A Critical Protection Level Derived from Dengue Infection Mathematical Model Considering Asymptomatic and Symptomatic Classes

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Abstract. In this paper we formulate a model of dengue fever transmission by considering the presence of asymptomatic and symptomatic compartments. The model takes the form as a system of differential equations representing a host-vector SIR (Susceptible – Infective - Recovered) disease transmission. It is assumed that both host and vector populations are constant. It is also assumed that reinfection of recovered hosts by the disease is possible due to a waning immunity in human body. We analyze the model to determine the qualitative behavior of the model solution and use the concept of effective basic reproduction number (Rp) as a control criteria of the disease transmission. The effect of mosquito biting protection (e.g. by using insect repellent) is also considered. We compute the long-term ratio of the asymptomatic and symptomatic classes and show a condition for which the iceberg phenomenon could appear.

1. Introduction

Dengue fever has long been endemic in tropical and sub-tropical areas. It is caused by four dengue virus serotypes and transmitted via the bites of female Aedes aegypti mosquitoes. The clinical manifestations of the disease vary from asymptomatic to fatal. Based on the symptoms, the clinical manifestations of the dengue virus infection can be broadly grouped into two categories: asymptomatic (without symptoms) and symptomatic (with symptoms). The latter may lead to the common cold (viral syndrome), Dengue Fever (DF), or Dengue Hemorrhagic Fever (DHF) including dengue Shock Syndrome (DSS) [1]. Figure 1 shows the diagram for the clinical manifestations of the dengue virus infection.

Fever is common in infants, children and some adults who are infected with dengue virus for the first time (a primary dengue infection). It is usually indistinguishable from the fever caused by other viral infections. DF can affect both children and adults, but it commonly affects children below the age of 15. Basically it is an acute biphasic fever characterized by headache and skin rash. Although it is basically harmless, the disease can reduce the function of the body, for instance causing muscle characterized by fever followed by signs of blood circulatory failure causing serious bleeding in many parts of body [1].
Asymptomatic
Symptomatic
Fever
Dengue 
Fever
Dengue 
Haemorrhagic 
Fever
Without 
Blooding
With 
Blooding
No Shock
DSS
Dengue 
Infection
Figure 1. Diagram of Dengue Infection manifestation [16].

Dengue virulence occurred in 1998 in Indonesia, when thousands of clinically diagnosed DHF cases were found [2]. The maximum number of DHF/DSS cases reported during the month when the dengue fever peaked supports the DHF/DSS iceberg theory [3]. In relation to many dengue outbreaks, Balasubramanian, a senior consultant pediatrician at the Child Trust Hospital India, pointed out that hospitals only see the tip of the iceberg. He argued that for every one case in the hospital, there should be at least nine cases among the population, indicated by mild fever and almost no symptoms [4]. A person infected by the dengue virus for the first time generally does not enter the DHF or DSS stage. A primary or first infection usually results in no symptoms or only shows symptoms similar to the common cold, or at worst DF. However, a second infection and the subsequent infections may lead to DHF or DSS. Evidence shows that a person can be exposed to the DHF stage more than twice if their immunity is reduced, i.e. when the body immunity is waning [5].

To date, there have been a lot of mathematical models used in the study of the transmission of the dengue fever. Many of the models only use one strain of the dengue virus. These models include dengue models using constant population [7], varying population [8], and models incorporating the vaccination factor [6, 10, 11]. Although many mathematical models for the dengue fever transmission have made great contribution [6, 7, 8, 9, 10, 12], almost all of them neglect the details, such as the iceberg phenomenon, the waning immunity that causes re-infection by the same/different strain, and the presence/absence of symptoms.

An extensive review has been done in [13]. In this study, we develop a mathematical model for the dengue transmission by simultaneously incorporating these details. It is assumed that when a person has contracted dengue fever, after the recovery they can be re-infected due to the waning immunity in their body, regardless of the virus strain. We generalize an SIR (Susceptible - Infective - Recovered) dengue transmission model by dividing the infected class in the SIR model into the asymptomatic class and symptomatic class. The purpose is to facilitate the study of the condition in which the iceberg phenomenon can appear. The details of the model are given in the following section.

