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Modeling the Transmission Dynamics of Typhoid in Malaria Endemic Settings

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Abstract

Typhoid and malaria co-infection is a major public health problem in many developing countries. In this paper, a deterministic model for malaria and typhoid co-infection is proposed and analyzed. It has been established that the model exhibits a backward bifurcation phenomenon. Overall, the study reveals that a typhoid outbreak in malaria endemic settings may lead to higher cumulative cases of dually-infected individuals displaying clinical symptoms of both infections than singly-infected individuals displaying clinical symptoms of either malaria or typhoid.

Keywords: Typhoid; Malaria; Co-infection; Reproductive number; Numerical results

MSC (2010) No.: 92D30, 92D25

1. Introduction

Malaria and typhoid fever are among the most endemic diseases in the tropics [Uneke (2008)]. Both diseases have been associated with poverty and underdevelopment with significant morbidity and mortality. An association between malaria and typhoid fever was first described in the medical literature in the middle of the 19^{th} century, and was named typho-malarial fever by

the United States Army [Uneke (2008), Smith (1982)]. However, by the end of 19th century, laboratory tests had eliminated this theory as they found that it was either one thing or the other, or in rare instances, co-infection with both Salmonella typhi and the Plasmodium species. In the last two decades, this relationship between the two diseases has been substantiated by studies from Africa and India [Ammah et al. (1999)]

Malaria is a tropical disease of man caused by some species of plasmodium and characterized by fever, malaise and weakness. Malaria is the infectious disease that causes incidence estimates of 2 to 3 million deaths and 300 to 500 million clinical cases in the world [Eze et al. (2011)]. There are four species of Plasmodium that infect humans: *Plasmodium falciparum, Plasmodium vivax, Plasmodium malariae* and Plasmodium *ovale*. *Plasmodium falciparum* is the major human parasite responsible for high morbidity and mortality. Infection with *Plasmodium falciparum* is associated with developing fever, a high number of parasites in the blood and pathogenesis, including severe anaemia, body weight loss and cerebral malaria in humans [Niikura et al. (2008), Eze et al. (2011)].

Typhoid fever is also an infectious disease. It is caused by species of Salmonella. The species and strains of Salmonella that commonly cause typhoid fever in humans are *Salmonella paratyphi A, Salmonella paratyphi B, Salmonella paratyphi C* and *Salmonella paratyphi D* [WHO (2003)]. The different serotypes *of Salmonella* can coinfect an individual or cause infections differently. Like malaria fever, *Salmonella* infection is characterised by fever, weakness, anaemia, body weight loss, vomiting and sometimes diarrhoea [Samal and Sahu (1991)]. The detection of high antibody titre for Salmonella is not always indicative of current infection(s) [Eze et al. (2011)]. Therefore, stool and/or blood culture from the patients is/are confirmatory [WHO (2003)].

The co-infection of malaria parasite and *Salmonella* species is common, especially in the tropics where malaria is endemic. The common detection of high antibody titre of these Salmonella serotypes in malaria patients has made some people to believe that malaria infection can progress to typhoid or that malaria always co-infect with typhoid/paratyphoid in all patients. Hence, some people treat malaria and typhoid concurrently once they have high antibody titre for Salmonella serotypes, even without adequate laboratory diagnoses for malaria and vice versa [Eze et al. (2011)].

Mathematical models have become invaluable management tools for epidemiologists, both shedding light on the mechanisms underlying the observed dynamics as well as making quantitative predictions on the effectiveness of different control measures, (for example see Agarwal and Verma (2012), Kar and Mondal (2012), Mushayabasa et al. (2012), Naresh and Pandey (2012)). The literature and development of mathematical epidemiology is well documented and can be found in Brauer and Castillo-chavez (2000). Important results on the transmission dynamics of typhoid only have been revealed in the last decade, for instance see Gonzlez-Guzman (1989), Mushayabasa (2011), Laura et al. (2009), Mushayabasa et al. (2013a), Mushayabasa et al. (2013b), to mention a few. Similarly, investigating the transmission dynamics of malaria only has been an interesting area for a number of researchers recently, for instance see studies by Chitnis et al. (2006), Li (2011) and Oksun and Makinde (2011) to mention a few. Although, several mathematical models for either typhoid or malaria infection(s)

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only have been proposed recently, not much has been discussed on their co-infection using the aid of mathematical models.

In view of the above we propose a deterministic mathematical model to investigate the effects of typhoid outbreak in malaria endemic settings. In this study it is assumed that co-infected individuals displaying clinical symptoms of one disease may be treated either both infections or single infection. Further we assume that individuals successful treated of infection(s) recover with temporary immunity.

2. Model Formulation

In this Section, we wish to examine the impact of typhoid and malaria co-infection, but initially we will examine the transmission dynamics of typhoid and malaria separately.

2.1. Compartmental Model for the Transmission Dynamics of Typhoid Fever Only

In this section, we introduce a typhoid model incorporating typhoid treatment and typhoid carriers. The total population $N_t(\tau)$ is sub-divided into five classes namely; the susceptible class S_t (these are individuals who have not yet contracted the disease), the infectious class I_t (these are individuals who are displaying clinical symptoms of typhoid fever and are capable of passing on the infection), treated/recovered class R_t, and the chronic enteric carriers C_t (this comprises of individuals who sheds typhoid bacilli for more than 12 months after onset of acute illness. Although, there is a possibility of one to become a chronic enteric carrier with no history of clinical illness [CDC (2005)], in this study we assume that individuals who are chronic enteric carriers would have displayed clinical symptoms of typhoid before). Thus the total population N_t at time τ is given by

$$N_t(\tau) = S_t(\tau) + I_t(\tau) + C_t(\tau) + R_t(\tau).$$

We have considered direct transmission (short cycle) of the disease (direct person-to-person contact transmission of typhoid fever) only, although individuals can be infected indirectly through consumption, mainly of water and sometimes of food, that has been contaminated by sewage containing the excrement of people suffering from the disease. Since much less is known about the induction of acquired immunity during successful treatment of bacterial infections, including typhoid [Griffin et al. 2009], in this study we have assumed that individuals who recover from typhoid acquire temporary immunity which wanes out at rate θ_t. The model has the compartmental structure of the classical *SEIRS* epidemic model and is described by the following system of non-linear differential equations

$$\frac{dS_t}{d\tau} = \Pi - \beta_t(I_t + \eta C_t)S_t - \mu_t S_t + \theta_t R_t, \tag{2.1.1}$$

$$\frac{dI_t}{d\tau} = \beta_t(I_t + \eta C_t)S_t - (\kappa\alpha + \phi + \mu_t + \delta_t)I_t, \tag{2.1.2}$$

$$\frac{dC_t}{d\tau} = \kappa\alpha I_t - (\omega + \delta_t + \mu_t)C_t, \tag{2.1.3}$$

$$\frac{dR_t}{d\tau} = \omega C_t + \phi I_t - (\mu_t + \theta_t)R_t. \tag{2.1.4}$$

