determine the priorities of decision making.

To assign plausible values to these coefficients, it is worthwhile to revise some arguments from the literature. Generally speaking, the value of C_1 can be associated with an average daily cost of having one infected human host, which consists of two basic elements: expenses related to medical treatment and societal costs associated with temporary disability leave. In Colombia, an average cost of one dengue case was estimated by 600 dollars in 2010,[36] and another study[37] conducted in eight Asian and Latin-American countries displayed similar results. Because dengue infection lasts approximately $1/\gamma = 1/0.1 = 10$ days, the *daily* average cost of one infected human host can be set as $C_1 = 60$ dollars.

TABLE 3 Description of control strategies based on different types of insecticide

Strategy No.	Description	Value of u_{max}	Weight C_2	Amount B_0	Total cost B
Strategy 1	Low-lethality cheap insecticide	0.2	3	10.1502	30.4506
Strategy 2	Medium-lethality insecticide	0.5	4.5	14.1392	63.6264
Strategy 3	High-lethality expensive insecticide	0.8	6	13.6072	81.6432

Another weight coefficient, C_2, is associated with unit cost of the insecticide to be used for vector control. Such unit cost usually depends on the insecticide efficiency in the sense that high-lethality insecticides are more expensive than low-lethality insecticides. In the frameworks of our model, the maximum efficiency of insecticide is defined by u_{max} and the latter may vary between 12% and 98%.[27] Therefore, it would be useful to consider three different types of control interventions based on spraying of insecticides with different lethalities:

Strategy 1: 20%-lethality relatively cheap insecticide;

Strategy 2: 50%-lethality reasonably priced insecticide;

Strategy 3: 80%-lethality relatively expensive insecticide.

Because we do not possess any viable information regarding the unit costs of the mentioned insecticides, it seems reasonable to assume[13] the unit costs of insecticides with high, medium, and low lethality be related to the total daily unit cost C_1 of having one infected human host in the following way:

- $C_2 = C_1/20$ when cheap low-lethality insecticide with $u_{max} = 0.2$ is used (**Strategy 1**);
- $C_2 = C_1/15$ when moderately priced medium-lethality insecticide with $u_{max} = 0.5$ is used (**Strategy 2**);
- $C_2 = C_1/10$ when expensive high-lethality insecticide with $u_{max} = 0.8$ is used (**Strategy 3**).

These numbers look reasonable for the preliminary investigation, while the value of C_2 for practical application can be determined in accordance with real price of available insecticide. Table 3 (columns 1-4) systemizes the descriptions of three basic control intervention strategies corresponding to each type of insecticide.

For better visibility and more expedient interpretations of our numerical results, it is convenient to introduce an additional variable, $C_h(t)$, defined by

$$C_h(t) = H(0) + \int_0^t \alpha \, p_H \, \xi \, V(s) \, (1 - H(s)) \, ds \tag{17}$$

that expresses the cumulative fraction of all human infections during the observation period $[0, T]$ while ignoring posterior recuperation of the infected human hosts. This variable is usually referred to as *cumulative incidence*, meaning that $C_h(t)$ effectively accumulates, in form of proportion, all human infections between $t = 0$ and $t = T$.

4.2 | Optimal solutions without budget constraints

Before proceeding to analyze the impact of resource limitation on overall performance of optimal control strategies and their effect on the disease control, we should have reasonable estimations for

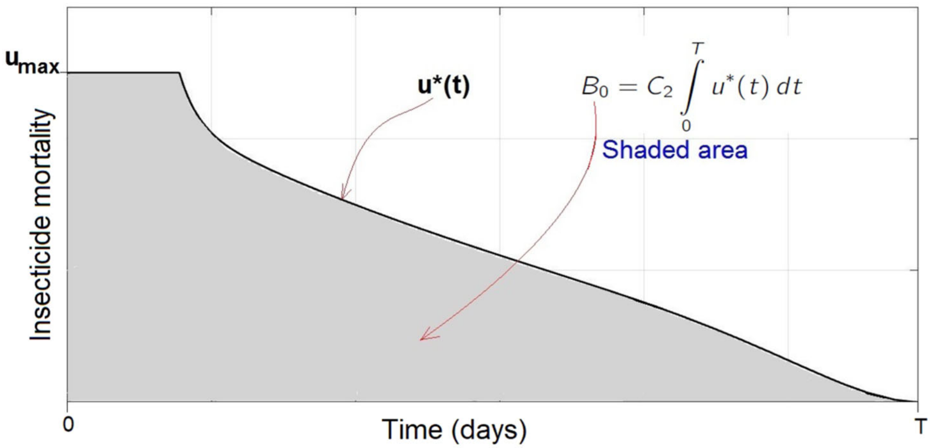

FIGURE 5 Geometric interpretation of $B_0 = \frac{B}{C_2}$

the costs of optimal strategies *in absence* of resource limitation. To accomplish this task, we should ignore for the moment the isoperimetric constraint (3) and solve numerically (using GPOPS-II software package) the optimal control problem

$$\min_{0 \le u \le u_{\max}} \mathcal{J}(u) = \min_{0 \le u \le u_{\max}} \int_0^T \left[C_1 H(t) + \frac{C_2}{2} u^2(t) \right] dt, \tag{18}$$

subject to

$$\frac{dV}{dt} = \alpha\, p_V\, H(1 - V) - [\delta + u(t)]\, V, \quad V(0) = V_0, \tag{19a}$$

$$\frac{dH}{dt} = \alpha\, p_H\, \xi\, V(1 - H) - \gamma\, H, \quad H(0) = H_0, \tag{19b}$$

$$\frac{dC_h}{dt} = \alpha\, p_H\, \xi\, V\,(1 - H), \quad C_h(0) = H_0, \tag{19c}$$

where the variable $C_h(t)$ has been added to the dynamical system. Note that differential equation (19c) is equivalent to (17). In general terms, numerical solutions of the optimal control problem (18)-(19) can be viewed as special case of the problem already considered by Sepulveda and Vasilieva,[13] where numerical solutions were computed by the *forward-backward method*.[20]

