

Cost-Effective Optimal Control Analysis To Co-Infection Model Of Dengue Fever And Typhoid Fever

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ABSTRACT

This study deals with the application of mathematical modeling in analyzing the transmission dynamics of diseases. In particular we develop an algebraic model that describes the interaction between two common diseases, namely dengue and typhoid fevers. To realistically describe the interdependence among agents that influence the spread of both diseases, we consider an environment of three populations: vector, human, and bacteria, which in total consist of ten compartments. In order to be able to intervene the system, we equip the model with four control variables, namely mosquito eradication, the use of mosquito repellent, treatment of individuals carrying and infected with typhoid, and education on healthy living. The well-known Pontryagin maximum principle was carried out in deriving necessary conditions for optimal controls and the so-called forward-backward sweep method combining with the fourth order Runge-Kutta algorithm was utilized in the implementation of numerical solutions. A series of control scenarios were evaluated based on their benefits obtained and costs incurred. An ACER and ICER based cost effectiveness analysis was conducted to characterize the best control strategy. In a case study with 1000 human populations, it is suggested that a strategy with all control alternatives provides the most effective results.

Keywords: Co-infection, cost effectiveness, dengue fever, numerical simulation, optimal control, typhoid fever.

Mathematics Subject Classification: 62P10

1. INTRODUCTION

Dengue fever is caused by the *dengue* virus of the genus *Flavivirus*, family *Flaviviridae*. The virus enters the human body through the bite of an infective female *Aedes Aegyptus* mosquito, then infected humans become the source of the virus for the uninfected mosquitoes. One of the ways to prevent disease transmission can be carried out by eradicating mosquito nests by mosquito fogging, the aim of the mosquito fogging operations is to kill, or 'knock-down', any adult dengue mosquitoes that may be carrying the dengue virus (WHO, 2014). This disease is commonly found in tropical and subtropical regions, according to data from (WHO, 2018a) Asia Pacific borne 75% of the burden of dengue fever in the world between 2004 and 2010, while Indonesia was reported as the 2nd country with the largest cases of dengue fever in among 30 endemic countries (WHO, 2012).

Typhoid fever disease is an acute infection of the small intestine caused by *Salmonella typhi* of genus *Salmonella*, family *Enterobacteriaceae*. *S. Typhi* bacteria enter the human body through the consumption of contaminated food and water, even today was a common problem in overcrowded cities that had no adequate sewage system (Emmeluth, 2004). Typhoid fever sufferers can excrete more than one trillion bacteria in each gram of their stools, when people who are infected and carriers do not thoroughly wash their hands after defecation, they risk passing the bacteria to others, the germ from feces of typhoid fever sufferers and carriers are carried by fingers and flies that land on food and water are then consumed by healthy people (Emmeluth, 2004; Jarrow, 2015; WHO, 2020). To control the typhoid fever epidemic, WHO recommends vaccinations, health education, improving water quality and sanitation, and training health professionals in diagnosing and treating patients with fever symptoms (WHO, 2018b). Typhoid fever is endemic in Asia, Africa, Latin America, the Caribbean, and Oceania, but 80% of cases come from Bangladesh, China, India, Indonesia, Laos, Nepal, Pakistan, and Vietnam. In these countries, typhoid fever is most common in disadvantaged areas (Brusch, 2019).

Co-infection with dengue and typhoid fever is a condition in which a person has been infected by the *dengue* virus and the *S. Typhi* bacteria. Considering both diseases are endemic in several countries, especially in developing countries with poor sanitation conditions, tropical or subtropical areas such as Indonesia and India. The person may be infected by both diseases simultaneously, so should always be considered when treating patients with fever prolonged (Seshan *et al.*, 2016).

The research by Soegijanto *et al.* (2018) found that in infecting humans, the *dengue* virus and *salmonella* bacteria can coexist in the human body for more than ten days. *Dengue* virus and *S. Typhi* infections may overlap, especially during the first few days, and cannot be distinguished by the same symptom, namely fever (Basuki, 2003). Meanwhile, the research by Lee *et al.* (2005) stated that although the reasons for the coinfection of dengue fever and typhoid have not been widely studied, a prolonged fever of more than five days can be a risk factor for the coinfection. The reason that might increase the coinfection is that dengue fever causes damage to the intestinal mucosal barrier. Clinicians must be aware of the potential for the coinfection when treating patients with dengue virus infection and the challenges in making the right diagnosis (Srinivasaraghavan *et al.*, 2015).

From several studies in India concluded that the coinfection of dengue and typhoid were common (Kumar *et al.*, 2017; Chauhan *et al.*, 2019). However, the coinfection of the disease is rarely reported (Bansal *et al.*, 2014). A study on patients at Kasturba hospital located in north Delhi carried out between August-November 2013 by Sharma *et al.*, (2014) reported that out of 141 dengue fever positive patients, eleven (7.8%) were co-infected with typhoid. Agrawal & Bajaj (2016) case report in New Delhi, of 251 dengue fever patients (September 2015-November 2015) found nine (3.5%) coinfection patients with typhoid. From the research by Srinivasaraghavan *et al.* (2015) in South India, as many as 632 patients with fever (January 2017-September 2017) reported that 94 (14%) patients were positive for dengue, and 32 of these dengue patients were co-infected with typhoid. Furthermore by Chauhan *et al.* (2019) conducted at Muzaffarnagar Medical College, India, as many as 403

patients (August 2017 - November 2017) with fever reported that 154 (38.2%) patients were positive for dengue fever, 71 patients (17.6%) were positive for typhoid, and 28 patients (6.9%) were co-infected with both diseases. Then a case report from Cambodia by Kasper *et al.* (2012), as many as 94 patients with co-infection cases (December 2006-December 2009) found three (3.19%) patients co-infected with dengue and typhoid. Meanwhile, a case report from Indonesia by Soegijanto *et al.* (2018), from fifty children with dengue virus infection (January 2017-April 2017) at Soerya Hospital, found that 12 children were co-infected with both dengue fever and typhoid.

Mathematical modeling has become an important tool in understanding the dynamics of disease transmission and also in the decision-making process regarding intervention mechanisms for disease control (Okosun & Makinde, 2014). The mathematical models of disease coinfection that have been discussed and developed include Mushayabasa *et. al.* (2014) constructed a mathematical model of the spread of malaria-typhoid coinfection, where the malaria disease submodel SEIR-SEI in which compartment *E* represents the exposed subpopulation, the typhoid fever disease submodel SICRS with assuming that typhoid is transmitted directly from infected humans. A person who is infected with both diseases by showing symptoms of one disease can be treated in two ways, namely combination treatment and treatment for each disease. In their study was not used the optimum control strategy. In the same year, Okosun & Makinde (2014) introduced a co-infected model malaria-cholera with the optimal control where SIRS-SI as a malaria disease submodel and SIRS-B as a cholera disease submodel. Their model includes five different control strategies, such as malaria prevention (treated bednets), malaria treatment, cholera prevention (sanitation and proper hygiene), cholera treatment, and combined therapy for malaria-cholera infection. The research by Mutua *et. al.* (2015), the authors are the first to develop an improved realistic typhoid model (SICR-B) that combines human population systems with environmental components based on the assumption that typhoid spreads via bacteria in the environment that contaminate food and water. They further develop the dynamics malaria-typhoid co-infected model using their new typhoid model and standard malaria model. Furthermore, Tilahun *et. al.* (2018) examined the pneumonia-typhoid co-infected model were using SIRS as the pneumonia disease submodel and SIRS-B as the typhoid disease submodel. Their research applied an optimum control strategy, and the optimum cost was analyzed using the Incremental Cost-Effectiveness Ratio (ICER). Aldila & Agustin (2018) examined the dengue fever-chikungunya co-infected model without applied optimum control strategy. The model used the SIRS-SI model which the infected mosquito population consists of three categories, namely mosquitoes infected with *dengue* virus, mosquitoes infected with chikungunya, and both disease infected. Later in the same year, Bonyah *et. al.* (2018), the authors examined the optimum control model for dengue fever-Zika coinfection by adopting the SIRS-SI model where infected mosquitoes consisted of mosquitoes infected with *dengue* virus and mosquitoes infected with *Zika* virus. Rayhan *et. al.* (2018) introduced a coinfection model TB-HIV/AIDS with the optimal control.

However, a few studies of mathematics modeling have not been carried out on the formulation and applicate of optimal control theory and cost-effectiveness analysis. To the best of our knowledge, no work has been to investigate the dynamics of dengue fever-typhoid co-infected in mathematical

modeling by applying the optimum control method and cost-effectiveness analysis. The existence of case reports (Kasper *et. al.*, 2012; Sharma *et. al.*, 2014; Agrawal & Bajaj, 2016; Kumar *et. al.*, 2017; Soegijanto *et. al.*, 2018) and several studies (Basuki, 2003; Bansal *et. al.*, 2014; Srinivasaraghavan *et. al.*, 2015; Kumar *et. al.*, 2017; Soegijanto *et. al.*, 2018; Chauhan *et. al.*, 2019), motivated us to conduct this study. In this paper, we build a mathematical model for the coinfection of dengue fever and typhoid fever which is formulated by considering existing models in previous research studies as a submodel, the SIRS-SI model for dengue fever and the SICRS-B model for typhoid fever. We developed a deterministic mathematics model to investigate the dynamics of dengue fever-typhoid fever with optimal control strategies and investigate the cost-effectiveness of the applied control strategies. Our model includes four different control strategies, namely mosquito eradication, the use of mosquito repellent, treatment of individuals carrying and infected with typhoid, and education on healthy living as a time-dependent control measure to determine the optimal strategy.

2. MODEL DESCRIPTION AND FORMULATION

We formulate a SIRS-SI model for dengue fever. Meanwhile, since mainly the typhoid disease spread through food and water contaminated by bacteria in the environment. If there is the transmission of typhoid through direct person-to-person contact is then negligible (Mutua *et. al.*, 2015). Therefore we consider a SICR-B (Susceptible-Infected-Carrier-Removed-Bacteria) model developed by Mutua *et. al.* (2015) that their model combines human population systems with environmental components to combine real biological phenomena, constant transmission rates. We assume that humans who recover from the disease will acquire temporary immunity that will decrease to a certain level that the typhoid disease model becomes SICRS-B and the force of infection of the model with a non-constant rate (Michaelis-Menten function) as in (Mushayabasa 2011; Tilahun *et. al.* 2017).

2.1 Dengue fever only model.

Similar to the previous studies (Sari *et. al.* 2017, Aldila & Agustin 2018, Bonyah *et. al.* 2018, Fakhruddin *et. al.* 2019), we consider a dengue fever model, SIRS-SI, consisting of three human compartments (susceptible S_H , infected I_D , and recovered R) and two mosquito compartments (susceptible S_V , and infected I_V). Our assumptions in the model are as follows:

1. We assume that humans and mosquitoes to be born susceptible. Also, there is no natural protection.
2. Susceptible humans and susceptible mosquitoes enter the model with constant recruitment rates of Λ_h and Λ_v , respectively.
3. The incubation period is negligible so that the infected population can transmit the disease directly.
4. Dengue fever transmission only occurs from direct contact between mosquitoes and humans. Transmitted cannot come to pass from humans to humans or mosquito to the mosquito.
5. The spread of the dengue fever if the infected mosquito bites susceptible human, then there will be a transmission that results in the human becomes infected. If the infected human is bitten by the

susceptible mosquito, resulting in transmitted of the dengue virus to the mosquito, the mosquito becomes infected (Sari *et. al.* 2017). The infection rate of susceptible humans defined as

$$\lambda_D = \beta_h \frac{bI_V}{N_H} \quad (1)$$

where b is the number average of mosquito bites per day so that there will be bN_V mosquito bites per day. Parameter β_h is the probability of transmission to susceptible humans per mosquito bite, and $\frac{I_V}{N_V}$ is the probability that the bitten is an infective mosquito. Thus, humans will receive as much as $\frac{bN_V}{N_H} \frac{I_V}{N_V}$ infected mosquito bite per day. The term $\frac{I_D}{N_H}$ represents the probability of the bitten human by a susceptible mosquito is an infective one and β_v is the probability of transmission from infected humans to susceptible mosquitoes per bite so that the mosquito is infected at a rate $\beta_v \frac{bI_D}{N_H}$.