New recruits join the model at rate Π and they are assumed to be susceptible to typhoid, μ_t is the natural mortality rate, β_t denotes typhoid transmission rate, κ is the fraction of symptomatic typhoid patients who become carriers at rate α, ϕ is the treatment rate of symptomatic infectious individuals, ω is the treatment rate for the carriers, δ_t is the disease related mortality rate for individuals in class I_t and C_t. The modification factor $\eta(\eta > 0)$ captures the relative infectiousness of chronic enteric carrier relative to symptomatic individuals. If $0 < \eta < 1$, it implies that a symptomatic individual is highly likely to pass on the infection to a susceptible individuals compared to a chronic enteric carrier, $\eta = 1$ implies that both symptomatic individuals and chronic enteric carriers have equal chances of passing on the infection to the susceptible individuals, and $\eta > 1$ implies that chronic enteric carriers are more likely to pass on the infection compared to symptomatic individuals.

2.1.1. Feasible Region

Dynamics of equations ((2.1.1)-(2.1.4)) will be analyzed in the closed set

$$\Omega = \left\{ (S_t, I_t, C_t, R_t) \in \mathbb{R}_+^4 : N_t \le \frac{\Pi}{\mu_t} \right\}.$$

The set Ω is positively invariant and attracting. Hence, existence, uniqueness and continuation results for system ((2.1.1)-(2.1.4)) holds in this closed set.

2.1.2. Reproduction Number

System (1) has an infection-free equilibrium point (denoted by ε^0) given by

$$\varepsilon^0 \left\{ (S_t^0, I_t^0, C_t^0, R_t^0) = \left(\frac{\Pi}{\mu_t}, 0, 0, 0 \right) \right.$$

The reproductive number is defined as the spectral radius of an irreducible or primitive non-negative (next-generation matrix) [Diekmann et al. (1990)]. Biologically, the reproductive number captures the power of the disease to invade the population. Using the approach in van den Driessche and Watmough (2002), and adopting the matrix notations therein, the matrices for

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new infection terms F and the transfer terms V, evaluated at infection-free equilibrium point are given by

$$F = \begin{bmatrix} \frac{\beta_t \Pi}{\mu_t} & \frac{\beta_t \eta \Pi}{\mu_t} \\ 0 & 0 \end{bmatrix} \quad \text{and} \quad V = \begin{bmatrix} k_1 & 0 \\ -\kappa\alpha & k_2 \end{bmatrix},$$

with $k_1 = \kappa\alpha + \phi + \mu_t + \delta_t$ and $k_2 = \omega + \mu_t + \delta_t$. The reproductive number is given by the spectral radius (the dominant eigenvalue) of the matrix, FV^{-1} denoted by $\rho(FV^{-1})$. Thus, the reproductive number is

$$R_t = \rho(FV^{-1}) = \frac{\Pi\beta_t(\kappa\alpha\eta + k_2)}{\mu_t k_1 k_2}.$$

The following result follows from Theorem 2 in van den Driessche and Watmough (2002).

Theorem 2.1.

The infection-free equilibrium of system (1) is locally-asymptotically stable if $R_t \leq 1$, and unstable whenever $R_t > 1$.

2.1.3. Global Stability of the Typhoid Fever-Free Equilibrium

Theorem 2.2.

The infection-free equilibrium point ε^0 is globally-asymptotically stable in the feasible region Ω if $R_t \leq 1$.

Consider the following Lyapunov function

$$F = \frac{\beta_t(\kappa\alpha\eta + k_2)}{k_1 k_2} I_t + \frac{\beta_t \eta}{k_2} C_t.$$

Its Lyapunov derivative along the solutions to system (1) is

$$F' = \frac{\beta_t(\kappa\alpha\eta + k_2)}{k_1 k_2} I_t' + \frac{\beta_t \eta}{k_2} C_t'$$

$$= \beta_t(I_t + \eta C_t)\left(\frac{\Pi\beta_t(\kappa\alpha\eta + k_2)}{\mu_t k_1 k_2} S_t - 1\right)$$

$$\leq \beta_t(I_t+\eta C_t)\left(\frac{\Pi\beta_t(\kappa\alpha\eta+k_2)}{\mu_t k_1 k_2}-1\right)$$

$$=\beta_t(I_t+\eta C_t)(R_t-1).$$

Thus, $F'\leq 0$ if $R_t\leq 1$. Furthermore, $F'=0$ if and only if $I_t=C_t=R_t=0$ or $R_t=1$, and, $S_t=S_t^0$. Hence, F is a Lyapunov function on, Ω. Since Ω is invariant and attracting, it follows that the largest compact invariant set in $\{(S_t,I_t,C_t,R_t)\in\Omega: F'=0\}$ is the singleton $\{\varepsilon^0\}$. Using LaSalle's Invariance Principle [Lasalle (1976)] it follows that every solution to system (1), with initial conditions in Ω approaches ε^0 as $\tau\to\infty$. That is, $(I_t,C_t,R_t)\to(0,0,0)$ as $\tau\to\infty$ Substituting $I_t=C_t=R_t=0$ in system (1) gives ε^0 as $\tau\to\infty$. Thus, ε^0 is globally asymptotically stable in Ω whenever $R_t\leq 1$.