After obtaining the optimal solutions, $u^*(t)$, of the optimal control problem (18)-(19) for three settings corresponding to **Strategies 1-3** (see columns 1-4 in Table 3), we can estimate their related marginal costs, B, by the following formula:

$$\text{Cost of } u^*(t) = B = C_2\, B_0 = C_2 \int_0^T u^*(t)\, dt, \tag{20}$$

where B_0 expresses the amount of each type of the insecticide needed for implementation of the corresponding strategy. The reference values of B_0 and B are given in Table 3 (columns 5-6), while Figure 5 displays the geometric interpretation of B_0.

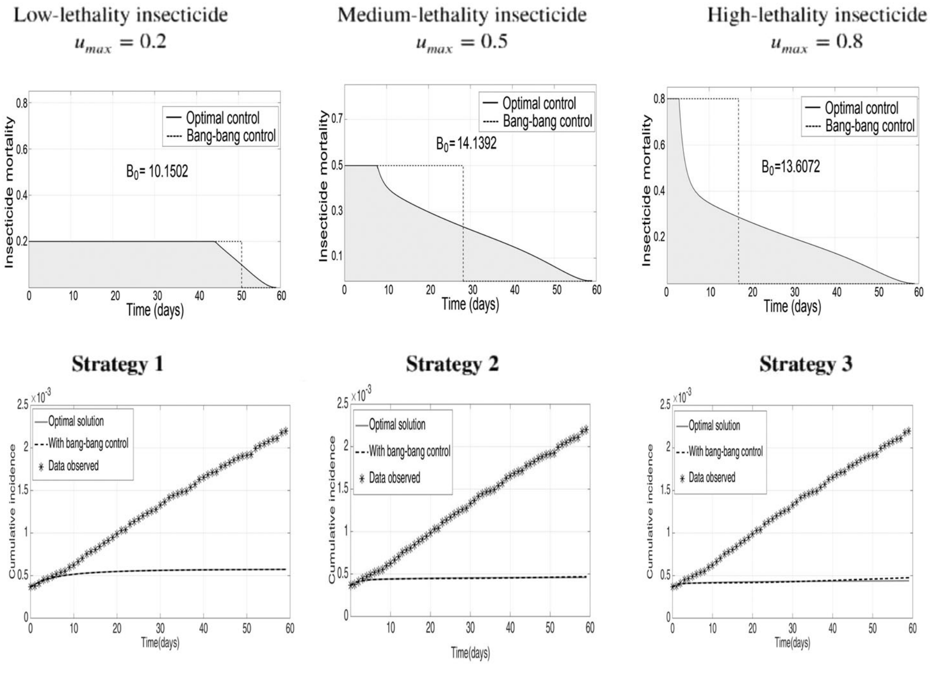

FIGURE 6 Profiles of optimal controls $u^*(t)$ and their bang-bang alternatives $\bar{u}(t)$ *(upper row)* with corresponding cumulative incidence curves $C_h^*(t) = C_h(t; u^*(t))$ and $\bar{C}_h(t) = C_h(t; \bar{u}(t))$ versus observed incidence data $\widehat{C}_h(t_j)$ *(lower row)* for three strategies defined in Table 3

Note that the total cost B of the optimal strategy $u^*(t)$ estimated by formula (20) essentially depends on the insecticide's lethality (cf. last column in Table 3). Additionally, the quantities $B_0 = \frac{B}{C_2}$ also differ according to insecticide lethality. Although it was tempting to use a "uniformed" amount B_0 for all three types of insecticide, we decided to treat them separately in order to make more visible the effect of budget cuts on the outcomes of $u^*(t)$ versus $\bar{u}(t)$ for each particular type of the insecticide.

For further analysis, it is also helpful to have at hand the numerical solutions $\bar{C}_h(t)$ of (19c), under *baseline options* $\bar{u}(t)$ for three control strategies described in Table 3 and defined by the corresponding values of B in accordance with formula (16).

The upper row of Figure 6 presents the optimal solutions $u^*(t), t \in [0, 60]$ and their corresponding baseline options $\bar{u}(t), t \in [0, 60]$ (*bang-bang* controls), while the lower row of Figure 6 displays the cumulative incidence curves $C_h^*(t) = C_h(t; u^*(t)), t \in [0, T]$ (solid lines) under optimal control policies $u^*(t)$ and $\overline{C}_h(t) = C_h(t; \bar{u}(t)), t \in [0, 60]$ (dashed lines) under the baseline alternatives of bang-bang type $\bar{u}(t)$ for three strategies defined in Table 3 versus cumulative incidences $\widehat{C}_h(t_j)$ obtained from the observation data gathered in Cali during 2010 dengue outbreak (star isolated points) with $t_j, j = 1, 2, \dots, 60$ denoting the j-th day of the observation period.