6. Infected individuals may recover at rate γ and become susceptible at a rate ω . Dengue virus has four types of serotypes, namely DEN-1, DEN-2, DEN-3, and DEN-4 where being infected with one of the four serotypes will provide lifelong antibodies against that serotype but not the other three serotypes, therefore it is assumed that humans who recovered from dengue will be susceptible again. A person will lose immunity to the other three serotypes (*heterologous immunity*) within twelve weeks and become susceptible more (Derouich *et. al.* 2003).
7. Parameters μ_h and μ_v denote the natural mortality rate of the human and mortality rate of mosquito, respectively. We assume that if there is a dengue fever-induced mortality rate of infected humans at rate ε so that the death of infected humans at rate $\mu_h + \varepsilon$.
8. There is no recoverable (immune) in the vector population (mosquitoes) will always carry a dengue virus in their body for all their life (Derouich *et. al.* 2003, Sari *et. al.* 2017).

The mathematics model for the dengue fever transmission that we study is as follows:

$$\frac{dS_H}{dt} = \Lambda_h - (\lambda_D + \mu_h)S_H + \omega R, \quad (2a)$$

$$\frac{dI_D}{dt} = \lambda_D S_H - \gamma I_D - (\mu_h + \varepsilon)I_D, \quad (2b)$$

$$\frac{dR}{dt} = \gamma I_D - \mu_h R - \omega R, \quad (2c)$$

$$\frac{dS_V}{dt} = \Lambda_v - \beta_v \frac{bI_D}{N_H} S_V - \mu_v S_V, \quad (2d)$$

$$\frac{dI_V}{dt} = \beta_v \frac{bI_D}{N_H} S_V - \mu_v I_V, \quad (2e)$$

where $\lambda_D = \frac{\beta_h b I_V}{N_H}$.

2.2 Typhoid fever only model.

The model, SICRS-B, considers the typhoid fever causing bacteria *S. Typhi* population in environmental (B) and the human population. The human population consists of four classes, susceptible S_H , infected I_T , carrier C , and recovered R . Carriers are people who are colonized by *Salmonella typhi* bacteria without showing any symptoms of the disease (healthy) and who are potential source of infection to others by indiscriminately contaminating foods and water carelessly

during preparation and handling (Tilahun *et. al.* 2017). In our model assume that carrier individuals are individuals who have previously been infected with typhoid, then become carriers of bacteria in the intestinal tract and gallbladder for years (chronic carrier) without causing the person to become sick, this happens because to not getting the right treatment or due to other factors in the sufferer (WHO 2018b, Mutua *et. al.* 2015). Infected individuals in both infectious and carrier state excrete bacteria into the environment (Mutua *et. al.*, 2015; Tilahun *et. al.* 2017, Tilahun *et. al.* 2018). The model was developed with the following assumptions:

1. Susceptible individuals enter the infected class with a force of infection as follows

$$\lambda_B = \frac{B\sigma}{\kappa+B} \quad (3)$$

where the ingestion rate is σ , B is the bacteria population, κ is the bacteria concentration in foods or waters, so $\frac{B}{\kappa+B}$ is the probability of individuals consuming foods or waters contaminated typhoid causing bacteria.

2. Infected individuals enter the carrier-class at the rate δ_1 or enter the cured class at the rate δ_2 or enter to recovered-class with natural immunity at the rate τ .
3. Parameters θ_1 and θ_2 are the average of bacterial excretion to the environment of the infected-class and carrier-class, respectively. we assume that θ_1 is higher than that by θ_2 . Although low excretion of bacteria by the carrier-class, they play a prominent role in the transmission of typhoid because of their very long duration without showing any sickness (Jarrow 2015, Mutua, *et. al.* 2015, Awoke 2019).
4. Recovered individuals will gain temporary immunity that will decrease at rate ω (Mushayabasa 2011, Mushayabasa *et. al.* 2014, Tilahun *et. al.* 2017, Tilahun *et. al.* 2018).
5. Mortality rate of pathogen (non-infectious) at a rate μ_b , there is typhoid-an-induced mortality rate of infected humans at rate ρ so that the death of infected humans at rate $\mu_h + \rho$.
6. The Growth of organisms is often described with the logistic models (Pearl 1927, Juneja, *et. al.* 2009, Baker *et.al.* 2011, Mutua *et. al.* 2015, Bakhtiar 2016). We assume that bacteria salmonella in the environment (food and water contaminated) grows according to the logistic growth rate as follows $rB(1 - \frac{B}{K})$ where r and K represent per capita intrinsic growth rate and carrying capacity. The number of bacteria due to natural growth of rB . If the remaining environmental storage capacity is $(K - B)$ bacteria then there are still $\frac{(K-B)}{K}$ parts of the environment that are still habitable and proportional to population growth.

The developed model can express as the following differential equation.

$$\frac{dS_H}{dt} = \Lambda_h + \omega R - (\lambda_B + \mu_h)S_H, \quad (4a)$$

$$\frac{dI_T}{dt} = \lambda_B S_H - (\delta_1 + \delta_2 + \mu_h + \rho)I_T, \quad (4b)$$

$$\frac{dC}{dt} = \delta_1 I_T - (\tau + \mu_h)C, \quad (4c)$$

$$\frac{dR}{dt} = \delta_2 I_T + \tau C - (\omega + \mu_h)R, \quad (4d)$$

$$\frac{dB}{dt} = rB \left(1 - \frac{B}{K} \right) + \theta_1 I_T + \theta_2 C - \mu_b B, \quad (4e)$$

where $\lambda_B = \frac{B\sigma}{\kappa+B}$.

2.3 Dengue fever-typhoid fever co-infection model with control

Based on the typhoid model (2a)-(2e) and dengue fever model (4a)-(4e), we now construct a co-infection model using both models were developed. We consider an environment of three populations: vector (mosquito), human, and bacteria, which in total consist of ten compartments. The total human population denoted by N_H is therefore divided into seven subpopulations, namely susceptible (S_H), infected with dengue fever (I_D), infected with typhoid fever (I_T), carrier (C), co-infected (I_{DT}), carrier individual infected with dengue fever (I_{DC}), and recovered (R). So that $N_H = S_H + I_D + I_T + C + I_{DT} + I_{DC} + R$. The total vector population, denoted by N_V , is subdivided into susceptible mosquitoes (S_V), mosquitoes infected (I_V). Thus, $N_V = S_V + I_V$. B is the bacteria population. The compartmental diagram of our co-infection model is showing in Figure 1. All variables and parameters of the co-infected model are describing in Table 1. The co-infection compartmental model depicted in Figure 1 is developed under the following additional assumptions regarding co-infection:

1. The total populations are non-constant.
2. The number of populations in compartments at time t is given by $S_H(t)$, $I_D(t)$, $I_T(t)$, $C(t)$, $I_{DT}(t)$, $I_{DC}(t)$, dan $R(t)$, $S_V(t)$, $I_V(t)$, and $B(t)$.
3. An individual infected with dengue fever is bitten by a susceptible mosquito, resulting in the transmission of the dengue virus to the mosquito. So, the mosquito is infected at a rate

$$\lambda_V = \frac{\beta_v b (I_D + I_{DT} + I_{DC})}{N_H} \quad (5)$$

where β_v is the probability of transmission from infected humans to susceptible mosquitoes per bite, and b is the number average of mosquito bites per day. The term $(I_D + I_{DT} + I_{DC})/N_H$ represents the probability of the bitten human by a susceptible mosquito is an infective one. Thus, the number of new cases per unit of time is given by $\lambda_V S_V$.

4. Co-infection with both diseases cannot occur directly, but gradually from being infected with dengue fever to further infection (co-infection) with typhoid or vice versa.
5. In infecting humans, the dengue virus and salmonella bacteria can coexist for more than ten days. So that dengue fever-typhoid co-infection may occur (Soegijanto *et. al.* 2018).
6. Dengue fever can make the body's immune system decrease drastically. So, the bacteria in the body are more active and infectious. So it is assumed that carriers infected with dengue will be susceptible to further infection with typhoid disease.
7. Carriers infected with dengue fever join the recovered class at a rate h_1 or recovery of dengue fever join the carrier-class at a rate h_2 or join the coinfection-class at a rate h_3 .
8. Individuals in co-infection class (I_{DT}) of both diseases have a high mortality rate and are given by $\mu_h + \varepsilon + \rho$.

9. Individuals infected with both diseases join the recovered class at a rate ϕ_1 (dengue fever and typhoid recovered at the same time) or at a rate ϕ_2 join the I_D class who recovered from typhoid only or at a rate ϕ_3 join the I_T class who recovered from dengue fever only.
10. Individuals infected with both diseases can only infect mosquitoes with the dengue virus.

To be able to intervene in the system to reduce the number of dengue fever infected and typhoid infected in an area, we equip the model with four control variables.

- i. u_1 is an efforts to prevent dengue fever by controlling the mosquito population. These actions include eradicating mosquito nests using fogging (the mosquito fogging using insecticide).
- ii. u_2 is an effort to prevent dengue fever, reducing human contact with mosquitoes to avoid transmission from mosquitoes to humans and vice versa. Actions include the use of mosquito repellents (mosquito repellent lotion or mosquito nets).
- iii. u_3 is complete treatment (detection and administration of therapy with antibiotics according to doses and periodic examinations) effort of typhoid fever infected and carriers individuals.
- iv. u_4 is the prevention of typhoid fever disease using public health education to improve hygiene and healthy living habits, especially the culture of proper hand washing, cooking food properly and clean from processing to serving, so protect susceptible from contacting Salmonella bacteria.

If typhoid sufferers are not treated or the treatment is inadequate, or there are predisposing factors in the patient so that bacteria are difficult to destroy from the body, they will become carriers. This is what underlies us in setting the u_3 control.

The interaction of the three populations with the control effect is interpreted in the compartment model shown in Figure 1. The number of mosquito populations that were successfully controlled with u_1 was expressed as $u_1 S_V$ and $u_1 I_V$. Individuals are susceptible to becoming infected with dengue due to contact with infected mosquitoes at high levels of infection λ_D , and if u_2 is applied by susceptible individuals, it means there will be $(1 - u_2)$ infected human by dengue fever so that the infection rate becomes $(1 - u_2)\lambda_D$, and then if u_2 is given to an individual infected with dengue fever, the rate of infecting mosquitoes will be $(1 - u_2)\lambda_V$. The number of infected individuals with typhoid and carriers that were successfully controlled with u_3 as $u_3 I_T$, $u_3 C$, and $u_3 I_{DC}$. The term $u_4 \lambda_B S_H$ and $u_4 \lambda_B I_D$ are the numbers of individuals who were success controlled by applying u_4 , so that $(1 - u_4)\lambda_B S_H$ and $(1 - u_4)\lambda_B I_D$ are the numbers of typhoid susceptible individuals who failed to control.