2. Model formulation

In constructing the mathematical model, we assume that the host and vector populations have constant sizes and constant rates for birth and death, which are $\mu_h$ and $\mu_v$, respectively. In [7], the majority of individuals in the host population eventually become permanently immune with long-term
immunity. In our model, individuals in the host population either become immune or lose their immunity.

In this model, we assume that susceptible hosts are divided into two categories: $S_0$ (susceptible virgin) from newborns and $Z_0$ (susceptible with previous infection) from recovered individuals who have lost their immunity. This division is based on the fact that, using the IgG and IgM test, dengue infection in a person can be detected when they were previously infected with the dengue virus. The infected class is divided into two more classes: $I$, the asymptomatic infection in humans, and $Y$, the symptomatic infection in humans (DF, DHF, DSS). There is no dengue transmission from $Y$ since we assume that infection in this class is detectable, hence it can be easily isolated easily. $Z$ refers to recovered patients. The vector population, due to its short lifespan, is divided into the susceptible $V_0$ and the infective $V_1$. The model is represented by the diagrams shown in Figures 2 and 3, with the description of the parameters given in Table 1.

![Figure 2. Host Transmission Diagram.](image1.png)

![Figure 3. Vector Transmission Diagram.](image2.png)

We also assume that the susceptible host may use a level of protection against being bitten by mosquitoes, for example by applying an insect repellent. In this case $p = 0$ means no protection at all, while $p = 1$ means full protection (everybody is fully protected).

| Parameter | Description                              |
|-----------|------------------------------------------|
| $\mu_h$  | Natural death rate for host               |
| $\mu_v$  | Natural death rate for vector             |
| $\alpha_i$ | Probability of successful transmission from in host |
| $\alpha_v$ | Probability of successful transmission from in vector |
| $\xi$    | Wanning immunity rate                     |
| $b_r$    | Biting rate                              |
| $\gamma$ | Recovery rate                            |
The dynamical equation for host and vector are:

\[
\begin{align*}
\frac{dS}{dt} &= \mu_h N_h - \frac{b_r a_1}{N_h} S_0 V_1 - \mu_h S_0 \\
\frac{dZ}{dt} &= \xi Z - \frac{b_r a_3}{N_h} Z_0 V_1 - \mu_h Z_0 \\
\frac{dI}{dt} &= \frac{b_r a_1}{N_h} S_0 V_1 - (\gamma + \mu_h) I \\
\frac{dY}{dt} &= \frac{b_r a_2}{N_h} Z_0 V_1 - (\gamma + \mu_h) Y \\
\frac{dZ}{dt} &= \gamma (I + Y) - (\mu_h + \xi) Z \\
\frac{dV_0}{dt} &= \mu_v N_v - \frac{b_r a_v}{N_h} V_0 I - \mu_v V_0 \\
\frac{dV_1}{dt} &= \frac{b_r a_v}{N_h} V_0 I - \mu_v V_1 
\end{align*}
\]

(1)

Note that \( N_h = S_0 + Z_0 + I + Y + Z \) is the total population of host, and \( N_v = V_0 + V_1 \) is the total population of vectors in the region of \( \Omega \), with \( \Omega = \{(S_0; Z_0; I; Y; V_0; V_1) \in [0; 1] | 0 \leq S_0 + Z_0 + I + Y + Z \leq N_h, 0 \leq V_0 + V_1 \leq N_v\} \). The description of the parameters used in the model is given in Table 1.