It is worthwhile to recall that Figure 6 displays solutions of the optimal control problem (18)-(19) where the budget constraint (3) is ignored and all resources (expressed by B_0 or B) required for policy implementation are supposed to be available.

Under such favorable conditions, the impact of all three optimal strategies $u^*(t)$, as well as their corresponding *baseline* alternatives $\bar{u}(t)$, can be clearly visualized through the forms of $C_h^*(t)$ and $\overline{C}_h(t)$, both of which become almost horizontal after 5, 10, or 20 days starting from the policy implementation ($t = 0$) when low-lethality ($u_{\max} = 0.2$), medium-lethality ($u_{\max} = 0.5$), or high-lethality ($u_{\max} = 0.8$)

TABLE 4 Comparison of the outcomes produced by optimal control policies $u^*(t)$ and their baseline alternatives $\bar{u}(t)$, while considering three strategies based on different types of insecticides

	Insecticide lethality	Total infections averted by $u^*(t)$	Total infections averted by $\bar{u}(t)$	Difference $N_H[\overline{C}_h(T) - C_h^*(T)]$
Strategy 1	20%	1576	1576	0
Strategy 2	50%	1828	1812	16
Strategy 3	80%	1876	1795	81

insecticides are employed. In other words, almost no new disease cases are produced afterward, and the epidemics may eventually vanish. However, this expectation is somewhat deceptive and misleading. Because the insecticide spraying is suspended by the end of observation period T, the basic reproductive number $\mathscr{R}_0$ becomes greater than unity after T, meaning that any human infection will produce again more than one secondary infection, independently of the lethality of insecticide used for spraying.

Additionally, Figure 6 allows to contemplate the overall effect of control interventions performed either by employing the optimal control policy $u^*(t)$ or its baseline variant $\bar{u}(t)$, which becomes stronger as the lethality insecticide increases from 20% to 50%, and further to 80%. Indeed, the bottom row of Figure 6 shows that the span between the observed data (star isolated points) and curves of $C_h(t)$ and $\overline{C}_h(t)$ (solid and dashed lines, respectively) becomes wider as $u_{\max}$ grows from 20% (chart on the left side) to 50% (chart in the middle), and further to 80% (chart on the right side).

It should be noted that the difference in actions of optimal and baseline control policies with regard to the number of human infections averted by $u^*(t)$ and $\bar{u}(t)$, respectively, is rather small and the gap between solid and dashed curves in the three lower charts of Figure 6 is almost invisible under the chosen scaling (except for the right-hand chart). On the other hand, the total number of human infections avoided by application of $u^*(t)$ and $\bar{u}(t)$ can be fairly assessed by the following formulas:

$$\text{Total No. of infections averted by } u^*(t) = N_H \cdot \left[\widehat{C}_h(T) - C_h^*(T)\right], \tag{21a}$$

$$\text{Total No. of infections averted by } \bar{u}(t) = N_H \cdot \left[\widehat{C}_h(T) - \overline{C}_h(T)\right], \tag{21b}$$

where N_H stands for the total number of inhabitants residing in Cali, Colombia and $\widehat{C}_h(T)$ is the cumulative incidence of dengue obtained from real data gathered in Cali, Colombia during 2010 dengue outbreak. Here, we have assumed that $N_H = 2370\,000$ people in accordance with official statistics.[4]

Table 4 resumes calculations carried out by formulas (21) and helps us assess the outcomes of optimal control policies $u^*(t)$ and their corresponding baseline alternative actions $\bar{u}(t)$ of bang-bang type, which are usually performed in practice by local healthcare authorities.

It is worthwhile to recall that, for each strategy defined by the type of insecticide, control policies $u^*(t)$ and $\bar{u}(t)$ have the same total cost B (see the last column of Table 3), but their effects are not the same (cf. columns 3 and 4 in Table 4). However, all three strategies have a common feature related to the type if insecticide which remains valid for both control intervention policies employed (that is, either $u^*(t)$ or $\bar{u}(t)$). Namely, the total number of human infections prevented by either control policy grows as the lethality of insecticide increases (which seems reasonable and rather expected). The latter stays in line with the variation of the basic reproductive number $\mathscr{R}_0$ during the control intervention: higher insecticide lethality induces smaller transitory value of $\mathscr{R}_0$, that is, a lesser number of secondary infections produced by one infective individual.

TABLE 5 Description of three resource limitation cases

	Description	Budget reduction
Case 1	Mild resource limitation	20%
Case 2	Moderate resource limitation	40%
Case 3	Severe resource limitation	60%

Additionally, direct comparison of the outcomes of control intervention policies $u^*(t)$ and $\bar{u}(t)$ (cf. columns 3 and 4 in Table 4) results in the following observations and recommendations:

1. When low-lethality insecticide is used (**Strategy 1**), both $u^*(t)$ and $\bar{u}(t)$ perform equally well, and both of them can be recommended for practical implementation. Yet, when **Strategy 1** is employed, the optimal control policy $u^*(t)$ performs "slightly better" than its corresponding baseline option $\bar{u}(t)$ in the sense that the difference $N_H[\overline{C}_h(T) - C_h^*(T)]$ is strictly positive. However, the integer part of this difference (or its floor value) is equal to zero. This explains the presence of 0 in the last column of Table 4.
2. When medium-lethality insecticide (**Strategy 2**) or high-lethality insecticide (**Strategy 3**) is used, the optimal control policy $u^*(t)$ performs better than its baseline alternative $\bar{u}(t)$ and renders additional averted infections (about 1% or 4.5% extra vs $\bar{u}(t)$, respectively), while the costs of both policies remain the same for each type of insecticide employed. Therefore, it is recommended for local healthcare authorities to apply optimal control policies whenever medium- or high-lethality insecticide is used and there are sufficient funds for their implementation.