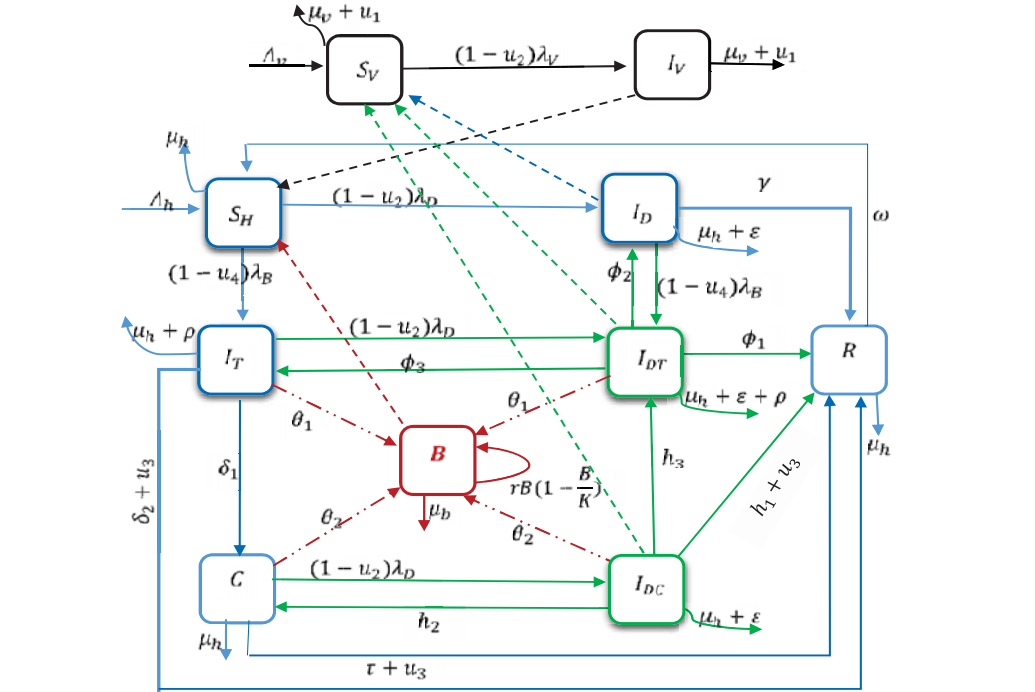


Figure 1. Compartmental diagram for co-infection model with control

Figure 1. can be written in terms of ten systems of differential equations.

$$\frac{dS_H}{dt} = \Lambda_h - (1 - u_2)\lambda_D S_H - (1 - u_4)\lambda_B S_H - \mu_h S_H + \omega R, \quad (6a)$$

$$\frac{dI_D}{dt} = (1 - u_2)\lambda_D S_H - (1 - u_4)\lambda_B I_D + \phi_2 I_{DT} - (\gamma + \mu_h + \varepsilon)I_D, \quad (6b)$$

$$\frac{dI_T}{dt} = (1 - u_4)\lambda_B S_H - (1 - u_2)\lambda_D I_T + \phi_3 I_{DT} - (\delta_2 + u_3)I_T - (\delta_1 + \mu_h + \rho)I_T, \quad (6c)$$

$$\frac{dC}{dt} = \delta_1 I_T - (\tau + u_3)C - (1 - u_2)\lambda_D C + h_2 I_{DC} - \mu_h C, \quad (6d)$$

$$\frac{dI_{DT}}{dt} = (1 - u_4)\lambda_B I_D + (1 - u_2)\lambda_D I_T + h_3 I_{DC} - (\phi_1 + \phi_2 + \phi_3 + \mu_h + \varepsilon + \rho)I_{DT}, \quad (6e)$$

$$\frac{dI_{DC}}{dt} = (1 - u_2)\lambda_D C - (h_1 + u_3)I_{DC} - (h_2 + h_3 + \mu_h + \varepsilon)I_{DC}, \quad (6f)$$

$$\frac{dR}{dt} = \gamma I_D + (\delta_2 + u_3)I_T + (\tau + u_3)C + \phi_1 I_{DT} + (h_1 + u_3)I_{DC} - (\mu_h + \omega)R, \quad (6g)$$

$$\frac{dS_V}{dt} = \Lambda_v - (1 - u_2)\lambda_v S_V - (\mu_v + u_1)S_V, \quad (6h)$$

$$\frac{dI_V}{dt} = (1 - u_2)\lambda_V S_V - (\mu_v + u_1)I_V, \quad (6i)$$

$$\frac{dB}{dt} = \theta_1(I_T + I_{DT}) + \theta_2(C + I_{DC}) + rB\left(1 - \frac{B}{K}\right) - \mu_b B, \quad (6j)$$

where $\lambda_V = \frac{\beta_V b}{N_H} (I_D + I_{DT} + I_{DC})$, $\lambda_D = \frac{\beta_H b I_V}{N_H}$, and $\lambda_B = \frac{B\sigma}{\kappa+B}$, with initial condition

$$S_H(0) = S_{H_0}, I_D(0) = I_{D_0}, I_T(0) = I_{T_0}, C(0) = C_0, I_{DT}(0) = I_{DT_0}, I_{DC}(0) = I_{DC_0}, R(0) = R_0, S_V(0) = S_{V_0}, I_V(0) = I_{V_0}, B(0) = B_0, \text{ and parameters and variables of the model is positive.} \quad (7)$$

Table 1. Description parameters of model

Variable	Description	Unit
$S_H(t)$	The number of susceptible individuals at time t	People
$I_D(t)$	The number of infected with dengue fever individuals at time t	People
$I_T(t)$	The number of infected with typhoid fever individuals at time t	People
$C(t)$	The number of carrier individuals at time t	People
$I_{DT}(t)$	The number of infected with both dengue fever and typhoid fever individuals at time t	People
$I_{DC}(t)$	The number of carrier infected dengue fever at time t	People
$R(t)$	The number of recovered individuals at time t	People
$N_H(t)$	Total human population at time t	People
$S_V(t)$	The number of susceptible mosquitoes at time t	Mosquito
$I_V(t)$	The number of infected mosquitoes at time t	Mosquito
$N_V(t)$	Total mosquito population at time t	Mosquito
$B(t)$	The number of bacteria population (salmonella) at time t	cells/ml
Parameter	Description	Unit
Dengue fever parameters		
Λ_h	Recruitment rate of humans (by birth or immigration)	people/day
Λ_v	Recruitment rate of mosquitoes	mosquito/day
μ_h	Natural death rate of humans	1/day
μ_v	Natural death rate of mosquitoes	1/day
b	Biting rate of mosquitoes	1/day
γ	Recovery rate of dengue fever infected individual	1/day
β_h	Probability of human getting infected per mosquito bite	-
β_v	probability of transmission from infected humans to susceptible mosquitoes per bite	-
ε	Dengue fever-induced death rate	1/day
Coinfection parameters		
ω	Rate of loss of natural immunity	1/day
ϕ_1	Recovery rate of co-infected individual	1/day
ϕ_2	Co-infected who recovered from typhoid fever only	1/day
ϕ_3	Co-infected who recovered from dengue fever only	1/day
h_1	Recovery rate of carrier infected dengue fever	1/day
h_2	Carrier infected dengue fever who recovered from dengue fever only	1/day
h_3	Rate of progression from carrier infected dengue fever to co-infected	1/day
Typhoid fever parameters		
ρ	Typhoid-induced death rate	1/day
δ_1	Rate of progression from infective to carriers	1/day
δ_2	Recovery rate of typhoid	1/day
τ	Recovery rate from carriers by natural immunity	1/day
μ_b	Bacteria mortality rate	1/day
θ_1	Bacteria excretion (infected)	cells/ml/people/day
θ_2	Bacteria excretion (carriers)	cells/ml/people/day
K	Carrying capacity	cells/ml/day

r	Per capita bacteria intrinsic growth rate (bacteria reproduction rate in environment)	1/day
σ	Rate of ingestion of typhoid causing bacteria	1/day
κ	Bacteria concentration in foods and water	cells/ml
Control variable	Description	Unit
$u_1(t)$	The proportion of mosquito population that fogging is applied to at time t	-
$u_2(t)$	The proportion of human population that mosquito repellent is applied to at time t	-
$u_3(t)$	The proportion of human population of infected with typhoid and carriers who apply complete treatment to at time t	-
$u_4(t)$	The proportion of human population of susceptible with typhoid that education on healthy living is applied to at time t	-

3. ANALYSIS OF OPTIMAL CONTROL

In this section, the optimal control of the dengue-typhoid fever co-infection model in (6a)-(6j) is studied. We assumed that the dynamics of state variable $X(t)$ can be controlled by a control variable $u(t)$. The aim of which is to minimize the number of the infected human population. Since we develop an algebraic model that describes the interaction between two common diseases, namely dengue and typhoid fevers, to intervene the system, we equip the model with four control variables. The first and second controls aim to control dengue fever disease and the other two controls to typhoid fever disease.

3.1. Optimal control problem

The optimum control problem is a problem of finding a control law $u_1(t)$, $u_2(t)$, $u_3(t)$, dan $u_4(t)$ among all admissible control which brings systems (6a)-(6j) from the initial state $X(0)$ on time $t = 0$ to a final state $X(T)$ on time $t = T$ satisfying the terminal conditions such that it optimize a objective functional. We make all control variables bounded, i.e.,

$$0 \leq u_i(t) \leq 1, \quad (8)$$

for $i = 1, 2, 3, 4$ for all $t \in [0, T]$ with T as the control period, we set $u_i(t) = 0$ as the lower bound and $u_i(t) = 1$ as the upper bound of the control effort since usually $u_i(t)$ represents a proportion. We denote by $\mathcal{U}$ the set of admissible controls is therefore defined as

$$\mathcal{U} = \{u | u_i(t) \text{ is Lebesgue measurable in } [0, T], u_i(t) \in [0, 1], t \in [0, T], i = 1, 2, 3, 4\}. \quad (9)$$

Our main control objective is to obtain the optimal levels of the controls and associated state variables that optimize the objective function. Thus, we formulate of the objective function by considering the performance given by

$$J(u) := \int_0^T (A_1 I_D + A_2 I_T + A_3 C + A_4 I_{DT} + A_5 I_{DC} + B_1 u_1^2 + B_2 u_2^2 + B_3 u_3^2 + B_4 u_4^2) dt, \quad (10)$$

where the coefficients $A_i (i = 1, 2, 3, 4, 5)$ and $B_i (i = 1, 2, 3, 4)$ are positive weights showing the relative importance of each term in (10). We assume that the control efforts are nonlinear in its condition, $B_i u_i^2$ (quadratic form). Efforts to control the disease by providing control certainly require costs. The coefficient B_i represents the cost weight in monetary units needed of each control variables, i.e., B_1 represents the cost weight needed to control the mosquito eradication, B_2 represents the cost weight

needed to control contact between human and mosquitoes the use of mosquito repellent, B_3 represents the cost weight is needed for treatment of individuals carrying and infected with typhoid, and B_4 states the cost weight needed for education on healthy living. Therefore, we are interested in finding an optimal control pair $u \in U$ that minimize the number of carriers, infectives, co-infection, and costs in objective function (10); we want to find u^* such that

$$J(u^*) = \min_{u \in U} J(u) \quad (11)$$

subject to the state system given by (6a)-(6j), initial conditions (7), bounded controls (8), and terminal times conditions $S_H(T)$, $I_D(T)$, $I_T(T)$, $C(T)$, $I_{DT}(T)$, $I_{DC}(T)$, $S_V(T)$, $I_V(T)$, $B(T)$ are all free.