2.1.4. Existence and Stability of the Endemic Equilibrium

System (1) has an endemic equilibrium point given by $\varepsilon^*=(S_t^*,I_t^*,C_t^*,R^*)$, where

$$S_t^*=\frac{\mu}{\Pi R_t},\quad I_t^*=\frac{\Pi k_2(\mu_t+\theta_t)(R_t-1)}{\theta(\mu_t+\delta_t)(\mu_t\omega+\kappa\alpha+\mu_t+\delta_t)},$$

$$C_t^*=\frac{\Pi\kappa\alpha(\mu_t+\theta_t)(R_t-1)}{(\kappa\alpha\theta_t\omega+k_2(\mu_t k_1+\theta_t(\kappa\alpha+\mu_t+\delta_t)))R_t}, \tag{2.1.5}$$

$$R_t^*=\frac{\Pi(\kappa\alpha\omega+\phi k_2)(R_t-1)}{(\kappa\alpha\theta_t\omega+k_2(\mu_t k_1+\theta_t(\kappa\alpha+\mu_t+\delta_t)))R_t}.$$

Based on the results in equation (2.1.5) Theorem 2.3 is established.

Theorem 2.3.

The endemic equilibrium point ε^* exists if $R_t>1$.

In order to investigate the global stability of the endemic equilibrium using the geometrical approach in Li and Muldowney (1996), we rewrite system ((2.1.1)-(2.1.4)) as

$$\frac{dS_t}{d\tau}=\Pi-\beta_t(I_t+\eta C_t)S_t-\mu_t S_t+\theta_t(N_t-S_t-I_t-C_t), \tag{2.1.6}$$

$$\frac{dI_t}{d\tau}=\beta_t(I_t+\eta C_t)S_t-k_1 I_t, \tag{2.1.7}$$

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$$\frac{dC_t}{d\tau} = \kappa\alpha I_t - k_2 C_t. \tag{2.1.8}$$

Theorem 2.4.

Let $x \to f(x) \in \mathbb{R}^3_+$ be C^1 function (class of functions whose derivatives are continuous) for x in a simply connected domain $D \subset \mathbb{R}^3_+$, where

$$x = \begin{pmatrix} S_t \\ I_t \\ C_t \end{pmatrix} \quad \text{and} \quad f(x) = \begin{pmatrix} \Pi - \beta_t(I_t + \eta C_t)S_t - \mu_t S_t + \theta_t(N_t - S_t - I_t - C_t) \\ \beta_t(I_t + \eta C_t)S_t - k_1 I_t \\ \kappa\alpha I_t - k_2 C_t \end{pmatrix}.$$

Consider the system of differential equations $x' = f(x)$ subject to initial conditions $(S_t^0, I_t^0, C_t^0)^T = x_0$. Let $x(\tau, x_0)$ be a solution of the system. System ((2.1.6)-(2.1.8)) has a unique endemic equilibrium point ε^* in D and there exists a compact absorbing set $K \subset D$. It is further assumed that system (2) satisfies the Bendixson criterion [Li and Muldowney (1996)], that is robust under C^1 local perturbations of f at all non-equilibrium non-wandering points of the system. Let $x \to M(x)$ be a 3×3 matrix valued function that is C^1 for $x \in D$ and assume that $M^{-1}(x)$ exists and is continuous for $x \in K$ then the unique endemic equilibrium point ε^* is globally stable in D if

$$\bar{q}_2 = \limsup_{\tau\to\infty} \frac{1}{\tau}\int_0^\tau m(Q(x(s, x_0)))ds, \qquad Q = P_f P^{-1} + PJ^{[2]}P^{-1}. \tag{2.1.9}$$

The value of P_f is obtained by replacing each entry p_{ij} in P by its directional derivative in the direction of $f, \nabla p_{ij}^* f$ and $m(Q)$ in the Lozinskii measure of Q with respect to a vector norm $|\cdot|$ in $\mathbb{R}^3_+$, defined by [see Coppel (1965) for more information],

$$m(Q) = \lim_{h\to 0^+} \frac{|I - hA| - 1}{h}. \tag{2.1.10}$$

The Jacobian matrix of system ((2.1.3)-(2.1.5)) along (S_t, I_t, C_t) is given by

$$J = \begin{pmatrix} -\beta_t(I_t + \eta C_t) - (\theta_t + \mu_t) & -(\beta_t S_t + \theta_t) & -(\theta_t + \beta_t \eta S_t) \\ \beta_t(I_t + \eta C_t) & \beta_t S_t - k_1 & \beta_t \eta S_t \\ 0 & \kappa\alpha & -k_2 \end{pmatrix}.$$

The corresponding associated second additive compound matrix $J^{[2]}$ (for detailed discussion of compound matrices, their properties and their relations to differential equations we refer the readers to [Fiedler (1974)]), is given by

$$J^{[2]}=\begin{pmatrix} \beta_t(S_t-(I_t+\eta C_t))-(\theta_t+\mu_t+k_1) & \beta_t\eta S_t & \theta_t+\beta_t\eta S_t \\ \kappa\alpha & -\beta_t(I_t+\eta C_t)-(\theta_t+\mu_t+k_2) & -(\beta_t\eta S_t+\theta_t) \\ 0 & \beta_t(I_t+\eta C_t) & \beta_t S_t-(k_1+k_2) \end{pmatrix}.$$

Set $P(x)=P(S_t,I_t,C_t)$ as $P(x)=diag\left\{1,\frac{I_t}{C_t},\frac{I_t}{C_t}\right\}$.

Then,

$$P_f P^{-1}=diag\left\{0,\frac{I_t^{'}}{I_t}-\frac{C_t^{'}}{C_t},\frac{I_t^{'}}{I_t}-\frac{C_t^{'}}{C_t}\right\}.$$

Thus, $Q=P_f P^{-1}+PJ^{[2]}P^{-1}$ can be presented in the block form

$$Q=\begin{pmatrix} Q_{11} & Q_{12} \\ Q_{21} & Q_{22} \end{pmatrix},$$

where

$$Q_{11}=\beta_t(S_t-(I_t+\eta C_t))-(\theta_t+\mu_t+k_1),\qquad Q_{12}=\begin{pmatrix} \frac{\beta_t\eta S_t C_t}{I_t} & \frac{\beta_t\eta S_t C_t}{I_t}+\theta\frac{C_t}{I_t} \end{pmatrix},$$

$$Q_{21}=\begin{pmatrix} \frac{\kappa\alpha I_t}{C_t} \\ 0 \end{pmatrix},\qquad Q_{22}=\begin{pmatrix} -\beta_t(I_t+\eta C_t)-(\theta_t+\mu_t+k_2)+\frac{I_t^{'}}{I_t}-\frac{C_t^{'}}{C_t} & -(\beta_t S_t+\theta_t) \\ \beta_t(I_t+\eta C_t) & \beta_t S_t-(k_1+k_2)+\frac{I_t^{'}}{I_t}-\frac{C_t^{'}}{C_t} \end{pmatrix}.$$

Let (x,y,z) be a vector in $\mathbb{R}^3_+$ as $|(x,y,z)|=\max\{|x|,|y|+|z|\}$. For any vector $(x,y,z)\in\mathbb{R}^3_+$, let m denote the Lozinskii measure with respect to this norm. We can then obtain

$$m(Q)\le\sup\{g_1,g_2\}\ , \tag{2.1.11}$$

where, $g_1=m_1(Q_{11})+|Q_{12}|,\quad g_2=|Q_{21}|+m_1(Q_{22})$.