The model in this paper differs from known similar models that include the asymptomatic and symptomatic. In [14] and [15] the asymptomatic and symptomatic come from the same compartment, i.e. from susceptible people who get infected, through the introduction of a different transmission probability \( \beta_{has} \) (the dengue virus’s transmission probability from vector population to human population, changing it into an asymptomatic infectious human population) and \( \beta_{hsa} \) (the dengue virus’s transmission probability from vector population to human population, changing it into a symptomatic infectious human population). Other models such as in [16] cover the possibility of sequential infections with all four different serotype, by considering apparent (symptomatic) and non-apparent cases (asymptomatic), but assume that apparent cases may also appear as a first infection. The model also assumes that a re-infection cannot occur more than twice. The model in [17] presents a three-state infection. The three states of infection are respectively asymptomatic, partially asymptomatic, and fully asymptomatic. However, according the analysis’s conclusion, these are not conditions in which the iceberg phenomenon may occur.

3. Analysis of the model
3.1. Basic Reproduction Number

The basic reproduction number (BRN) is an important threshold number in epidemiology. It is defined as the number of secondary infections caused by one primary infection in an entirely susceptible population [18] and usually written as \( R_0 \). The value can be obtained through the construction of the next generation matrix [19, 20] of the infectious disease processes. of the infectious disease processes. Note that the next generation matrix is applied in cases when initially there is no infected individual in the host population. The BRN is also defined as the spectral radius or the largest eigen value of the next generation matrix, evaluated at the steady state population sizes in the absence of infection. It is widely known that, in many epidemiological models, \( R_0 > 1 \) indicates an epidemic case in which the infection progresses and grows away from zero infective. On the other hand, if \( R_0 < 1 \) then the disease will die out. It will be shown that such is the case for the present model.
The next generation matrix $G$ for system (1) is given by

$$MD^{-1} = \begin{bmatrix}
0 & 0 & (1-p)b_{ij} & \alpha_i \\
0 & 0 & 0 & \mu_v \\
(1-p)b_{ij} & \alpha_i N_v & \mu_v \\
N_h (\gamma + \mu_h) & 0 & 0 \\
\end{bmatrix}$$

(2)

If $X \in [I; V]$ where $i, j \in \{1, 2\}$, then $G_{ij}$ is the number of new cases in $X_j$ produced by one $X_i$ during the transmission period. For example the first row and the second column of $G$ show the number of infected hosts, produced by one infected vector during the period of transmission of $V$. Direct computation shows that the effective reproduction number (the BRN with protection $p$) is given by

$$R_p = \sqrt{\frac{(1-p)b_{ij}^2 N_h \alpha_i \alpha_v}{N_h (\gamma + \mu_h) \mu_v}}$$

(3)

and without protection we have the natural BRN.

$$R_0 = \sqrt{\frac{N_p \alpha_i \alpha_v}{N_h (\gamma + \mu_h) \mu_v}}$$

(4)

3.2. Equilibrium points

In this section we will discuss the equilibrium points of system (1) in the $\Omega$ region. It is shown that the positive equilibrium depends on the magnitude of $R_p$. We present some results regarding the existence of equilibrium points of system (1), which are as follows:

Proposition 3.1 The system (1) admits two equilibrium points: the disease free $E_0 = (N_h, 0, 0, 0, 0, N_v, 0)$ and the endemic equilibrium $E_e = (S_0^*, Z_0^*, I^*, Y^*, Z^*, V_0^*, V_1^*)$, where

$$S_0^* = \frac{N_h (A_1 + K \mathcal{R}_p^2) K}{(A_1 + K) \mathcal{R}_p^2},$$

(5)

$$Z_0^* = \frac{A_1 \mathcal{C} (\mathcal{R}_p^2 - 1) (A_1 + K \mathcal{R}_p^2) \xi}{M (A_1 + K) \mathcal{R}_p^2},$$

(6)

$$I^* = \frac{A_1 (\mathcal{R}_p^2 - 1) K}{A_1 + K \mathcal{C}}$$

(7)

$$Y^* = \frac{A_1 A_2 K (\mathcal{R}_p^2 - 1)^2 \xi Y}{M (A_1 + K) \mathcal{R}_p^2},$$