(12)

3.2. Optimality conditions

We apply Pontryagin's maximum principle (Pontryagin 1986, Tu 1994) to determine necessary conditions that a pair of optimal controls and corresponding state variables must satisfy solving this principle requires a Hamiltonian function defined in (6a)-(6j) and (10) as follows:

$$H(X, u, p) = A_1 I_D + A_2 I_T + A_3 C + A_4 I_{DT} + A_5 I_{DC} + \sum_{i=1}^4 B_i u_i^2 + \sum_{i=1}^{10} p_i f_i, \quad (13)$$

where $p_i = p_i(t)$ for $i \in \{1, 2, \dots, 10\}$ are the adjoint functions and f_i are the right-hand side of the equations system given in (3a)-(3j). According to Pontryagin maximum principle, optimality condition for the control problem are given by the following set of requirements:

i. The dynamical systems obtained from $\dot{X}_i = \frac{\partial H}{\partial p_i}$ for $i \in \{1, 2, \dots, 10\}$,

$$X_i \in \{S_H, I_D, I_T, C, I_{DT}, I_{DC}, R, S_V, I_V, B\}, \quad (14)$$

ii. Optimal controls derived from $\frac{\partial H}{\partial u_i} = 0$ for $i \in \{1, 2, 3, 4\}$, (15)

iii. The adjoint systems obtained from $\dot{p}_i = -\frac{\partial H}{\partial X_i}$ for $i \in \{1, 2, \dots, 10\}$, $X_i \in \{S_H, I_D, I_T, C, I_{DT}, I_{DC}, R, S_V, I_V, B\}$. (16)

The first optimality condition (14) is systems (6a)-(6j) itself, which will produce the optimal state solutions S_H^* , I_D^* , I_T^* , C^* , I_{DT}^* , I_{DC}^* , R^* , S_V^* , I_V^* , and B^* . Furthermore, other two optimality condition (15) and (16) are stated in the following theorems.

Theorems 1. The optimal controls $u^* = \{u_1^*, u_2^*, u_3^*, u_4^*\}$ are given by

$$u_1^* = \min \left\{ 1, \max \left\{ 0, \frac{p_8 S_V + p_9 I_V}{2B_1} \right\} \right\} \quad (17)$$

$$u_2^* = \min \left\{ 1, \max \left\{ 0, \frac{(p_2 - p_1)\beta_h b I_V S_H + (p_6 - p_4)\beta_h b I_V C + (p_5 - p_3)\beta_h b I_V I_T + (p_9 - p_8)\beta_v b (I_D + I_{DT} + I_{DC}) S_V}{2B_2(S_H + I_D + I_T + C + I_{DT} + I_{DC} + R)} \right\} \right\} \quad (18)$$

$$u_3^* = \min \left\{ 1, \max \left\{ 0, \frac{(p_4 - p_7)C + (p_3 - p_7)I_T + (p_6 - p_7)I_{DC}}{2B_3} \right\} \right\} \quad (19)$$

$$u_4^* = \min \left\{ 1, \max \left\{ 0, \frac{(p_3 - p_1)\sigma B S_H - (p_5 - p_2)\sigma B I_D}{2B_4(\kappa + B)} \right\} \right\} \quad (20)$$

Proof. By applying $\frac{\partial H}{\partial u_i} = 0$ for $i \in \{1, 2, 3, 4\}$ at $u_i = u_i^*$, we have the following conditions:

For $i = 1$,

$$2B_1u_1 - p_8S_V - p_9I_V = 0 \Leftrightarrow u_1^* = \frac{p_8S_V + p_9I_V}{2B_1}. \quad (21)$$

For $i = 2$,

$$2B_2u_2 - \frac{\beta_h b I_V ((p_2 - p_1)S_H + (p_5 - p_3)I_T + (p_6 - p_4)C) + (p_9 - p_8)\beta_v b (I_D + I_{DT} + I_{DC})S_V}{(S_H + I_D + I_T + C + I_{DT} + I_{DC} + R)} = 0 \Leftrightarrow$$

$$u_2^* = \frac{(p_2 - p_1)\beta_h b I_V S_H + (p_6 - p_4)\beta_h b I_V C + (p_5 - p_3)\beta_h b I_V I_T + (p_9 - p_8)\beta_v b (I_D + I_{DT} + I_{DC})S_V}{2B_2(S_H + I_D + I_T + C + I_{DT} + I_{DC} + R)}. \quad (22)$$

For $i = 3$,

$$2B_3u_3 - (p_4 - p_7)C - (p_3 - p_7)I_T - (p_6 - p_7)I_{DC} = 0 \Leftrightarrow$$

$$u_3^* = \frac{(p_4 - p_7)C + (p_3 - p_7)I_T + (p_6 - p_7)I_{DC}}{2B_3}. \quad (23)$$

For $i = 4$,

$$2B_4u_4 - \frac{B\sigma((p_3 - p_1)\sigma BS_H - (p_5 - p_2)\sigma BI_D)}{\kappa + B} = 0 \Leftrightarrow u_4^* = \frac{(p_3 - p_1)\sigma BS_H - (p_5 - p_2)\sigma BI_D}{2B_4(\kappa + B)} \quad (24)$$

By considering bounded controls $0 \leq u_i(t) \leq 1, i = 1, 2, 3, 4, t \in [0, T]$ we may write in a concise notation as in (17)-(20). ■

Theorems 2. *There exists adjoint variables $p_i(t)$ for $i \in \{1, 2, \dots, 10\}$ satisfy the following differential equation system:*

$$\dot{p}_1 = p_1 \left(\frac{(1 - u_2)\beta_h b I_V}{N_H} - \frac{(1 - u_2)\beta_h b I_V S_H}{N_H^2} + \frac{(1 - u_4)B\sigma}{\kappa + B} + \mu_h \right) + p_2 \left(\frac{(1 - u_2)\beta_h b I_V}{N_H} - \frac{(1 - u_2)\beta_h b I_V S_H}{N_H^2} \right)$$

$$- p_3 \left(\frac{(1 - u_4)B\sigma}{\kappa + B} + \frac{(1 - u_2)\beta_h b I_V I_T}{N_H^2} \right) + (p_6 - p_4) \left(\frac{(1 - u_2)\beta_h b I_V C}{N_H^2} \right)$$

$$+ p_5 \left(\frac{(1 - u_2)\beta_h b I_V I_T}{N_H^2} \right) + (p_9 - p_8) \left(\frac{(1 - u_2)\beta_v b (I_D + I_{DT} + I_{DC})S_V}{N_H^2} \right) \quad (25)$$

$$\dot{p}_2 = -A_1 - p_1 \left(\frac{(1 - u_2)\beta_h b I_V S_H}{N_H^2} \right) + p_2 \left(\frac{(1 - u_2)\beta_h b I_V S_H}{N_H^2} + \frac{(1 - u_4)B\sigma}{\kappa + B} + \gamma + \mu_h + \varepsilon \right)$$

$$- p_3 \left(\frac{(1 - u_2)\beta_h b I_V I_T}{N_H^2} \right) + (p_6 - p_4) \left(\frac{(1 - u_2)\beta_h b I_V C}{N_H^2} \right)$$

$$+ p_5 \left(\frac{(1 - u_2)\beta_h b I_V I_T}{N_H^2} - \frac{(1 - u_4)B\sigma}{\kappa + B} \right) - \gamma p_7$$

$$+ (p_8 - p_9)S_V \left(\frac{(1 - u_2)\beta_v b}{N_H} - \frac{(1 - u_2)\beta_v b (I_D + I_{DT} + I_{DC})}{N_H^2} \right), \quad (26)$$

$$\dot{p}_3 = -A_2 + (p_2 - p_1) \left(\frac{(1 - u_2)\beta_h b I_V S_H}{N_H^2} \right)$$

$$+ p_3 \left(\frac{(1 - u_2)\beta_h b I_V}{N_H} - \frac{(1 - u_2)\beta_h b I_V I_T}{N_H^2} + \delta_2 + u_3 + \delta_1 + \mu_h + \rho \right)$$

$$\begin{aligned}
 & -p_4 \left(\delta_1 + \frac{(1-u_2)\beta_h b I_V C}{N_H^2} \right) + p_5 \left(\frac{(1-u_2)\beta_h b I_V I_T}{N_H^2} - \frac{(1-u_2)\beta_h b I_V}{N_H} \right) \\
 & + p_6 \left(\frac{(1-u_2)\beta_h b I_V C}{N_H^2} \right) - p_7 (\delta_2 + u_3) \\
 & + (p_9 - p_8) \left(\frac{(1-u_2)\beta_v b (I_D + I_{DT} + I_{DC}) S_V}{N_H^2} \right) - p_{10} \theta_1,
 \end{aligned} \tag{27}$$

$$\begin{aligned}
 \dot{p}_4 = & -A_3 + (p_2 - p_1) \left(\frac{(1-u_2)\beta_h b I_V S_H}{N_H^2} \right) + (p_5 - p_3) \left(\frac{(1-u_2)\beta_h b I_V I_T}{N_H^2} \right) \\
 & + p_4 \left(\tau + u_3 + \mu_h + \frac{(1-u_2)\beta_h b I_V}{N_H} - \frac{(1-u_2)\beta_h b I_V C}{N_H^2} \right) \\
 & + p_6 \left(\frac{(1-u_2)\beta_h b I_V C}{N_H^2} - \frac{(1-u_2)\beta_h b I_V}{N_H} \right) - p_7 (\tau + u_3) \\
 & + (p_9 - p_8) \left(\frac{(1-u_2)\beta_v b (I_D + I_{DT} + I_{DC}) S_V}{N_H^2} \right) - p_{10} \theta_2,
 \end{aligned} \tag{28}$$

$$\begin{aligned}
 \dot{p}_5 = & -A_4 - p_1 \left(\frac{(1-u_2)\beta_h b I_V S_H}{N_H^2} \right) + p_2 \left(\frac{(1-u_2)\beta_h b I_V S_H}{N_H^2} - \phi_2 \right) - p_3 \left(\frac{(1-u_2)\beta_h b I_V I_T}{N_H^2} + \phi_3 \right) \\
 & + (p_6 - p_4) \left(\frac{(1-u_2)\beta_h b I_V C}{N_H^2} \right) + p_5 \left(\frac{(1-u_2)\beta_h b I_V I_T}{N_H^2} + \phi_3 + \phi_2 + \phi_1 + \mu_h + \varepsilon + \rho \right) \\
 & - p_7 \phi_1 + (p_8 - p_9) S_V \left(\frac{(1-u_2)\beta_v b}{N_H} - \frac{(1-u_2)\beta_v b (I_D + I_{DT} + I_{DC})}{N_H^2} \right) \\
 & - p_{10} \theta_1,
 \end{aligned} \tag{29}$$

$$\begin{aligned}
 \dot{p}_6 = & -A_5 + (p_2 - p_1) \left(\frac{(1-u_2)\beta_h b I_V S_H}{N_H^2} \right) - p_3 \left(\frac{(1-u_2)\beta_h b I_V I_T}{N_H^2} \right) - p_4 \left(\frac{(1-u_2)\beta_h b I_V C}{N_H^2} + h_2 \right) \\
 & + p_5 \left(\frac{(1-u_2)\beta_h b I_V I_T}{N_H^2} - h_3 \right) + p_6 \left(\frac{(1-u_2)\beta_h b I_V C}{N_H^2} + h_3 + h_2 + h_1 + u_3 + \mu_h + \varepsilon \right) \\
 & - p_7 (h_1 + u_3) + (p_8 - p_9) S_V \left(\frac{(1-u_2)\beta_v b}{N_H} - \frac{(1-u_2)\beta_v b (I_D + I_{DT} + I_{DC})}{N_H^2} \right) \\
 & - p_{10} \theta_2,
 \end{aligned} \tag{30}$$