Therefore,

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$$g_2 = -2\mu_t - \omega - \delta_t - \theta_t + \frac{I_t^{'}}{I_t} - \frac{C_t^{'}}{C_t} + \kappa\alpha\frac{I_t}{C_t}. \tag{2.1.12}$$

Using the identity

$$\frac{C_t^{'}}{C_t} = \kappa\alpha\frac{I_t}{C_t} - (\omega + \delta_t + \mu_t), \tag{2.1.13}$$

it follows that

$$g_2 = \frac{I_t^{'}}{I_t} - (\mu_t + \theta_t). \tag{2.1.14}$$

For g_1 we have

$$g_1 = -2\mu_t - (\kappa\alpha + \phi + \delta_t + \theta_t) - \beta_t(I_t + \eta C_t) + \beta_t S_t + \frac{\beta_t \eta S_t C_t}{I_t}.$$

Using the identity

$$\beta_t S_t + \frac{\beta_t \eta S_t C_t}{I_t} = \frac{I_t^{'}}{I_t} + (\kappa\alpha + \phi + \mu_t + \delta_t), \tag{2.1.15}$$

it follows that

$$g_1 = \frac{I_t^{'}}{I_t} - (\mu_t + \theta_t) - \beta_t(I_t + \eta C_t)$$

$$\leq \frac{I_t^{'}}{I_t} - (\mu_t + \theta_t). \tag{2.1.16}$$

Hence,

$$\sup\{g_1(t), g_2(t)\} \leq \frac{I_t^{'}}{I_t} - (\mu_t + \theta_t).$$

Thus,

$$\int_0^{\sigma} \sup\{g_1(\tau), g_2(\tau)\}\, d\tau \leq \log I_t\,|_0^{\sigma} - (\mu + \theta_t) = -\frac{1}{2}(\mu_t + \theta_t)\sigma < 0. \tag{2.1.17}$$

Results in equation (2.1.17) shows that $\bar{q}_2 < 0,$ which shows that the endemic equilibrium (ε^*) exists and is globally asymptotically stable if $R_t > 1.$

2.2. Compartmental Model for the Transmission Dynamics of Malaria Only

In this section, we adopt a mathematical model for the transmission dynamics of malaria proposed by Jia (2011). To account for the transmission dynamics between humans and the vector, the vector population is subdivided into classes of the susceptible S_v, exposed E_v, and infective I_v, so that the total vector population is given by $N_v = S_v + E_v + I_v$. Since the life span of mosquitoes is shorter than their infective period, it has been assumed that there are no recovered mosquitoes in the model. Further, the human population consists of the following classes: the susceptible S_h, the exposed E_h, the infectious I_h, and the treated/recovered R_h. Thus, the total human population at time τ is given by

$$N_h = S_h + E_h + I_h + R_h. \tag{2.2.1}$$

The transmission dynamics of malaria among humans is given the following system of differential equations ((2.2.2)-(2.2.5))

$$\frac{dS_h}{d\tau} = \Lambda_h - \frac{\beta_v r I_v S_h}{N_h} - \mu_h S_h + \theta R_h, \tag{2.2.2}$$

$$\frac{dE_h}{d\tau} = \frac{\beta_v r I_v S_h}{N_h} - (\gamma_h + \mu_h) E_h, \tag{2.2.3}$$

$$\frac{dI_h}{d\tau} = \gamma_h E_h - (\mu_h + \delta_h + \eta_h) I_h, \tag{2.2.4}$$

$$\frac{dR_h}{d\tau} = \eta_h I_h - (\mu_h + \theta_h) R_h. \tag{2.2.5}$$

The dynamics of malaria among the vector population is described by the model in system ((2.2.6)-(2.2.8))

$$\frac{dS_v}{d\tau} = \Lambda_v - \frac{\beta_h r I_h S_v}{N_v} - \mu_v S_v, \tag{2.2.6}$$

$$\frac{dE_v}{d\tau} = \frac{\beta_v r I_h S_v}{N_v} - (\gamma_v + \mu_v) E_v, \tag{2.2.7}$$

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$$\frac{dI_v}{d\tau} = \gamma_v E_v - \mu_v I_h, \tag{2.2.8}$$

where Λ_h and Λ_v are input flows of the susceptible humans and mosquitoes including births, μ_h and δ_h are natural and disease-induced death rates for humans, respectively; β_v is the transmission probability to a human per infected bite, r is the number of bites on a human by an individual mosquito per unit time, η_h is the recovery of humans, θ_h is the rate of loss of immunity for recovered humans, β_h is the transmission probability per bite to a susceptible mosquito from an infective human, γ_h is the developing rate of exposed humans becoming infectious, γ_v is the rate at which incubating mosquitoes become infectious, μ_v is the natural death rate of the mosquitoes.

2.2.1. Analytical Results

Comprehensive analytical results for the malaria model are presented in Jia (2011), hence we will not repeat the computations involved in establishing these results. For more information we refer the reader to Jia (2011). According to Jia (2011) the reproductive number for system ((2.2.2)-(2.2.5)) and ((2.2.6)-(2.2.8)) is

$$R_M = \frac{r}{\mu_v}\sqrt{\frac{\Lambda_v \beta_h \beta_v \gamma_h \gamma_v \mu_v}{\Lambda_h(\mu_h+\gamma_h)(\mu_h+\delta_h+\eta_h)(\mu_v+\gamma_v)}}. \tag{2.3.9}$$