The situation described in this subsection does not involve any budget constraint of the form (3) meaning that public healthcare authorities must possess enough resources (available stock of insecticide or monetary funds) for implementation of the optimal control policy $u^*(t)$. In practice, however, healthcare entities may not have sufficient supplies of insecticide (and of desired lethality) for accomplishing the optimal control policy $u^*(t)$ and, therefore, they would face up a challenging task of adjusting the policy to available resources. In other words, they would seek to solve the optimal control problem with budget constraint (3) in the form (7)-(8).

On the other hand, a bang-bang type control policy $\bar{u}(t)$ can be easily adjusted to available stock of insecticide with determined lethality by reducing the overall time of insecticide spraying action to $T^* \in (0, T)$ (see formula (16)). This may be the primary reason why public healthcare authorities prefer to deal with bang-bang control policies in practice, even if they do realize that $\bar{u}(t)$ are capable of preventing less human infections than $u^*(t)$ while using the same amount of insecticide.

In the following subsection, we present a series of experiments based on different scenarios for budget reductions, which provide solid arguments in favor of using optimal control policy $u^*(t)$ instead of more common bang-bang one $\bar{u}(t)$, especially when dealing with limited resources.

4.3 | Optimal solutions under limited budget

We start by considering three particular cases with regard to budget reduction, which are defined in Table 5 and correspond to mild (20%), moderate (40%), and severe (60%) limitation in supplies (if we deal with insecticide stock B_0) or in monetary funds (if we deal with monetary budget B). These particular cases are then combined with three possible types of insecticides with low, medium, and high lethality corresponding to **Strategies 1**, **2**, and **3** defined in Subsection 4.2 (see details in Table 4).

As a result, we obtain nine scenarios summarized in Table 6. Each scenario is denoted as **Scenario**

TABLE 6 Description of nine scenarios

	Maximum lethality u_{max}	Unit cost C_2	Budget reduction for $B = C_2\ B_0$
Scenario 1-1	0.2	3	$0.8\ B_0 = 8.12$
Scenario 2-1	0.5	4.5	$0.8\ B_0 = 11.31$
Scenario 3-1	0.8	6	$0.8\ B_0 = 10.88$
Scenario 1-2	0.2	3	$0.6\ B_0 = 6.09$
Scenario 2-2	0.5	4.5	$0.6\ B_0 = 8.48$
Scenario 3-2	0.8	6	$0.6\ B_0 = 8.16$
Scenario 1-3	0.2	3	$0.4\ B_0 = 4.06$
Scenario 2-3	0.5	4.5	$0.4\ B_0 = 5.65$
Scenario 3-3	0.8	6	$0.4\ B_0 = 5.44$

i–j, with $i, j = 1, 2, 3$, where i stands for the **Strategy i**, $i = 1, 2, 3$ (cf. Table 4) and j indicates the **Case j**, $j = 1, 2, 3$ of resource limitation (cf. Table 5).

Each **Scenario i–j** ($i, j = 1, 2, 3$) requires to solve numerically (using GPOPS-II software package) the following optimal control problem:

$$\min_{0 \le u \le u_{\max}} \mathcal{J}(u) = \min_{0 \le u \le u_{\max}} \int_0^T \left[C_1 H(t) + \frac{C_2}{2} u^2(t) \right] dt, \tag{22}$$

subject to

$$\frac{dV}{dt} = \alpha\, p_V\ H(1 - V) - [\delta + u(t)]\, V, \quad V(0) = V_0, \tag{23a}$$

$$\frac{dH}{dt} = \alpha\, p_H\, \xi\, V(1 - H) - \gamma\, H, \quad H(0) = H_0, \tag{23b}$$

$$\frac{dC_h}{dt} = \alpha\, p_H\, \xi\, V\, (1 - H), \quad C_h(0) = H_0, \tag{23c}$$

$$\frac{dZ}{dt} = C_2 u(t), \quad Z(0) = 0, \quad Z(T) = B. \tag{23d}$$

In what follows, we present numerical solutions of the optimal control problem (22)-(23) separately for each case of budget reduction described in Table 5.

4.3.1 | Mild resource limitation: 20% budget cut

Here, we start by considering an effect of 20% budget cut on the forms and underlying outcomes (expressed by the cumulative incidence curves $C_h^*(t)$ and $\bar{C}_h(t)$) of the optimal control policy $u^*(t)$ and its corresponding baseline alternative $\bar{u}(t)$. To model this mild budget cut, we replace the total budget B needed for implementation of the optimal control policy by 0.8 B and also adjust the form of bang-bang control $\bar{u}(t)$ to this updated value via formula (16). Further, we solve numerically the optimal control problem (22)-(23) three times with values of parameters given in rows 1-3 of Table 6, which correspond to **Scenarios 1-1, 2-1, and 3-1**, and thus obtain the profiles of $u^*(t)$ and $C_h^*(t)$, while the profile $\bar{C}_h(t)$ is generated by numerical solution of the system (23) with $\bar{u}(t)$ instead $u(t)$.