$$\begin{aligned}
 \dot{p}_7 = & -p_1 \left(\omega + \frac{(1-u_2)\beta_h b I_V S_H}{N_H^2} \right) + p_2 \left(\frac{(1-u_2)\beta_h b I_V S_H}{N_H^2} \right) + (p_5 - p_3) \left(\frac{(1-u_2)\beta_h b I_V I_T}{N_H^2} \right) + (p_6 \\
 & - p_4) \left(\frac{(1-u_2)\beta_h b I_V C}{N_H^2} \right) + p_7 (\mu_h + \omega) \\
 & + (p_9 - p_8) S_V \left(\frac{(1-u_2)\beta_v b (I_D + I_{DT} + I_{DC})}{N_H^2} \right)
 \end{aligned} \tag{31}$$

$$\dot{p}_8 = p_8 \left(\mu_v + u_1 + \frac{(1-u_2)\beta_v b (I_D + I_{DT} + I_{DC})}{N_H} \right) - p_9 \left(\frac{(1-u_2)\beta_v b (I_D + I_{DT} + I_{DC})}{N_H} \right) \tag{32}$$

$$\begin{aligned}
 \dot{p}_9 = & (p_1 - p_2) \left(\frac{(1-u_2)\beta_h b S_H}{N_H} \right) + (p_3 - p_5) \left(\frac{(1-u_2)\beta_h b I_T}{N_H} \right) + (p_4 - p_6) \left(\frac{(1-u_2)\beta_h b C}{N_H} \right) + p_9 (\mu_v \\
 & + u_1)
 \end{aligned} \tag{33}$$

$$\dot{p}_{10} = (p_1 - p_3) \left(\frac{(1-u_4)\sigma \kappa S_H}{(\kappa + B)^2} \right) + (p_2 - p_5) \left(\frac{(1-u_4)\sigma \kappa I_D}{(\kappa + B)^2} \right) - p_{10} \left(r - \frac{2rB}{K} - \mu_b \right) \tag{34}$$

$$\text{with transversality conditions, } p_i(T) = 0, \quad i \in \{1, 2, \dots, 10\}. \tag{35}$$

Proof. When applying conditions (16), recall that λ_V , λ_D , and λ_B is a function of all state variables as given in (4). Transversality conditions (35) emerge as we set that all state variables at all terminal times are free(12). ■

4. NUMERICAL SIMULATIONS

In this section, we perform a numerical simulation of the optimal control model. By controlling certainly subpopulations according to strategy, it will be seen how the costs and effects of control in each strategy on other subpopulations. Numerical solutions of the optimal control problem of dengue fever-typhoid co-infection model presented in Section 3. are obtained by forwardly solving the dynamical system (6a)-(6j) with initial conditions (7) and backwardly the adjoint system (25)-(34) with terminal time conditions (35) by using controls (17)-(20). So, we use the forward-backward sweep method (Lenhart & Workman 2007, Saleem *et. al.* 2014), and the fourth-order Runge–Kutta (Lenhart & Workman 2007) was implemented to achieve the optimal solutions. We proposed the following nine strategies for numerical simulation of the co-infection model:

1. Using mosquito eradication by insecticide effort for dengue fever and using treatment effort for typhoid ($u_1 \neq 0$; $u_3 \neq$; $u_2 = u_4 = 0$).
2. Using mosquito repellent efforts for dengue fever and using treatment effort for typhoid ($u_2 \neq 0$; $u_3 \neq$; $u_1 = u_4 = 0$).
3. Using mosquito eradication by insecticide efforts for dengue fever and using education on healthy living efforts for typhoid ($u_1 \neq 0$; $u_4 \neq$; $u_2 = u_3 = 0$).
4. Using mosquito repellent efforts for dengue fever and using education on healthy living efforts for typhoid ($u_2 \neq 0$; $u_4 \neq$; $u_1 = u_3 = 0$).
5. Using mosquito eradication by insecticide efforts for dengue fever and using both intervention efforts for typhoid ($u_1 \neq 0$; $u_3 \neq$; $u_4 \neq 0$; $u_2 = 0$).
6. Using mosquito repellent efforts for dengue fever and using both interventions efforts for typhoid ($u_2 \neq 0$; $u_3 \neq$; $u_4 \neq 0$; $u_1 = 0$).
7. Using both intervention efforts for dengue fever and using treatment effort for typhoid ($u_1 \neq 0$; $u_2 \neq$; $u_3 \neq 0$; $u_4 = 0$).
8. Using both interventions efforts for dengue fever and using education on healthy living efforts for typhoid ($u_1 \neq 0$; $u_2 \neq$; $u_4 \neq 0$; $u_3 = 0$).
9. Using all intervention efforts ($u_1 \neq 0$; $u_2 \neq$; $u_3 \neq 0$; $u_4 \neq 0$).

We consider a small community with a total humans population of 1000, vectors population of 700, and bacteria of 300. We assumed $B_1 = 1000$ and $B_2 = 100$ describes the cost of mosquito eradication by insecticide (u_1) that is more expensive than using mosquito repellents (u_2), and $B_3 = 1000$ and $B_4 = 100$ shows that the cost of treatment (u_3) is more expensive than the cost of education on healthy living (u_4). In additional, we also use following individual weight values $A_1 = A_2 = A_3 = A_4 = A_5 = 0.5$, and $T = 60$ days.

Table 2. Parameters and variables values of the co-infection model (6a)-(6j)

Parameter	Value	Reference	Parameter	Value	Reference
$S_H(0)$	870	-	h_1	0.8/14	*
$I_D(0)$	50	-	h_2	0.005/14	*
$I_T(0)$	20	-	h_3	0.195/14	*
$C(0)$	35	-	δ_1	0.04	Mutua <i>et. al.</i> (2015)
$I_{DT}(0)$	12	-	δ_2	0.0357	Mutua <i>et. al.</i> (2015)
$I_{DC}(0)$	13	-	τ	0.000315	Mutua <i>et. al.</i> (2015)
$R(0)$	0	-	μ_b	0.0345	Mutua <i>et. al.</i> (2015)
$S_V(0)$	500	-	θ_1	0.9	Mutua <i>et. al.</i> (2015)
$I_V(0)$	200	-	θ_2	0.8	Mutua <i>et. al.</i> (2015)
$B(0)$	300	-	K	1000	*
Λ_h	1	*	r	0.014	Mutua <i>et. al.</i> (2015)
Λ_v	700/30	**	σ	0.9	Tilahun <i>et. al.</i> (2017)
μ_h	1/(60x365)	Wu & Wong (2019)	κ	50000	Tilahun <i>et. al.</i> (2017)
μ_v	[0.05-0.082]; 1/30	Wu & Wong (2019)	ε	0.00000266	**
b	(0-0.5]; 0.5	Wu & Wong (2019)	ρ	0.05/365	**
γ	1/14	Wu & Wong (2019)	ω	1/(12x7)	**
β_h	(0-1); 0.3	Wu & Wong (2019)	Variable Value		
β_v	(0-1); 0.1	Wu & Wong (2019)	$u_1(t)$	[0,1]	
ϕ_1	0.8/14	*	$u_2(t)$	[0,1]	
ϕ_2	0.075/14	*	$u_3(t)$	[0,1]	
ϕ_3	0.125/14	*	$u_4(t)$	[0,1]	

* Hypothetical; ** Assumed

4.1. Control with mosquito eradication (u_1) and treatment for typhoid (u_3)

If these two interventions are applied concurrently then u_1 and u_3 controls were active at rate 0.33 and 0.2 respectively on the first day after that can be reduced to the end of the period to provide the optimal contribution are depicted in Figure 2(a). We observed in Figure 2(b) that the number of dengue fever infected individuals I_D was effectively controlled, in Figure 2(c) show a continuous rise in the number of typhoid infected individuals I_T cases although the significant difference between without control and controlled. The impact of Strategy 1 also is observed in Figure 2(d) that the number of carriers C was controlled significantly at first but began to increase slowly at the final time. Figure 2(e) and Figure 2(f) are also effectively controlled what shows the number of co-infected individuals I_{DT} and dengue fever infected carrier individuals I_{DC} are significantly reduced, meanwhile I_{DT} has reached zero on the 20th day.

4.2. Control with mosquito repellent (u_2) and treatment for typhoid (u_3)

The optimal controls of this strategy are depicted in Figure 3(a), we simulate the model using a combination of u_2 and u_3 controls are applied concurrently then u_2 and u_3 were active at rate 0.62 and 0.19 respectively on the first day after which it can be reduced until the end of the implementation of intervention period to provide the optimal contribution. Figure 3(b) show that the strategy is effectively putting the number of dengue fever infected individuals I_D under control only until the 35th day, but Figure 3(c), Figure 3(d), and Figure 3(f) are also effectively controlled, where the number of

carrier individuals C , co-infected individuals I_{DT} , and dengue fever infected carrier individuals I_{DC} is significantly reduced, although C start rising at the end period.