3. Co-Infection Model

The total human population at time τ, denoted by N is subdivided into mutually-exclusive compartments, namely: the susceptible S, individuals exposed to malaria only E_m, infectious individuals singly infected with malaria I_m, infectious individuals singly-infected with typhoid I_t, singly-infected typhoid carriers C, infectious typhoid patients exposed to malaria H_1, individuals dually infected with typhoid and malaria and display clinical symptoms of both diseases I_{mt}, typhoid carriers exposed to malaria H_2, dually-infected typhoid carriers who display clinical symptoms of malaria only H_3 and the recovery population R. Thus,

$$N = S + E_m + I_m + I_t + C + I_{mt} + H_1 + H_2 + H_3 + R. \tag{3.1}$$

The vector population is subdivided into classes of the susceptible S_v, exposed E_v, and infective I_v, so that the total vector population is given by

$$N_v = S_v + E_v + I_v. \tag{3.2}$$

Susceptible individuals acquire typhoid infection at rate λ_t given by

$$\lambda_t = \beta_t(I_t + H_1 + \eta(C + H_2) + \eta_1(I_{mt} + H_3)), \tag{3.3}$$

where β_t denotes typhoid transmission rate, $\eta > 0$ accounts for the assumed unequal typhoid transmission probability between symptomatic typhoid individuals in classes I_t , H_1 compared to typhoid carriers in class C and H_1, $\eta_1 > 1$accounts for the assumed increase in infectiousness for dually infected individuals in class I_{mt} and H_3 compared to singly-infected individuals. Susceptible individuals are infected with malaria at rate λ_v given by

$$\lambda_v = \frac{\beta_v r I_v}{N}. \tag{3.4}$$

In (3.3) β_v represents the transmission probability to a human per infected bite and, r , denotes the number of bites on a human by an individual mosquito per unit time. The population of susceptible individuals diminishes due to natural mortality at rate μ . It is increased by the recruitment of individuals (assumed susceptible) into the population at rate Λ_h and the transfer of recovery individuals (at rate θ) due to waning of temporary immunity acquired after successful treatment. Putting all these gives the following equation for the rate of change of the susceptible population

$$\frac{dS}{d\tau} = \Lambda_h - (\lambda_t + \lambda_m)S - \mu S + \theta R. \tag{3.5}$$

The population of individuals exposed to malaria is generated following the infection of susceptible population at rate λ_m, and the recovery of a fraction *f*, of individuals in class H_1 who would have been treated typhoid infection only (at rate σ). It reduces due to natural mortality (at rate μ), progression of individuals from exposed to infectious (at rate γ_1), and infection by typhoid bacteria (at rate λ_t). Thus,

$$\frac{dE_m}{d\tau} = \lambda_m S = (\mu + \gamma_1 + \lambda_t)E_m + f\sigma H_1. \tag{3.6}$$

The population of infectious individuals singly infected with malaria is generated through progression of individuals exposed to malaria only (at rate γ_1). It diminishes due to natural mortality (at rate μ), treatment/recovery (at rate ϕ_1), malaria-induced mortality (at rate δ_m) and infection by typhoid bacteria (at rate λ_t). Thus,

$$\frac{dI_m}{d\tau} = \gamma_1 E_m - (\mu + \phi_1 + \delta_t + \lambda_t)I_m. \tag{3.7}$$

The population of infectious individuals singly infected with typhoid is generated by the infection of susceptible individuals in class *S* (at rate λ_t). It reduces due to natural mortality (at rate μ), typhoid-induced death (at rate δ_t), recovery/treatment (at rate ϕ_2), progression of a fraction κ into typhoid carriers (at rate γ_2), and infection by malaria (at rate λ_m). Thus,

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$$\frac{dI_t}{d\tau} = \lambda_t S - (\mu + \phi_2 + \delta_t + \kappa\gamma_2 + \lambda_m) I_t. \tag{3.8}$$

The population of individuals in class H_1 is generated through the infection of individuals exposed to malaria by typhoid (at rate λ_t), infection of symptomatic and singly-infected typhoid individuals by malaria (at rate λ_m). It diminishes due to natural mortality (at rate μ), transfer to I_{mt} class (at rate γ_3), typhoid induced death (at rate δ_t) and recovery/treatment (at rate σ). Since these individuals will be displaying clinical symptoms of typhoid only we assume that a fraction f of the infected individuals who will seek treatment might be treated typhoid only and the remainder (1- f) might have a chance to be treated both infections**.** If $f = 0$ it implies that these individuals would be treated typhoid infection only. Thus,

$$\frac{dH_1}{d\tau} = \lambda_t E_m + \lambda_m I_t - (\mu + \gamma_3 + \delta_t + \sigma) H_1. \tag{3.9}$$

The population of dually-infected individuals displaying clinical symptoms of both infections is generated by progression of individuals in class H_1 (at rate γ_3), and infection of individuals who display clinical symptoms of malaria only (I_m) by typhoid bacteria (at rate λ_t). It diminishes due to natural mortality (at rate μ), typhoid induced mortality (at rate δ_t), malaria related mortality (at rate δ_m). Although the signs and symptoms of malaria and typhoid fever do overlap, it was observed in Pakistan that subjects with dual infection had significantly higher rates of nausea, vomiting, abdominal pain, and diarrhea, all common presenting features of enteric fever [Prasanna (2011)]. Hence, we assume that dually-infected individuals displaying clinical symptoms of both diseases are treated (at rate ϕ_3). Thus,

$$\frac{dI_{mt}}{dt} = \lambda_t I_m - \gamma_3 H_1 - (\mu + \phi_3 + \delta_t + \delta_m) I_{mt}. \tag{3.10}$$

The population of singly-infected typhoid carriers (C) is generated through progression of a fraction κ of singly infected individuals displaying clinical symptoms of the disease into typhoid carriers (at rate γ_2) and recovery/treatment (at rate σ). Since individuals in class H_3 will be displaying clinical symptoms of malaria-only, we assume that a fraction f of the individuals who seek treatment might be treated malaria only and the remainder (1- f) might have a chance to be treated both infections. The population diminishes due to natural death (at rate μ), typhoid related mortality (at rate δ_t), infection by malaria (at rate λ_m), treatment/recovery (at rate ϕ_4). Thus,

$$\frac{dC}{d\tau} = \kappa\gamma_2 I_t + f\sigma H_3 - (\mu + \delta_t + \phi_4 + \lambda_m) C. \tag{3.11}$$