(8)

$$Z^* = \frac{A_1 Y (\mathcal{R}_p^2 - 1) (A_1 + A_1 (\mathcal{R}_p^2 - 1) + K \mathcal{R}_p^2)}{M (A_1 + K) \mathcal{R}_p^2},$$

(9)

$$V_0^* = \frac{N_p (A_1 + K)}{A_1 + K \mathcal{R}_p^2},$$

(10)

$$V_1^* = \frac{K (\mathcal{R}_p^2 - 1) N_v}{A_1 + K \mathcal{R}_p^2},$$

(11)

with

$$A_i = (1 - p) b_i \alpha_i N_p, \quad i = 1, 2; \quad K = N_h \mu_h; \quad C = \gamma + \mu_h; \quad D = \delta \alpha_2 \quad (12)$$

$$M = K \mathcal{R}_p^2 D C + \mu_h \left( A_1 + A_2 (\mathcal{R}_p^2 - 1) \right) D + A_2 (\mathcal{R}_p^2 - 1) \gamma \mu_h + A_1 D$$

(13)

Proposition 3.1 is easily proven as a consequence of direct computation. The next proposition provides a condition for the local stability of the disease-free equilibrium state $E_0$. The proof is deduced from the stability theorem for the disease-free equilibrium of general compartmental model [21].
3.3. Stability of the disease-free equilibrium

The following proposition provides the stability criteria for the disease-free equilibrium $E_0$.

**Proposition 3.2** $E_0$ is a locally asymptotically stable disease-free equilibrium whenever $R_0 < 1$. $E_0$ is an unstable disease-free equilibrium whenever $R_0 > 1$.

**Proof.** The Jacobian matrix $J(E_0)$ of system (1) is given by

$$
J_{E_0} = \begin{bmatrix}
-\mu_h & 0 & 0 & 0 & - (1-p) b_r \alpha_2 \\
0 & -\mu_h & 0 & 0 & 0 \\
0 & 0 & -\gamma - \mu_h & 0 & 0 \\
0 & 0 & 0 & -\mu_h & 0 \\
0 & 0 & -\gamma & -\mu_h & 0 \\
0 & 0 & 0 & 0 & -\mu_p \\
0 & 0 & \frac{(1-p) b_r N_e \alpha_p}{N_h} & 0 & 0 \\
0 & 0 & \frac{(1-p) b_r N_e \alpha_p}{N_h} & 0 & 0 \\
0 & 0 & 0 & 0 & 0 \\
\end{bmatrix}
$$

The eigenvalues of $J(E_0)$ are $-\mu_h$ with multiplicity 2, $-(\mu_h + \gamma)$ with multiplicity 1, and the roots of polynomial $p_1(x) = a_4 x^2 + b_1 x + c_1$, where:

$$
\begin{align*}
    a_4 &= \frac{N_h}{\mu_h} > 0 \\
b_1 &= \gamma + \mu_h + \mu_p > 0 \\
c_1 &= \mu_p (\gamma + \mu_h) N_h \left( 1 - R_0^2 \right)
\end{align*}
$$

The coefficient $c_1 > 0$ if $R_0 < 1$, hence all the roots of polynomial $p_1$ have negative real part when $R_0 < 1$. This means that $E_0$ is locally asymptotically stable when $R_0 < 1$, with a saddle point where $R_0 > 1$. This proves the proposition. ■

Note that from Propositions 3.1 and 3.2, if $R_0 > 1$ then there exists an endemic equilibrium point. On the other hand, if $R_0 < 1$ then the endemic equilibrium disappears and the disease-free equilibrium becomes stable. Hence, to eliminate the disease it is enough to make the value of $R_0 < 1$. This can be done by controlling the value of protection level $p$. The condition $R_0 < 1$ is equivalent to $p > 1 - \frac{1}{R_0}$.