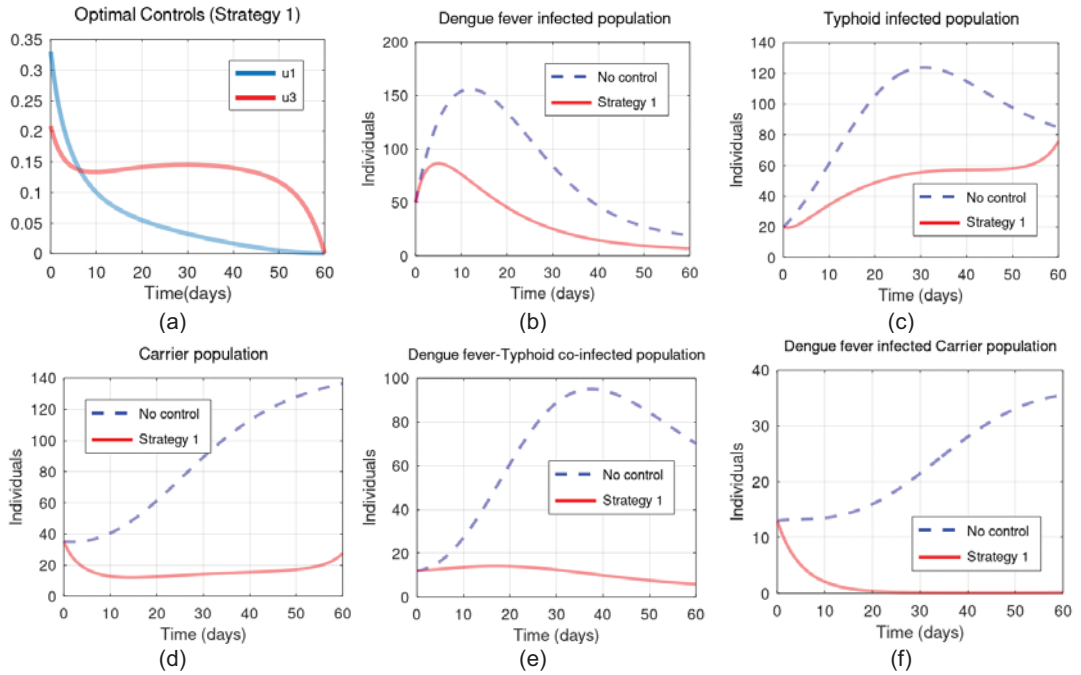


Figure 2. The dynamics of disease transmission and optimal control of Strategy 1

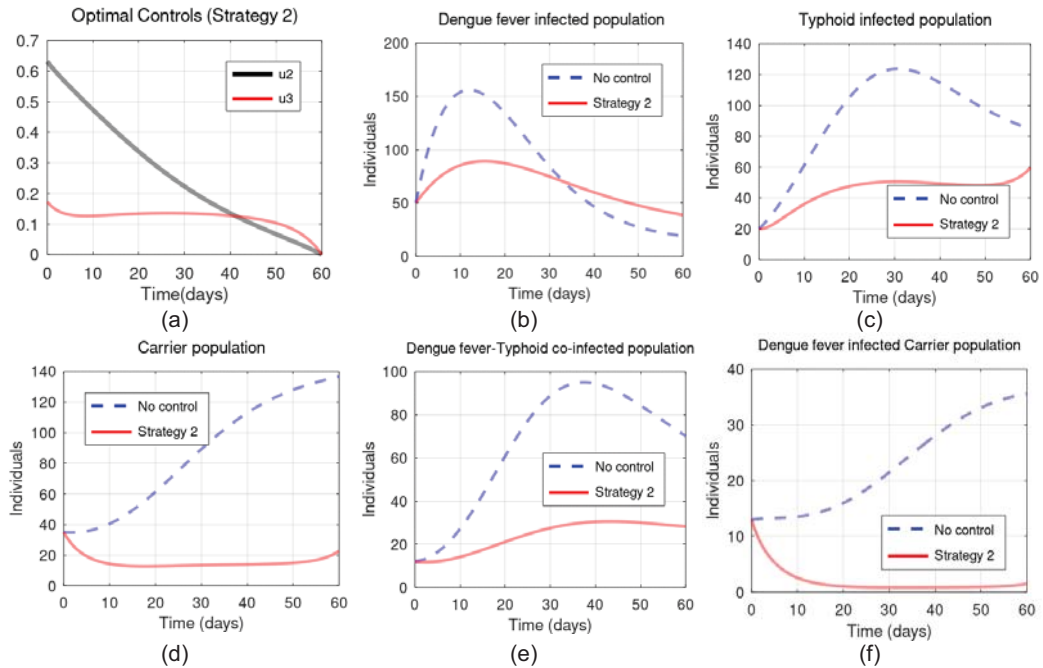


Figure 3. The dynamics of disease transmission and optimal control of Strategy 2

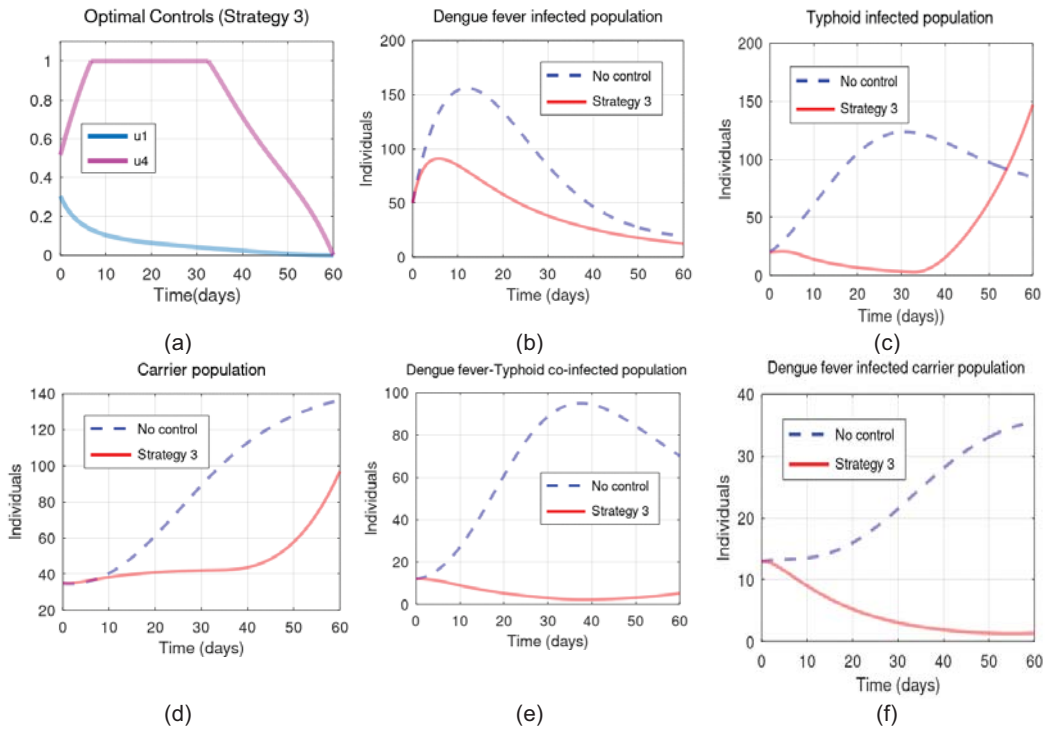


Figure 4. The dynamics of disease transmission and optimal control of Strategy 3

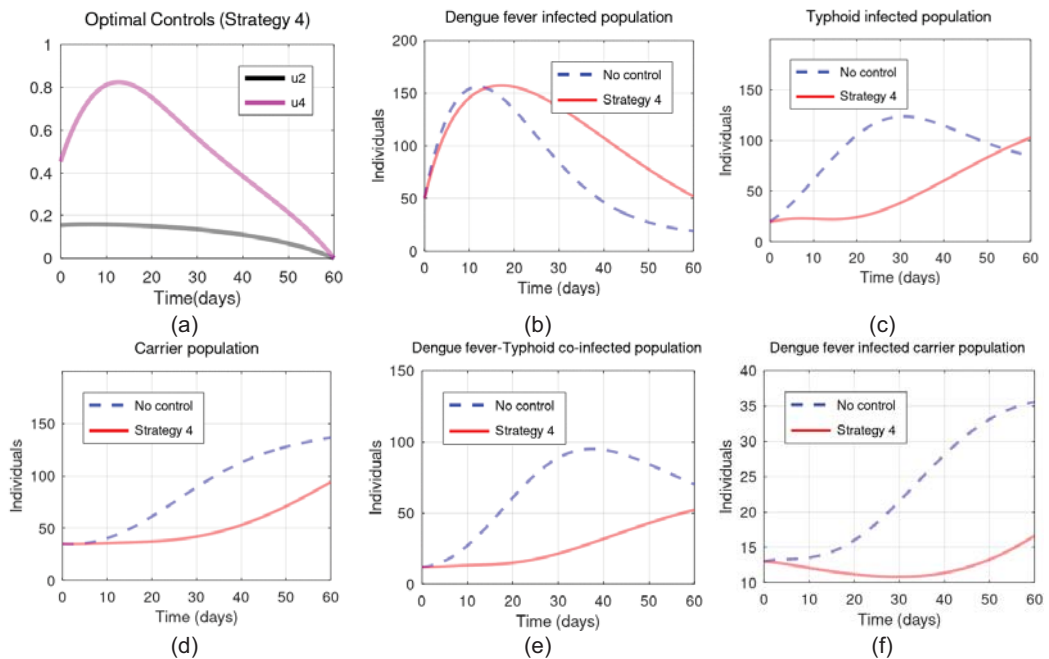


Figure 5. The dynamics of disease transmission and optimal control of Strategy 4

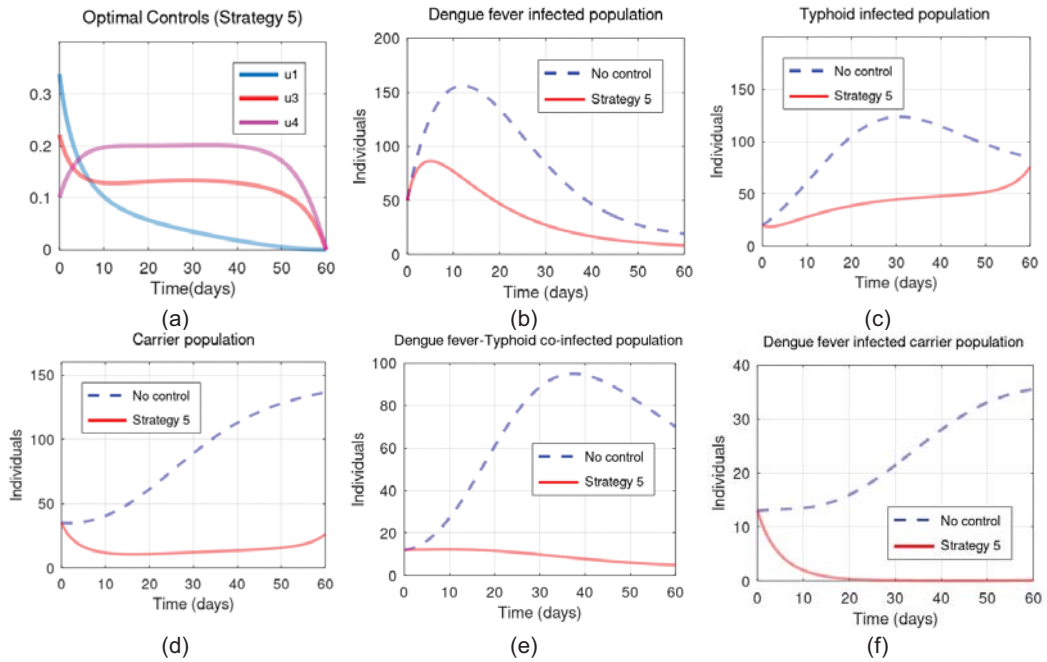


Figure 6. The dynamics of disease transmission and optimal control of Strategy 5

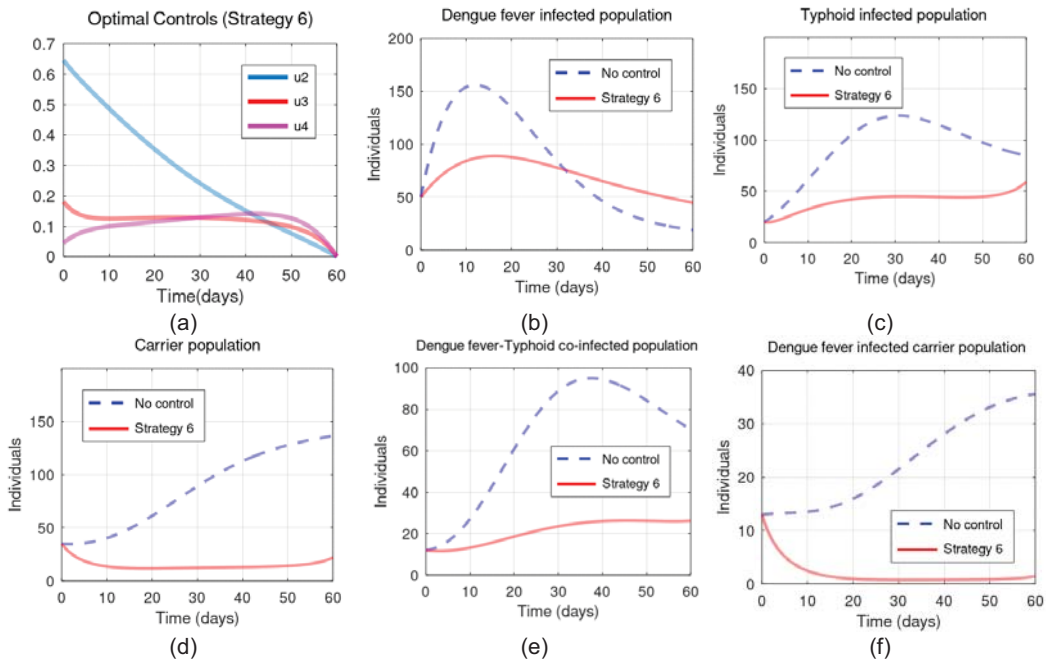


Figure 7. The dynamics of disease transmission and optimal control of Strategy 6

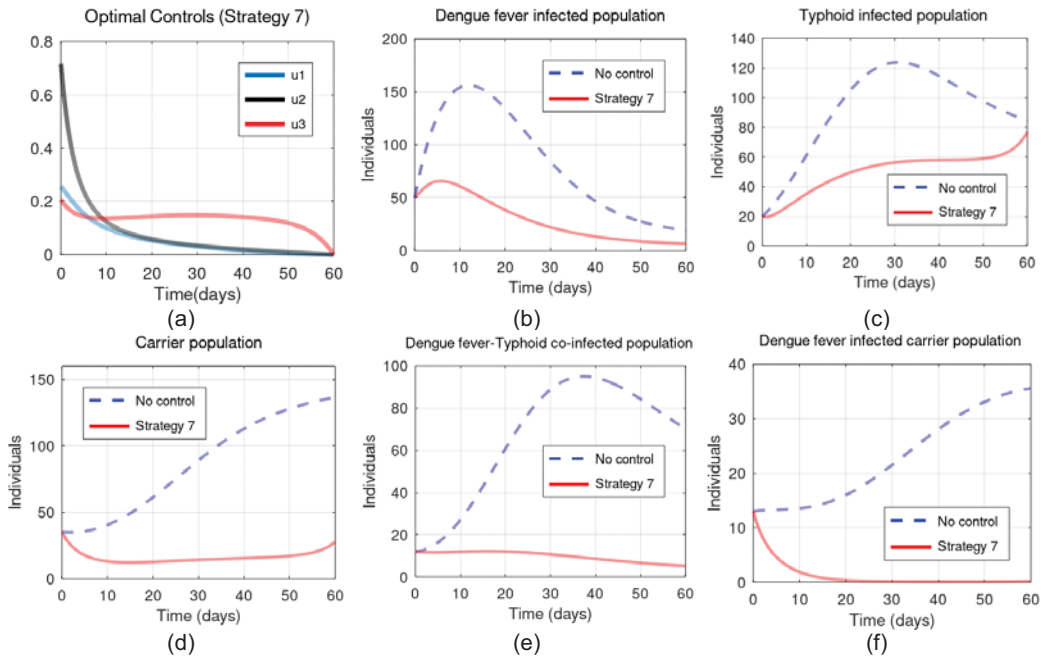


Figure 8. The dynamics of disease transmission and optimal control of Strategy 7

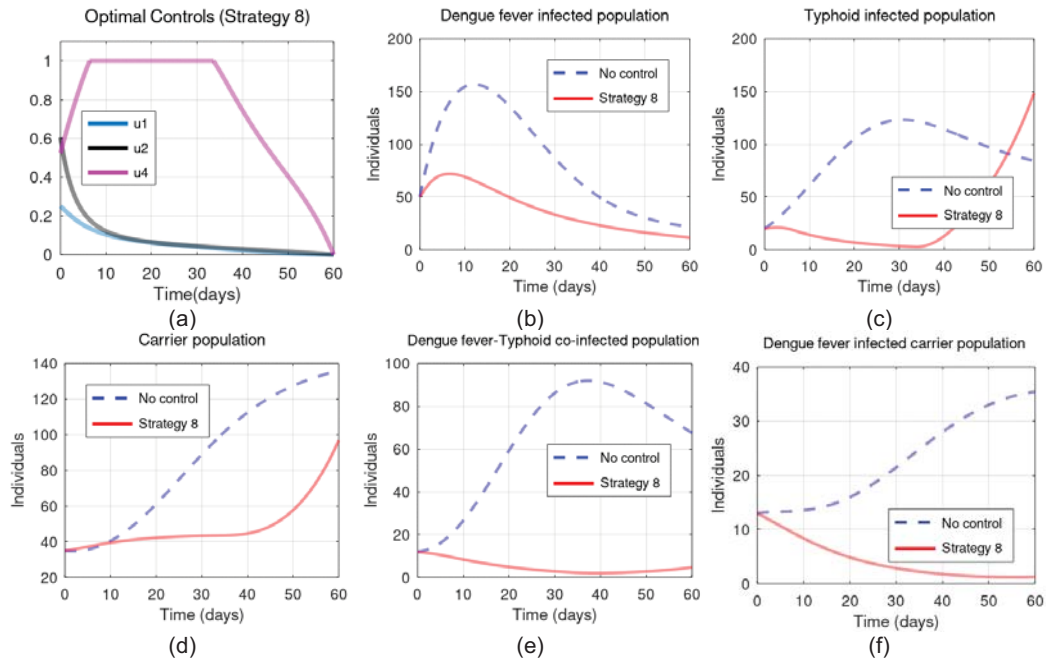


Figure 9. The dynamics of disease transmission and optimal control of Strategy 8

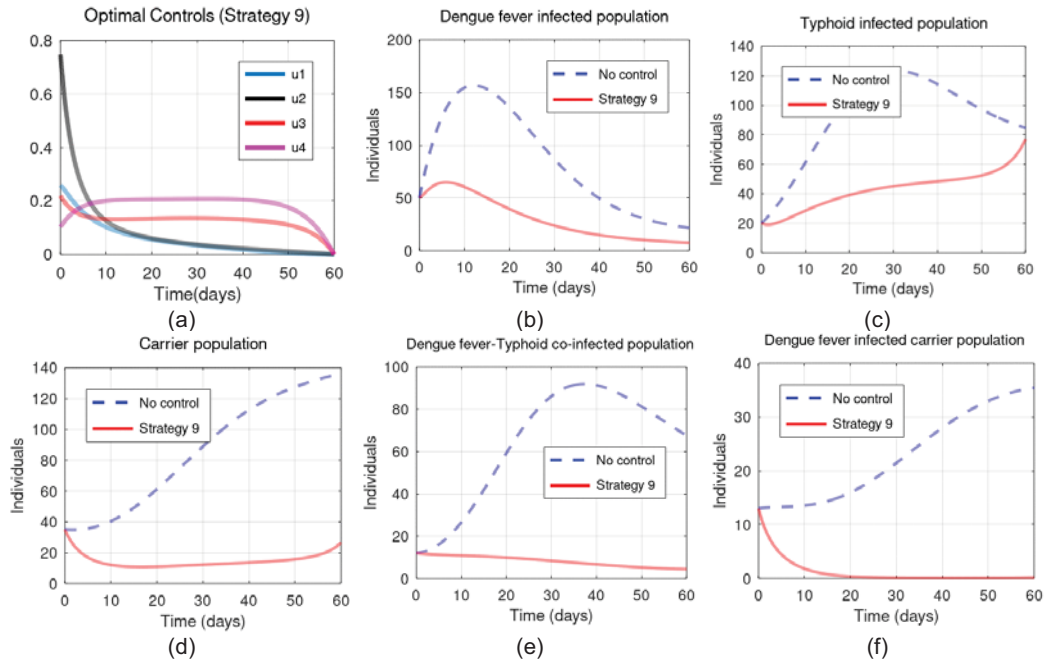


Figure 10. The dynamics of disease transmission and optimal control of Strategy 9

4.3. Control with mosquito eradication (u_1) and education on healthy living (u_4)

The optimal controls are depicted in Figure 4(a), we simulate the model using a combination of u_1 and u_4 controls are applied concurrently then to provide the optimal contribution, u_4 should be maximally applied, i.e., about the 8-32th days, meanwhile u_1 was active only during the first 50th days and it was active at rate 0.3 on the first day and then can be reduced. Figure 4(b) and Figure 4(f) clearly show that the number of dengue fever infected individuals I_D and dengue fever infected carrier individuals I_{DC} are effectively controlled. The number of typhoid infected individuals I_T is continuous reduced go to zero at 30th day then increased significantly until the end period and the number of carrier individuals C is continuous rise but slower than without control, shown in Figure 4(c) and Figure 4(d) respectively. Co-infected individuals I_{DT} shown in Figure 4(e) show significantly reduced although start rising slowly at the end period.

4.4. Control with mosquito repellent (u_2) and education on healthy living (u_4)

Figure 5(a) show that when these two interventions (u_2 and u_4) are applied concurrently then to provide the optimal contribution, u_2 should be applied at rate 0.19 on the first day then it can be reduced, meanwhile u_4 was active at rate 0.45 on the first day and then can be increased to the rate 0.8 before can then be significantly reduced to the end of the implementation of the intervention period. We observed in Figure 5(c), Figure 5(d), and Figure 5(e) a continuous rise in the number of typhoid infected individuals I_T , carrier individuals C , and co-infected individuals I_{DT} cases respectively, but the number of case lower than without control. The negative impact of this strategy is shown in Figure 5(b), where the controlled number of infected individuals I_D is greater than without control. The