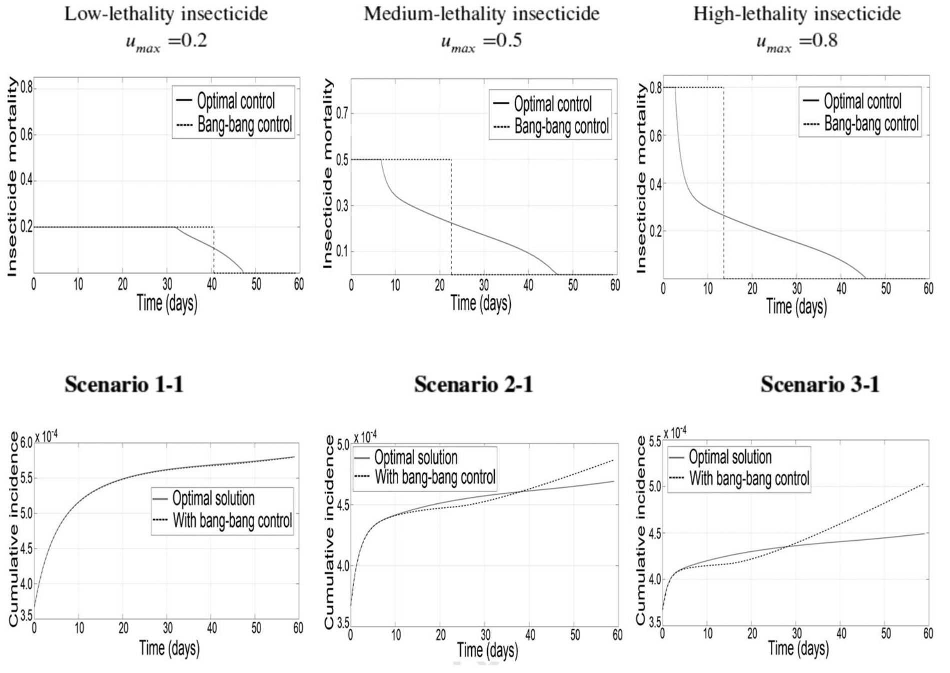

FIGURE 7 Profiles of optimal controls $u^*(t)$ and their bang-bang alternatives $\bar{u}(t)$ *(upper row)* with corresponding cumulative incidence curves $C_h^*(t)$ and $\bar{C}_h(t)$ *(lower row)* under mild resource limitation (20% budget cut, solid and dotted lines, respectively) for three different types of insecticides employed

Figure 7 displays the profiles of optimal controls $u^*(t)$ and their bang-bang alternatives $\bar{u}(t)$ *(upper row)* with underlying cumulative incidence curves $C_h^*(t)$ and $\bar{C}_h(t)$ *(lower row)* corresponding to **Scenarios 1-1, 2-1, and 3-1** described in Table 6, that is, under mild resource limitation (20% budget cut).

In this figure, as well as in following figures corresponding to subsequent scenarios (Figures 8 and 9), $u^*(t)$ and $C_h^*(t)$ are plotted by solid lines, while $\bar{u}(t)$ and $\bar{C}_h(t)$ are drawn by dotted lines.

The difference in outcomes of the optimal control policies $u^*(t)$ and their corresponding baseline alternative actions $\bar{u}(t)$ has become more visible now than in Figure 6 that provides illustrations to the initial case with fully available resources presented in Subsection 4.2. However, it is still difficult to visualize the difference between the final outcomes of control policies $u^*(t)$ and $\bar{u}(t)$ when low-lethality insecticide is employed (**Scenario 1-1**). In this context, formulas (21) could help us again by comparing the total numbers of human infection avoided by applying either $u^*(t)$ or $\bar{u}(t)$ with a case where no control measures are implemented at all (ie, when $u(t) = 0$ for $t \in [0, T]$ in the outcome of the dynamical system (19)).

Table 7 summarizes calculations carried out by formulas (21) and clearly shows that optimal control policies $u^*(t)$ perform better than their corresponding baseline alternative actions $\bar{u}(t)$ under mild resource limitation. Moreover, it can be asserted that an additional number of human infections averted by $u^*(t)$ versus $\bar{u}(t)$ increases as the insecticide lethality increases (cf. last column of Table 7).

It is interesting to note that when optimal control policies are employed for different types of insecticides, a budget reduction of 20% results in 1-1.2% reduction of avoided human infections (cf. first columns of Tables 4 and 7). On the other hand, the same budget cut of 20% may increase the number of human infections by 1-3.5% (depending on the insecticide type) when baseline control policies of