Here $p_c = 1 - \frac{1}{R_0}$ is called the Critical Protection Level. In an endemic case, Proposition 3.1. also gives the ratio of asymptomatic and symptomatic classes that is,

$$
\frac{I^*}{Y^*} = \frac{M}{A_2 \gamma \xi (R_0 - 1)}
$$

where $M$ and $A_2$ are given in equations (12) and (13). The above ratio indicates the presence or absence of the iceberg phenomenon. If $L$ is a sufficiently big number (e.g. nine, as in the introduction), then the condition in which the iceberg phenomenon may exist is

$$
M > L \left( R_0 - 1 \right) A_2 \gamma \xi
$$

The numerical example in Figure 4 shows that the condition is met when the probability of a successful dengue transmission for the previously infected and susceptible is sufficiently less than the probability of a successful dengue transmission for the naive and susceptible, i.e. $a_2 < a_1$. 


4. Numerical Simulation

Numerical examples are shown in this section. Figure 4 shows the plot of $I^*/Y^*$ as a function of the mosquito bite rate $b_r$. It reveals that the ratio for asymptomatic and symptomatic decreases when the mosquito bite rate increases, as suggested by equation (14).

Figure 4. The ratio of asymptomatic and symptomatic as a function of $br$. The parameter in the simulation are $N_v = 10000$, $N_h = 1000$, $\gamma = 1/7$, $\alpha_4 = 0.75$, $\alpha_5 = 0.5$, $\alpha_6 = 0.3$, $\xi = 0.4$, $\mu_v = 1/30$, $\mu_h = 1/(60 \times 365)$.

Figure 5 shows that for a fixed $\xi$ the ratio for asymptomatic and symptomatic decreases when the mosquito bite rate increases. It also shows that for a fixed $b_r$ the ratio for asymptomatic and symptomatic decreases when the body immunity increases. This suggests that the iceberg phenomenon may occur when the rates of both the mosquito bite and waning immunity are sufficiently small. The parameter in the simulation for Figure 5 are $N_v = 10000$, $N_h = 1000$, $\gamma = 1/7$, $\alpha_4 = 0.75$, $\alpha_5 = 0.5$, $\alpha_6 = 0.3$, $\xi = 0.4$, $\mu_v = 1/30$, $\mu_h = 1/(60 \times 365)$. Figures 6 shows the effect of protection on the dynamics of the infected host population. Figure 7 show that sufficient protection (higher than the critical protection level) may eliminate both the disease and the iceberg phenomenon.
Figure 5. (a) The ratio of asymptomatic and symptomatic as a function of $h$, and $\xi$ with the level curve given in (b).

Figure 6. The Dynamics of compartments $I$ and $Y$. (a) without protection ($p = 0$), (b) with not enough protection ($p = 0.1$), (c) with a sufficient protection ($p = 0.948$).
The parameter for Figure 6 are $N_v = 100000$, $N_h = 500000$, $\gamma = 1/7$, $\alpha_1 = 0.75$, $\alpha_2 = 0.5$, $\xi = 0.4$, $\mu_v = 1/30$, $\mu_h = 1/(60 \times 365)$, $S_0(0) = 30$, $Z_0(0) = 50$, $I(0) = 2$, $\Psi(0) = 3$, $V_0(0) = 50$, $V_1(0) = 50$, $R_0 = 19.21$, $R_p = 0.998$.

Figure 7. The graphs show the ratio of asymptomatic and symptomatic compartments. (a) without protection ($p = 0$), (b) with not enough protection ($p = 0.1$), (c) with a sufficient protection ($p = 0.948$). The parameter in simulation are $N_v = 100000$, $N_h = 500000$ and other parameter are the same as in Figure 6.

5. Conclusion

In this paper we developed a mathematical model of dengue transmission by separating the infected class in the SIR model into the asymptomatic and symptomatic classes, where the division is done to facilitate the analysis on which condition for the iceberg phenomenon could appear. The model and the numerical simulation show that an iceberg phenomenon may appear when both the biting rate and waning immunity is sufficiently small and they also reveal that enough protection (higher than the critical protection level) may eliminate the disease and the iceberg phenomenon simultaneously.

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