number of dengue fever infected carrier individuals I_{DC} has gone to zero at the 30th day then start slowly rising until at final time, so far, the case is significantly reduced during the implementation of the intervention period, depicted in Figure 5(f).

4.5. Control with mosquito eradication (u_1) and using both interventions for typhoid (u_3 and u_4)

This strategy is a combination of three interventions, i.e. u_1 , u_3 , and u_4 which are applied concurrently. To provide the optimal contribution then u_1 and u_3 were active at rate 0.35 and 0.21 respectively on the first day and then can be reduced, u_1 was applied for less than 50th days, meanwhile, u_4 was active at rate 0.1 on the first day then it should be increased to the rate 0.2 on the day the 8-45th then it should be reduced again until the end period. It is depicted in Figure 6(a). We observed in Figure 6(b) that the number of dengue fever infected individuals I_D was effectively controlled, in Figure 6(c) show a continuous rise in the number of typhoid infected individuals I_T cases though the significant difference between without control and controlled. The impact of this strategy is also observed in Figure 6(d) that the number of carrier individuals C was initially controlled significantly but start to slowly rise again at the final time. Figure 6(e) and Figure 6(f) are also effectively controlled, where the number of co-infected individuals I_{DT} and dengue fever infected carrier individuals I_{DC} is significantly reduced, at 20th day I_{DT} becomes zero cases.

4.6. Control with mosquito repellent (u_2) and using both interventions for typhoid (u_3 and u_4)

The optimal controls of this strategy are depicted in Figure 7(a), we simulate the model using a combination of u_2 , u_3 , and u_4 controls are applied concurrently then u_2 and u_3 were active at rate 0.65 and 0.19 respectively on the first day after which it can be reduced to the end of the implementation of intervention period to provide the optimal contribution, meanwhile u_4 was active at rate tends to fluctuate, on the first day at rate 0.05. We observed in Figure 7(c), Figure 7(d), Figure 7(e), and Figure 5(f) effective controlled in the number of typhoid infected individuals I_T , carrier individuals C , co-infected individuals I_{DT} , and dengue fever infected carrier individuals I_{DC} cases respectively where the number of case lower than without control though especially a continuous slowly rise in the number of I_T . The negative impact of this strategy is shown in Figure 7(b) show little difference between the cases without control and the controlled case of the number of infected individuals I_D even the last 30th days is greater than without control.