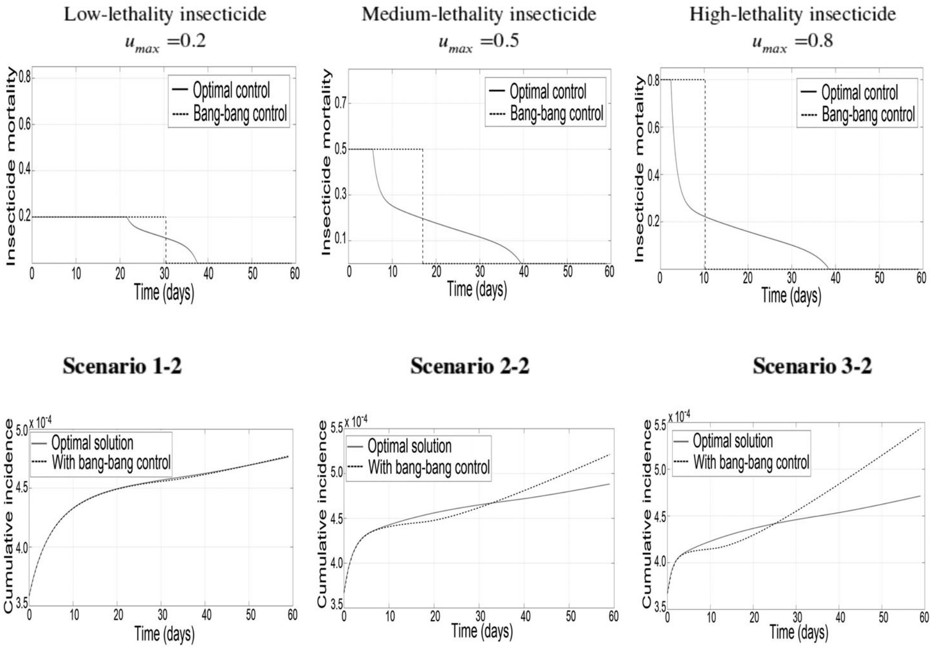

FIGURE 8 Profiles of optimal controls $u^*(t)$ and their bang-bang alternatives $\bar{u}(t)$ *(upper row)* with corresponding cumulative incidence curves $C_h^*(t)$ and $\bar{C}_h(t)$ *(lower row)* under moderate resource limitation (40% budget cut, solid and dotted lines, respectively) for three different types of insecticides employed

TABLE 7 Estimates of total number of averted infections under mild resource limitation (20% budget cut)

	Total infections averted by $u^*(t)$	**Total infections averted by $\bar{u}(t)$**	**Difference $N_H[\bar{C}_h(T) - C_h^*(T)]$**
Scenario 1-1	1560	1558	2
Scenario 2-1	1809	1770	39
Scenario 3-1	1854	1732	122

bang-bang type are implemented (cf. second columns of Tables 4 and 7). In other words, $u^*(t)$ are more resilient to mild budget cuts than $\bar{u}(t)$, and their endurance to mild budget reductions become more notable when the insecticide's lethality increases.

Finally, if we compare the difference in the total number of human infections averted by $u^*(t)$ versus $\bar{u}(t)$ with no resource limitation (see the last column of Table 4) and under mild budget cut of 20% (last column of Table 7), we come to the following conclusion. For all types of insecticides employed, a mild budget cut of 20% affects to lesser extent the overall performance of optimal control policies $u^*(t)$ than the performance of their baseline alternative actions $\bar{u}(t)$ of the same total cost, which are habitually performed in practice.

4.3.2 | Moderate resource limitation: 40% budget cut

To consider an effect of 40% budget cut on the forms and underlying outcomes (expressed by $C_h^*(t)$ and $\bar{C}_h(t)$) of the optimal control policy $u^*(t)$ and its corresponding baseline alternative $\bar{u}(t)$, we proceed in a similar way as described in Subsection 4.3.1 while taking $0.6B$ instead of B (see rows 4-6 in

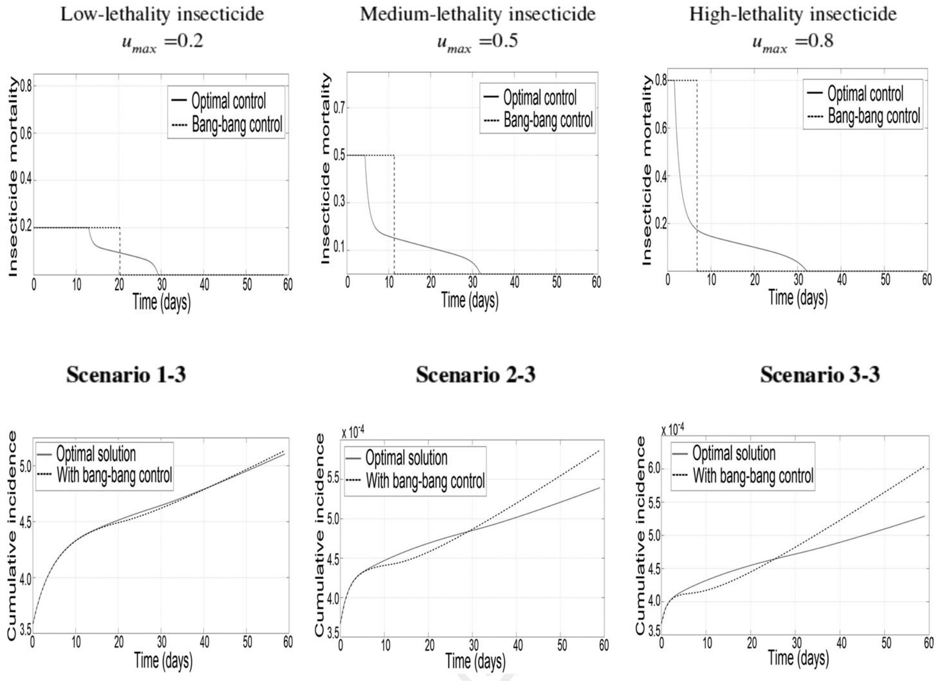

FIGURE 9 Profiles of optimal controls $u^*(t)$ and their bang-bang alternatives $\bar{u}(t)$ *(upper row)* with corresponding cumulative incidence curves $C_h^*(t)$ and $\bar{C}_h(t)$ *(lower row)* under severe resource limitation (60% budget cut, solid and dotted lines, respectively) for three different types of insecticides employed