The population of typhoid carriers exposed to malaria H_2 is generated through malaria infection of singly-infected typhoid carriers (at rate λ_m). It diminishes due to natural death (at rate μ), typhoid related death (at rate δ_t), progression of a fraction p of untreated individuals to class H_3 (at rate γ_4), transfer of individuals successfully treated of both infections (at rate (1- p) γ_4). Thus,

$$\frac{dH_2}{d\tau} = \lambda_m C - (\mu + \delta_t + \gamma_4)H_2. \tag{3.12}$$

The population of typhoid carriers who display clinical symptoms of malaria is generated by the progression of dually-infected individuals from class H_2 (at rate $p\gamma_4$). It diminishes due to natural death (at rate μ), typhoid related death (at rate $\delta_{t)}$, malaria-induced mortality (at rate δ_m) and recover/treatment (at rate σ). Thus,

$$\frac{dH_3}{d\tau} = p\gamma H_2 - (\mu + \delta_t + \delta_m + \sigma)H_3. \tag{3.13}$$

The recovery population R, is generated by the treatment of individuals singly-infected displaying clinical symptoms of malaria only (at rate ϕ_1), treatment of individuals singly infected and displaying clinical symptoms of typhoid (at rate ϕ_2), treatment of dually-infected individuals displaying clinical symptoms of both infections (at rate ϕ_3), treatment/recovery of singly-infected typhoid carriers only (at rate ϕ_4), recovery/treatment of the fraction (1- f) of individuals in classes H_1 and H_3 (at rate σ). It diminishes due to natural death (at rate μ) and waning out of immunity (at rate θ) Thus,

$$\frac{dR}{d\tau} = \phi_1 I_m + \phi_2 I_t + \phi_3 I_{mt} + \phi_4 C + (1-p)\gamma_4 H_2 + \sigma(1-f)(H_1 + H_3) - (\mu + \theta)R. \tag{3.14}$$

Equations (3.5)-(3.14) summarize the transmission dynamics of typhoid and malaria among the human population. The following system of non-linear ordinary differential equations describes the vector population:

$$\frac{dS_v}{d\tau} = \Lambda_v - \frac{\beta_h r(I_m + I_{mt} + H_3)S_v}{N} - \mu_v S_v, \tag{3.15}$$

$$\frac{dE_v}{d\tau} = \frac{\beta_v r(I_m + I_{mt} + H_3)}{N} S_v - (\gamma_v + \mu_v)E_v, \tag{3.16}$$

$$\frac{dI_v}{d\tau} = \gamma_v E_v - \mu_v I_h. \tag{3.17}$$

In system (3.15)-(3.17), Λ_v denotes the input flows of the susceptible mosquitoes including births, β_h is the transmission probability per bite to a susceptible mosquito from an infective human, r is the number of bites on a human by an individual mosquito per unit time, γ_v is the rate at which incubating mosquitoes become infectious, μ_v is the natural death rate of the mosquitoes.

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Table 1. Model Parameters and their baseline values

Symbol	Units	Baseline value	Source
Λ_h, Λ_v	Per day	100,1000	Okosun and Makinde (2011)
μ, μ_v	Per day	0.00004, 0.1429	Okosun and Makinde (2011)
β_h, β_v	-	0.09 , 0.083	Okosun and Makinde (2011)
η, η_1	-	1.2, 2.5	Estimate
γ_1, γ_v	Per day	0.059, 0.055	Okosun and Makinde (2011)
$\gamma_2, \gamma_3, \gamma_4$	Per day	0.1, 0.1, 0.15	Estimate
r	Per day	50	Estimate
δ_m	Per day	0.05	Okosun and Makinde (2011)
δ_t	Per day	0.01	CDC (2005)
κ, p	-	0.03, 0.05	Bhan et al
β_t	Per day	0.01	Mushayabasa et al (2013a)
f	-	0.05	Estimated
θ	Per day	0.0013	Okosun and Makinde (2011)
σ	Per day	0.2	Estimate
$\phi_1, \phi_2, \phi_3, \phi_4$	Per day	0.25, 0.2, 0.15,0.1	Estimate

3.1. The Reproductive Number

Using the next generation method it can easily be deduced that the reproductive number of the co-infection model (system (11) and (12)) is given by

$$R_{TM} = \max\{R_T, R_M\}. \tag{3.18}$$

In (3.18) R_T and R_M are respectively given by

$$R_T = \frac{\Lambda_h \beta_t (\kappa\eta\gamma_2 + \mu + \delta_t + \phi_4)}{\mu(\kappa\gamma_2 + \mu + \phi_2 + \delta_t)(\mu + \delta_t + \phi_4)}, \tag{3.20}$$

$$R_M = \frac{r}{\mu_v}\sqrt{\frac{\Lambda_v \beta_h \beta_v \gamma_h \gamma_v \mu_v}{\Lambda_h(\mu_h + \gamma_h)(\mu_h + \delta_h + \eta_h)(\mu_v + \gamma_v)}}. \tag{3.21}$$

In equation (3.20) R_T represents the average number of new typhoid cases generated by typhoid infectious individual during his/her infectious period in malaria endemic settings and similarly in

equation (3.21) R_M measures the power of malaria infection to invade the population in the presence of typhoid disease.

3.2. Stability of the Co-Infection Model Steady States

Results from the analysis of single infections (typhoid-only and malaria-only) reveals that a typhoid model has globally stable steady states and the malaria-only model exhibits a backward bifurcation phenomenon (results adapted from Li (2011) and reference there in). Combining these results one can easily establish that the co-infection model may exhibit the phenomenon of backward bifurcation where multiple endemic equilibria co-exist with a disease-free equilibrium.

4. Numerical Results and Discussion

To support analytical results in this study, we performed numerical simulations of the co-infection model using the MATLAB ODE solver, ode45, and parameter values in Table 2.

Numerical results in Figures 1-4 depicts cumulative population levels for $R_{TM} > 1$. Figure 4.1 shows that in the presence of typhoid and malaria infections in the community, then in the long-run they will be a higher population of recovery individuals than the susceptible population. In Figure 4.2 depicts the dynamics of individuals exposed to malaria only and those exposed to typhoid but displaying clinical symptoms of typhoid. We observe that in the long-run cumulative infections in this case will be dominated by individuals exposed to malaria infection only. Figure 4.3 illustrated the dynamics of singly and dually infected, but displaying clinical symptoms of the infection(s). Results in Figure 4.3 suggests that, on the onset cumulative infections will be dominated by malaria cases only up to a period of 15 days, there after cumulative infections will be dominated by dual infections. Although, this arguably might be a small fraction its impact on disease prevalence cannot be ignored since these individuals will continue to transmit typhoid even though they are no longer displaying clinical symptoms of the disease. Figure 4.4 illustrates the dynamics of typhoid carriers, both singly and dually infected. We observe that from the onset cases of typhoid carriers exposed to malaria will be dominated to a period of 600 days, there after cases of individuals singly infected with typhoid will be dominant.