4.7. Control with both interventions for dengue fever (u_1 and u_2) and treatment for typhoid (u_3)

When these three interventions are applied concurrently then u_1 , u_2 , and u_3 were active at rate 0.25, 0.7, and 0.2 respectively on the first day after which can be reduced to the end of the period to provide the optimal contribution are depicted in Figure 8(a). We observed in Figure 8(b), Figure 8(c), Figure 8(d), Figure 8(e), and Figure 8(f) show that the number of dengue fever infected individuals I_D , typhoid infected individuals I_T , carrier individuals C , co-infected individuals I_{DT} and dengue fever infected carrier individuals I_{DC} respectively were effectively controlled significantly difference between the cases without control and the controlled, though continuous rise especially in the number I_T .

4.8. Control with both interventions for dengue fever (u_1 and u_2) and education on healthy living for typhoid (u_4)

This strategy is a combination of three interventions, namely u_1 , u_2 , and u_4 what are applied concurrently. To provide the optimal contribution then u_1 and u_2 were active at rate 0.25 and 0.6 respectively on the first day and then can be reduced and applied for 50th days, meanwhile, u_4 was active at rate 0.55 on the first day then it should be increased to maximally applied during the longer time, i.e., 5-35th days and then reduced until the end period. It is depicted in Figure 9(a). We observed in Figure 9(b), and Figure 9(f) show that the number of dengue fever infected individuals I_D , and dengue fever infected carrier individuals I_{DC} were effectively controlled, goes to zero at the end of the intervention period. The number of typhoid infected individuals I_T and carrier individuals C shown in Figure 9(c) and Figure 9(d) respectively, show little significant difference between the cases without control and the controlled. While in Figure 9(f) the impact of this strategy in controlling the co-infected individuals I_{DT} yielded positive results because the number of I_{DT} significant decreases before start rising at the end period.

4.9. Control with all intervention (u_1 , u_2 , u_3 , and u_4)

When all interventions are applied shown in Figure 10(a), to provide the optimal contribution then u_1 , u_2 , and u_3 were active at rate 0.25, 0.75, and 0.2 respectively on the first day and then can be reduced, u_1 and u_2 were applied for less than 50th days, meanwhile, u_4 was active at rate 0.12 on the first day then it should be increased to the rate 0.8 on the day the 5-45th then it should be reduced again until the end period. The effectiveness of this strategy in controlling is seen in Figure 10(b)-10(f) clearly suggest that the number of cases of each I_D , I_T , C , I_{DT} , and I_{DC} are significantly reduced, though the I_T curve continuous slowly rise during of the intervention period.

According to Figure 2-10, the number of control measures applied does not get a significant difference. Meanwhile, efforts to control the disease by providing control certainly require costs, so choosing the best strategy needs to weigh the cost. To obtain information on the most cost-effective strategies, thus a cost-effectiveness analysis needs to be carried out which is described in Section 5.

5. COST-EFFECTIVENESS ANALYSIS

Cost-Effectiveness Analysis is an economic analysis to compare two or more health intervention options. By calculating the ratio of differences in costs and differences in outcomes between health intervention options. We aim to measure the cost-effectiveness of control the implementation of the control strategies implemented in the chapter (4) using the CEA method, a technique designed to help identify preferred options among possible alternatives (Bootman *et. al.* 1996). Using the CEA method, we calculated the value of ACER (Average Cost-Effectiveness Ratio) and ICER (Incremental Cost-Effectiveness Ratio). ICER is used to determine the number of added costs to generate each additional unit of benefit (Rascati 2014). ICER and ACER are calculated by the following formulae

$$\text{ICER} = \frac{\text{Incremental cost}}{\text{Incremental effectiveness (benefit)}} = \frac{\Delta C}{\Delta E} \quad (36)$$

$$\text{ACER} = \frac{\text{Total cost}}{\text{Total effectiveness (benefit)}} = \frac{C}{E}. \quad (37)$$

The ACER value is interpreted as the average cost use per unit of health benefit, implying that this calculation compares with no health intervention. The ACER value will complement the ICER calculation that the least effective intervention has the same ACER as its ICER, because it is compared with the alternative of 'doing nothing' (Philips 2009). To provide a single measure is the overall goal of CEA, the incremental cost-effectiveness ratio (ICER), what relates the amount of benefit derived by making an alternative health intervention choice to the difference in cost of those options (Smith & Roberts, 2010). The method used to calculate and interpret ICER depends on the number of strategies to be evaluated. Because of our study there are nine strategies, we required a method of calculating ICER that evaluated more than two strategies. We calculate ICER by considering the methods in Paulden (2020). In this work, the outcome is represented by the total health effects of each Strategy is used to determine the 'Total effectiveness (Benefit)' used are shown in Table 3. It is assumed that

$$E = \int_0^T (I_T + I_D + C + I_{DT} + I_{DC}) dt, \quad (38)$$

represents the total infected, co-infected, and carriers individuals during period $[0, T]$. The difference between E without control and E with controls of Strategy. The total control cost C_i of Strategy i during the control period $[0, T]$, we used cost function is given by

$$C_i(u) = \int_0^T \{B_1 u_1^2 + B_2 u_2^2 + B_3 u_3^2 + B_4 u_4^2\} dt, \quad (39)$$

where u_1, u_2, u_3 , and u_4 are optimal controls obtained by Strategy $i, i = 1, 2, \dots, 9$. Cost-effectiveness analysis measures cost in monetary terms and result in natural health units, indicating health improvements such as healing, saving lives, or reducing blood pressure. These results do not need to be convert to monetary values (Rascati 2014). The initial estimates of incremental values are reported in Table 3.

Tabel 3. The calculation of ACER and ICER

Strategy	Benefit (E)	Cost (C)	ACER	ΔE	ΔC	ICER	ΔE	ΔC	ICER
No control (0)	0	0	-	-	-	-	-	-	-
4	5932	1984	0.334457	D	D	D	D	D	D
2	11841	1482	0.125158	11841	1482	0.125158	ED	ED	ED
6	12129	1560	0.128617	D	D	D	D	D	D
3	13140	4348	0.330898	D	D	D	D	D	D
8	13594	4483	0.329778	D	D	D	D	D	D
1	14247	1493	0.104794	2406	11	0.004572	14247	1493	0.104794
7	14648	1580	0.107865	401	87	0.216958	ED	ED	ED
5	14802	1608	0.108634	154	28	0.181818	555	115	0.207207
9	15235	1704	0.111848	433	96	0.221709	433	96	0.221709

Incremental is denoted as Δ . ICER are not reported for dominated (D) strategies or extendedly dominated (ED)

However, calculating ICERs for more than two strategies requires a few steps. There are generally multiple ICERs to calculate, and there may be additional considerations to take into account such as *dominated* and *extendedly dominated* (Paulden 2020) by following the steps below

Step 1: Strategies are ranked in ascending order by the benefit shown in Table 3.

Step 2: Rule out any strategies that are dominated by one or more other strategies. The ranking in Table 3 shows that Strategy 4 contributed the least quantity of benefit, and Strategy 9 provided the most amount of effectiveness. Dominated strategies have either smaller benefits and higher or equal cost than at least one other strategies. Scanning down the benefit column of Table 3 identifies that Strategy 4 is dominated by Strategy 1,2,5,6,7,9, furthermore, Strategy 1 is dominated by Strategy 3, and then Strategy 8 is dominated by Strategy 1,5,7,9, and thus rule out.

Step 3: The next step is to calculate initial incremental values and rule out extendedly dominated strategies. There is no dominant strategy that provides the greatest benefit and least cost among the strategies, so we must calculate initial estimates of the incremental cost, incremental benefit, and ICERs between consecutive pairs of non-dominated strategies to find a cost-effective strategies. We calculate increment values between the following pairs of strategies to the first iteration, using (36) and (37) gives

$$ICER(2) = ACER(2) = \frac{1482}{11841} = 0.125158; \text{Strategy 2 vs No control,} \quad (40)$$

$$ICER(1) = \frac{1493 - 1482}{14247 - 11841} = 0.004572; \text{Strategy 1 vs Strategy 2,} \quad (41)$$

$$ICER(7) = \frac{1580 - 1493}{14648 - 14247} = 0.216958; \text{Strategy 7 vs Strategy 5,} \quad (42)$$

$$ICER(5) = \frac{1608 - 1580}{14802 - 14648} = 0.181818; \text{Strategy 5 vs Strategy 7,} \quad (43)$$

$$ICER(9) = \frac{1704 - 1608}{15235 - 14802} = 0.221709; \text{Strategy 9 vs Strategy 5,} \quad (44)$$

If a strategy has a higher ICER than a strategies that is non-dominated immediately below it, then that strategy is extendedly dominated. To identify extendedly dominated strategies, scanning down the ICER column in Table 3. Comparison of adjacent pairs between Strategy 2 and 1, between Strategy 7 and 5 reveals that Strategy 2 has a higher value of ICER than Strategy 1, and also Strategy 7 has a higher value of ICER than Strategy 5, thus is extendedly dominated by Strategy 1 and Strategy 5. Hence, strategies 2 and 7 are extendedly dominated and then ruled out.

Step 4: Next, recalculate incremental values. After ruling out strategies 2 and 7, Incremental values are required now between the following new adjacent pairs of non-dominated strategies in the second iteration:

$$ICER(1) = ACER(1) = \frac{1493}{14247} = 0.104794; \text{Strategy 1 vs No control,} \quad (45)$$

$$ICER(5) = \frac{1608 - 1493}{14802 - 14247} = 0.207207; \text{Strategy 5 vs Strategy 1,} \quad (46)$$

$$ICER(9) = \frac{1704 - 1608}{15235 - 14802} = 0.221709; \text{Strategy 9 vs Strategy 5,} \quad (47)$$

The recalculated incremental values are presented in Tabel 3. The new ICER column showed no additional strategy is extendedly dominated because the ICER (45), (46), and (47) consistently increases, so our ICER calculation is complete.

Based on the results of the calculations above, it provides information that strategies 1, 5, and 9 are the most cost-effective. This is very useful as an option that can be offered to policymakers rather than providing the single most cost-effective strategy. Strategy 1 is the cheapest with an additional cost of 0.104794 per one unit of additional benefit (ICER), strategy 5 has an ICER of 0.207207 per person that can be avoided from disease (benefits) compared to strategy 1, and strategy 9 is the most beneficial and has an ICER of 0.221709 per benefit compared to strategy 5.

4. DISCUSSION AND CONCLUSION

In controlling for both diseases, the strategy of combining dengue fever control measures with typhoid control is not always effective in reducing the infected, carrier, and co-infected population curves in a short time. The most effective combination of controls that provides the greatest benefit is the application of the four controls, namely fogging, the use of mosquito repellents (mosquito nets or mosquito repellent lotions), complete treatment control, and control of public health education simultaneously. However, the difference in the magnitude of the benefits provided is not significant when compared to only applying a combination of three controls (fogging, complete treatment, and public health education) or a combination of two controls (fogging and complete treatment).

The results of the cost-effectiveness analysis show that strategies 1, 5, and 9 are the most cost-effective strategies where strategy 1 is the cheapest because it has the smallest ICER. With a limited budget, the most cost-effective strategy depends on limited funds, namely:

- (1) If the available budget is less than 1608 (monetary unit), then strategy 1 is the most cost-effective; strategies 5 and 9 are the least economical;
- (2) If the available budget funds are at least 1608 and below 1704, then strategy 5 is the most cost-effective;
- (3) If the available budget is at least 1704 or greater, then strategy 9 is the most cost-effective.

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