TABLE 8 Estimates of total number of averted infections under moderate resource limitation (40% budget cut)

	Total infections averted by $u^*(t)$	Total infections averted by $\bar{u}(t)$	Difference $N_H[\bar{C}_h(T) - C_h^*(T)]$
Scenario 1-2	1508	1505	3
Scenario 2-2	1766	1692	74
Scenario 3-2	1804	1642	162

Table 6—**Scenarios i-2**, $i = 1, 2, 3$) for numerical solution of the optimal control problem (22)-(23) and for adjustment of $\bar{u}(t)$ via formula (16).

Figure 8 displays the profiles of optimal controls $u^*(t)$ and their bang-bang alternatives $\bar{u}(t)$ *(upper row)* with underlying cumulative incidence curves $C_h^*(t)$ and $\bar{C}_h(t)$ *(lower row)* corresponding to **Scenarios 1-2, 2-2, and 3-2** described in Table 6, that is, under moderate resource limitation (40% budget cut). As in the previous case (see Subsection 4.3.1), Table 8 provides the overall numbers of human infections that can be avoided by applying either $u^*(t)$ or $\bar{u}(t)$ under moderate resource limitation (40% budget cut).

It is natural to expect that higher budget cuts be (negatively) reflected in the capabilities of both $u^*(t)$ and $\bar{u}(t)$ for prevention of human infections. In effect, when the necessary budget B is reduced by 40%, the overall number of human infection avoided by $u^*(t)$ is reduced by 3.4-4.3% (cf. first columns of Tables 4 and 8). On the other hand, under the same budget cut of 40%, the number of human infections avoided by $\bar{u}(t)$ is reduced by 4.5-8.5% (cf. second columns of Tables 4 and 8). In other words, $u^*(t)$ still remain more resilient to budget cuts than $\bar{u}(t)$.

TABLE 9 Estimates of total number of averted infections under severe resource limitation (60% budget cut)

	Total infections averted by $u^*(t)$	Total infections averted by $\bar{u}(t)$	Difference $N_H[\bar{C}_h(T) - C_h^*(T)]$
Scenario 1-3	1356	1342	14
Scenario 2-3	1658	1545	113
Scenario 3-3	1675	1506	169

Additionally, both control policies $u^*(t)$ and $\bar{u}(t)$ have the same cost of implementation (expressed by $0.6B = 0.6C_2B_0$), but optimal control policies always perform better for all three types of insecticides with different lethalities and, similar to the previous case described in Subsection 4.3.1, the advantages of applying $u^*(t)$ versus $\bar{u}(t)$ become more visible as the lethality of insecticide increases (cf. last column in Table 8).

Let us explore whether this tendency remains in force when budget limitation becomes even tougher.

4.3.3 | Severe resource limitation: 60% budget cut

In this ultimate case, we replace B by $0.4B$ for numerical solution of the optimal control problem (22)-(23) and for adjustment of $\bar{u}(t)$ via formula (16) in accordance with rows 7-9 in Table 6 (**Scenarios i-3**, $i = 1, 2, 3$).

The results are given in Figure 9 and Table 9 and they clearly illustrate that the resource scarcity affects considerably the overall performance of both control policies. However, a drastic budget cut of 60% affects to a lesser extent the capacity of $u^*(t)$ for prevention of human infections, which is reduced by 9.3-13.9 % (cf. first columns of Tables 4 and 9). On the other hand, the same capacity of $\bar{u}(t)$ is reduced by 14.7-16.1 % (cf. second columns of Tables 4 and 9). Moreover, the difference between the outcomes of $u^*(t)$ and $\bar{u}(t)$ is more significant now than in previous two cases considered in Subsections 4.3.1 and 4.3.2—it suffices to compare the last column of Table 9 with corresponding columns in Tables 7 and 8.

From the above analysis of three cases described in Table 5, it can be now perceived that optimal control policies are more resilient to resource limitations, while their efficiency becomes more notable under stronger budget constraints and also with application of insecticides bearing higher lethality. Furthermore, optimal control policies designed for each strategy (based on certain type of insecticide)