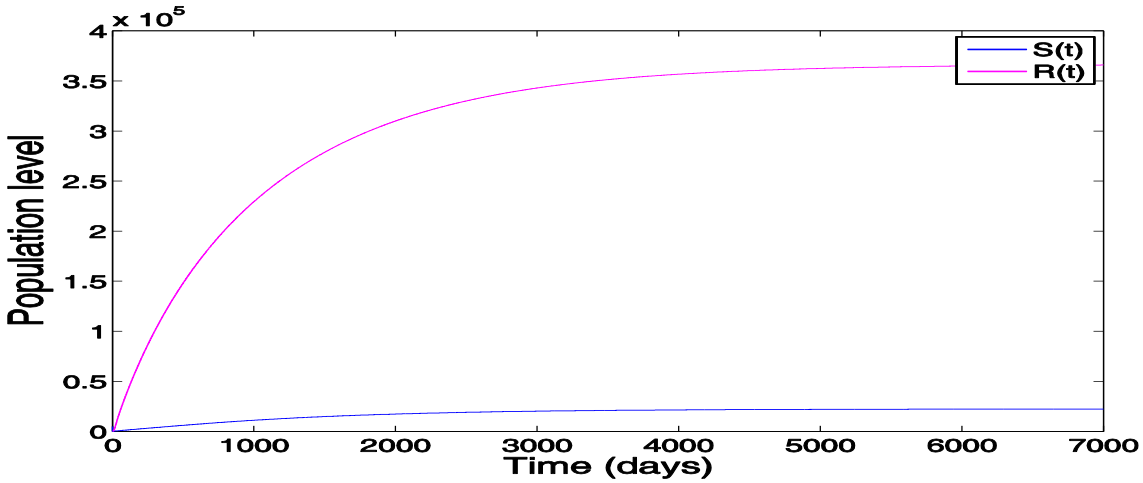

Figure 4.1. Numerical results of illustrating the dynamics of Equation (3.5) and (3.14)

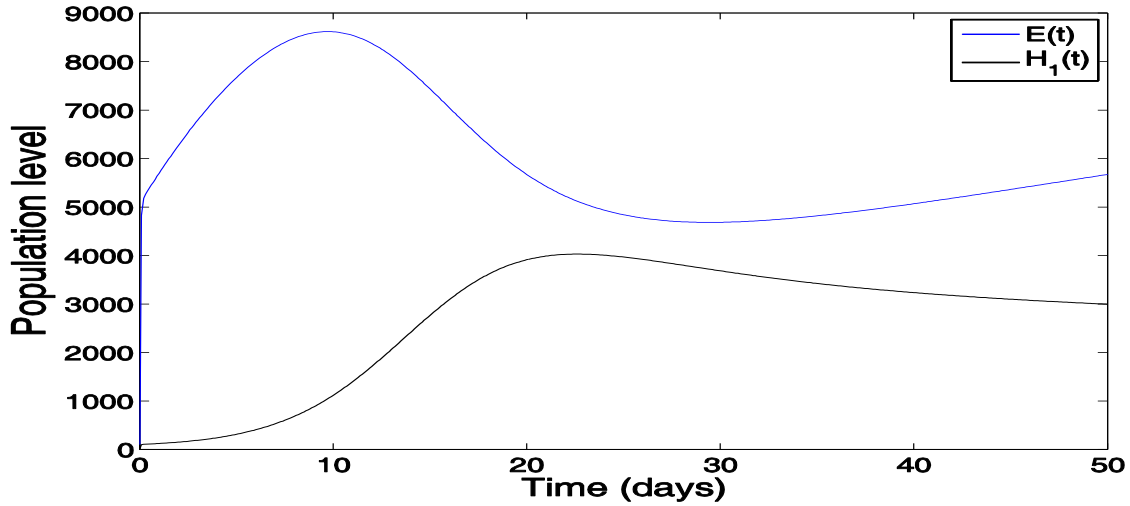

Figure 4.2. Simulations illustrating the dynamics individuals exposed to malaria infection only and individuals displaying clinical symptoms of typhoid but have been exposed to malaria

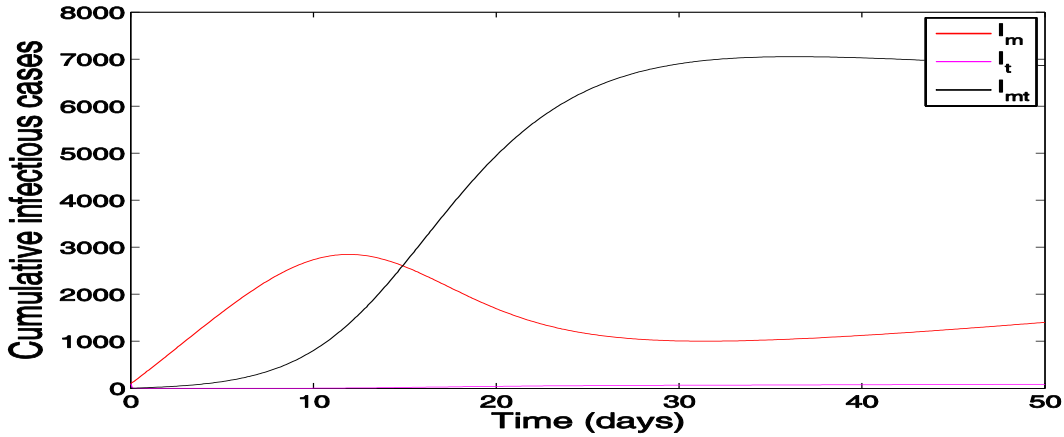

Figure 4.3. Simulations illustrating the dynamics of infected individuals displaying clinical symptoms of infection(s)