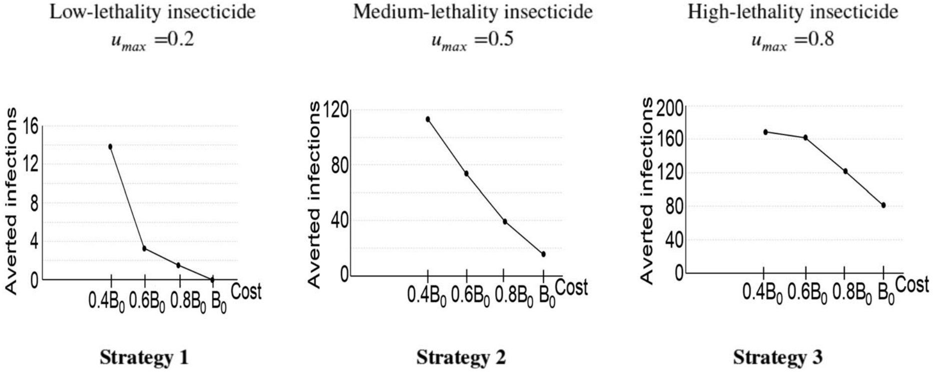

FIGURE 10 Graphical interpretation of additional benefits rendered by implementing the optimal control policy $u^*(t)$ versus its baseline alternative action $\bar{u}(t)$ expressed as a function of possible budget cuts

display structural robustness and capacity for adjustments to impose budget constraints, which makes them appealing for practical implementation.

5 | DISCUSSION AND CONCLUDING REMARKS

It is worth noting that at the beginning of the disease outbreak, local healthcare authorities may not always acquire a desired quantity of insecticide for not having sufficient funds, while local providers may not possess an existing stock of insecticide with desired lethality. Therefore, coercive measures seeking to suppress the disease outbreak are usually carried out in practice by quickly spraying all available insecticide stock (regardless of its lethality) at maximal rate of application. In mathematical terms, this approach is modeled by the baseline control policy $\bar{u}(t)$ of bang-bang type.

In this paper, we have shown that habitual control policies of bang-bang type are not the best for practical implementation. More precisely, let us recall that, for all scenarios considered in Subsections 4.2 and 4.3, the optimal control policies $u^*(t)$ and their corresponding bang-bang alternative actions $\bar{u}(t)$ have the same implementation costs. Nonetheless, their respective benefits, expressed by the number of averted human infections (see Tables 4 and 7-9), are different.

To compare the overall performance of the optimal control policies $u^*(t)$ and their baseline alternatives $\bar{u}(t)$, let us reorganize the data presented in Tables 4 and 7-9 and summarize all additional benefits rendered by $u^*(t)$ in Figure 10 that graphically expresses the dynamics of additional benefits obtained by employing $u^*(t)$ versus $\bar{u}(t)$ as a function of budget cuts and for each type of insecticide.

From the analysis performed in Subsection 4.3 for three types of insecticides (with low, medium, or high lethality), it is worth recalling that optimal control policies $u^*(t)$ demonstrate higher endurance and resilience to possible budget reductions, so their benefits become more visible under stronger budget constraints. The latter can be observed in all three charts of Figure 10 where the numbers of human infections prevented by $u^*(t)$ increase for smaller available budgets and for all types of insecticides used in vector control measures.

However, the benefits of employing $u^*(t)$ versus $\bar{u}(t)$ are less remarkable when vector control measures are based on low-lethality insecticide than on an insecticide with medium or high lethality (see Figure 10, left chart). In particular, additional benefits rendered by optimal control policy $u^*(t)$ are insignificant when low-lethality insecticide is applied either without budget constraints or under 20-40% budget cuts, while the operational structure of $u^*(t)$ is more sophisticated than that of $\bar{u}(t)$ and should require additional adjustments, which may possibly lead to additional operation costs. Therefore, in situations described above, traditional operational approach relying on baseline control actions $\bar{u}(t)$ is still acceptable.

On the other hand, as budget constraint becomes stronger (eg, 60% budget cut) while the lethality of insecticide remains low, it looks reasonable to replace the habitual *modus operandi* of bang-bang type, $\bar{u}(t)$, by more sophisticated optimal control policy $u^*(t)$, which may additionally prevent 14 human infections and save about 8.400 dollars to the healthcare system (here we have assumed the total societal cost of one human infection equal to 600 dollars[36,37]).

When insecticides with medium or high lethality are used for coercive short-term measures aimed at suppressing dengue outbreaks, the advantages of employing $u^*(t)$ become more apparent even if accounting for possible additional costs that relate to the change of operational mode. Namely, application of optimal control policies $u^*(t)$ instead of their habitual baseline alternative actions $\bar{u}(t)$ may additionally avoid between 16 and 169 human infections during a single disease outbreak (see Figure 10, central and right charts). The latter implies that local healthcare system may save between 9.600 and 101.400 dollars by only changing its operational mode for insecticide spraying. In a low-income country, such as Colombia, where more than 20% of children below 5 years of age do not have access to basic vaccination plans,[38] this is an important consideration. In effect, a complete vaccination scheme of hexavalent vaccine (three doses, protects against diphtheria, tetanus, pertussis, poliomyelitis, Haemophilus meningitis, and hepatitis B) costs about 117 dollars per one child according to information available online at http://www.finanzaspersonales.co/cuanto-cuesta/articulo/cuanto-cuesta-un-esquema-de-vacunacion/36245 (accessed on April 25, 2019). This simple example shows what kind of *real benefits* may provide the change in operational mode of insecticide spraying to public welfare in low-income countries.

In conclusion, we hope that the outcomes of this study will be sufficiently appealing to superordinate public health authorities in countries suffering from periodic or intermittent outbreaks of vector-borne infections and motivate them to make the necessary adjustments in operational mode of insecticide spraying.

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ORCID

Lilian Sofia Sepulveda-Salcedo https://orcid.org/0000-0002-7052-1851
Olga Vasilieva https://orcid.org/0000-0002-1886-2528

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