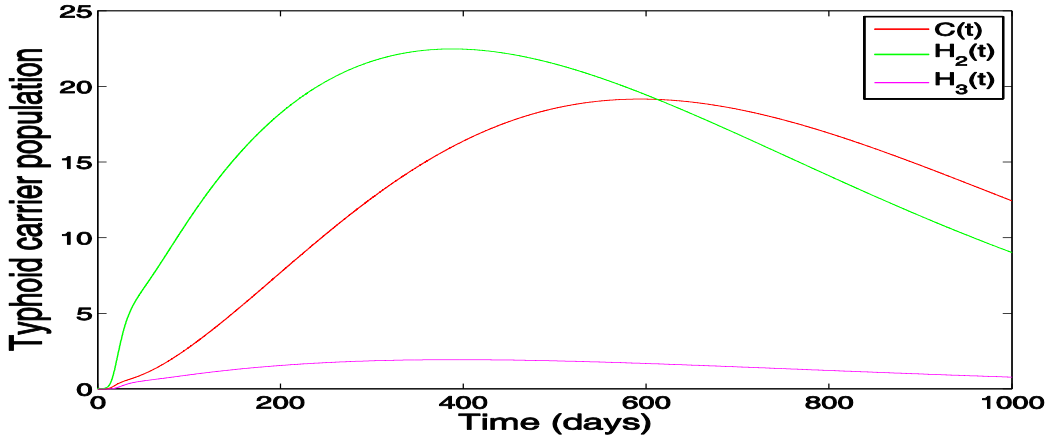

Figure 4. 4. Simulations showing the dynamics of the typhoid carrier population, both singly and dually infected

5. Concluding Remarks

A deterministic mathematical model for assessing the transmission dynamics of typhoid in malaria endemic settings has been proposed and analyzed. Initially, a sub-model for the transmission dynamics of typhoid-only has been developed and comprehensively discussed. Important results from the qualitative analysis of the typhoid sub-model suggest that, the model have globally stable equilibrium points, namely the infection-free and the endemic equilibrium. Secondly, we present a brief discussion of the malaria infection only model adopted from Li (2011). Essential results on the transmission dynamics of malaria only, adapted from Li (2011) shows that the model exhibits a backward bifurcation phenomenon (a scenario where multiple endemic equilibria co-exist with a disease-free equilibrium). Thirdly, we formulated the co-infection model making use of the two sub-models discussed earlier. The reproductive number for the co-infection has been computed. Based on the analytical results of the two sub-models we have established that the co-infection model exhibits a backward bifurcation phenomenon. Numerical results presented in this study suggests that a typhoid outbreak in malaria endemic settings may lead to higher population of dually infected individuals displaying clinical symptoms of both infections than the singly-infected population displaying clinical symptoms of the disease.

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APPENDIX

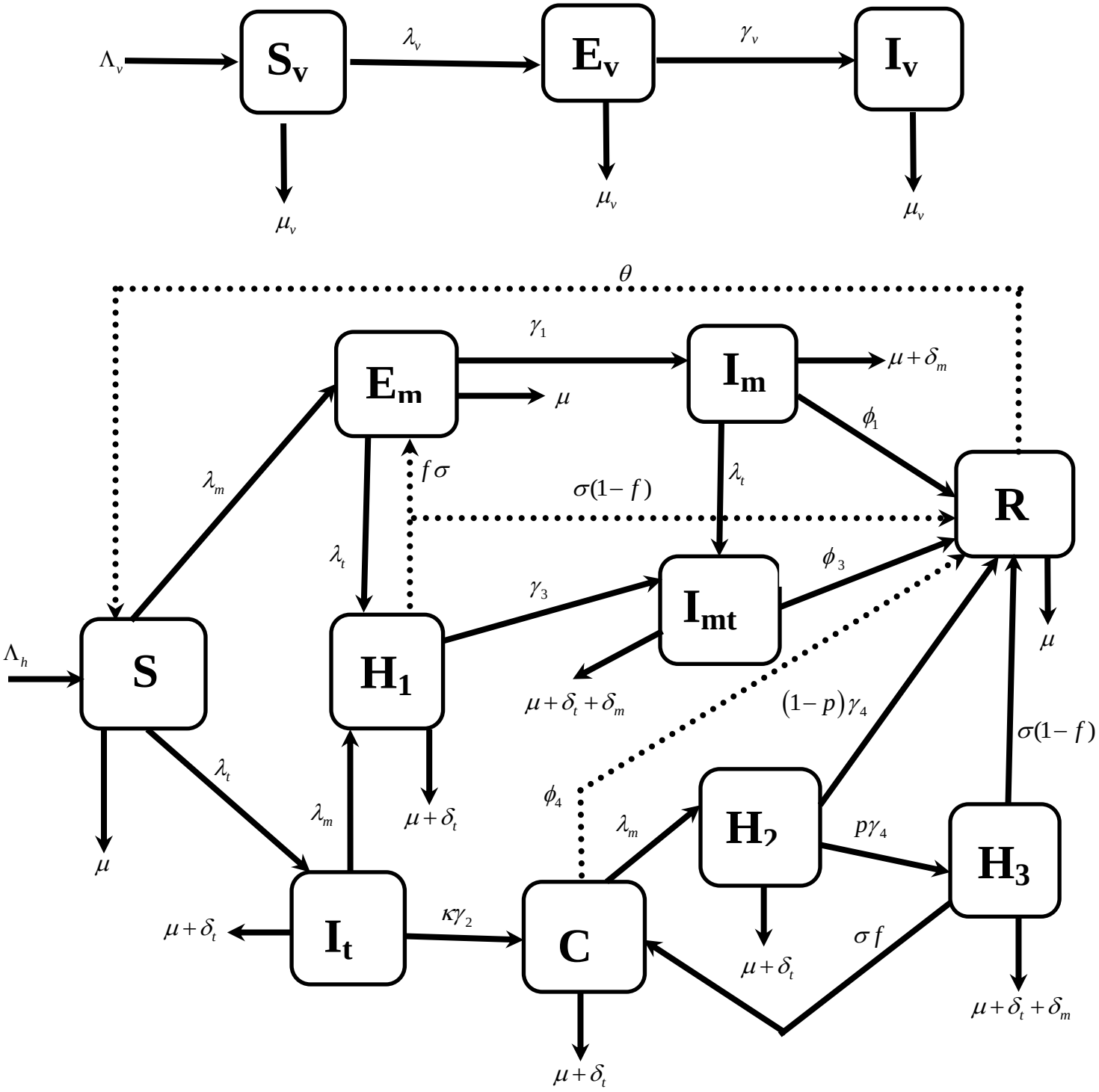

Figure 5. Model flow diagram