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Mathematical analysis of Yellow Fever transmission dynamics using Wolbachia and vaccination as control strategies

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Abstract

We present the mathematical analysis of yellow fever transmission dynamics using Wolbachia and vaccination as the control strategies. A deterministic ordinary differential equation model for yellow fever disease transmission dynamics within the human and mosquito populations is formulated. The model equilibrium points were obtained, while the criteria for their macrocosm and stability were investigated. Numerical simulations were carried out using a classical fourth order Runge-kutta method in MATLAB. From the simulations, we investigated and established that the disease can only be eradicated in our society if we encourage the populace to take the vaccines against the disease in the case of the disease insurgence. This is primarily due to the fact that the vaccinated humans do not respond to the infectivity of the Wolbachia-free mosquitoes' biting. Also effective, efficient and timely treatment of infectious persons must be carried out if we must contain the disease when it occurs.

Keywords: booster dose; endemic; Wolbachia; immunity; vaccination; yellow fever; model equation.

1 Introduction

Yellow fever is an acute viral disease that is endemic and enzootic in sub-Saharan Africa and tropical South America, which is marked by three phases of symptoms. These include: "the infectious or acute phase", characterized by fever, chills, loss of appetite, nausea, muscle pains particularly in the back and head ache. These symptoms ameliorate within five days and the "remission phase" set in, this is characterized by the sudden disappearance of the early symptoms. Within 24 hours, the chronic phase set in, which is characterized by the reappearance of the early symptoms along with new and more serious symptoms such as high fever, hemorrhage, abdominal pain and liver impairment begins causing jaundice i.e., yellowing of the skin and eyes which is why this disease is called "yellow fever" [1, 15, 19]. If this occurs, the peril of bleeding and kidney problem is increased [28]. It is caused by a flavivirus (peculiarly yellow fever virus of the genus Flavivirus) transmitted

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specially by the yellow fever mosquito, and is spread by the bite of an infected female mosquito [11]. It infects only humans, other primates and several types of mosquitoes [21]. Particularly in the early stages, this disease may be difficult to differentiate from other illness [31]. For a suspected case to be confirmed, blood sample testing with polymerase chain reaction is needed [11]. A safe and effectual vaccine against yellow fever subsist, and some countries demands vaccination for travelers [3, 6, 22]. Other attempts to forestall transmission include reducing the population of the transmitting mosquitoes. In a domain where yellow fever is plebeian, early diagnosis of cases and immunization of large parts of the population are crucial to forestall outbreaks. Up to half of those who got to the severe phase of the disease die within 7-10 days [28].

Yellow fever resulted in about 127,000 serious infection and 450,000 deaths in 2013 [31], with virtually 90 percent of these happening in African nations [11]. In an area of the world where the disease is common, nearly a billion of people lives there. It is plebeian in tropical areas of the continents of south America and Africa but not in Asia [5]. The number of cases of yellow fever has been increasing since the 1980s [13]. This is conceived to be ascribable to fewer people being immuned, more people living in cities, people often moving from one geographical area to another, and changing climate and increasing the mosquitoes home ground. The disease is conceived to have sprung up in Africa and outspread to south America through the slave trade in the 17th century. Several major outbreaks of the disease have occurred in the America, Africa, and Europe since the 17th century [14, 20, 24]. In the 18th and 19th centuries, the yellow fever was seen as one of the lethal, dangerous infections diseases. And the yellow fever virus became the first human virus to be isolated in 1927 [22]. In 1900, Walter Reed established that it was the first sickness shown to be transmissible by filtered human serum and transmitted by mosquitoes [10].

In tropical areas of Africa and the South Americas, Yellow fever virus (YFV) infects human and nonhuman primates, which is transmitted between primate hosts in the saliva of infected mosquitoes. The natural epidemiology of yellow fever on both continents is a cycling of the virus between forest mosquitoes and wild primates. We have **three cycles of secondary transmission to humans**, these are sylvatic (jungle), intermediate (savannah) and urban [16].

Yellow fever is common in tropical and subtropical areas of South America and Africa. Worldwide, about 600million people live in endemic areas. The world Health Organization [WHO] estimates 200,000 cases of disease and 30000 deaths a year occur [26, 27, 29, 30]. An estimated 90% of yellow fever infections occur in African continent [11]. In 2016, a large outbreak originated in Angola and spread to neighboring countries before being contained by a massive vaccination campaign [31, 32].

Yellow fever is distinguished from other viral hemorrhagic fever by the characteristic severity of liver damage and appearance of jaundice (hence flavus; latin for yellow). Moreover, damage to the kidneys frequently leads to extreme albuminuria and acute renal failure. Antibodies can be detected at this stage, while viremia is usually absent. Late central nervous system (CNS) manifestations, such as confusion seizure, and coma, presage death typically follows within seven to ten days of onset [4, 23, 25].

There is no specific treatment for yellow fever infection, only secondary, supportive care exists, i.e., the specialist treatment and support provided by doctors to prevent, control, or relieve complications and side effects and to improve the patients comfort and quality of life) [23]. Secondary care in an intensive care unit is required for complete care. Consequently, supportive care

is critical. Of course, most patients with yellow fever are unable to benefit from state-of-the-art medical care [17, 18]. Ideally a severe ill patient is admitted to the intensive care unit (ICU) and provided with vaso-active medications, fluid resuscitation, and ventilator support. Symptoms including DIC, hemorrhage, renal and hepatic dysfunction, and possible secondary infection are treated. The use of salicylates is contraindicated in yellow fever cases because of the increased risk of bleeding. Although humans can't spread yellow fever among themselves through casual contact, but the infection could possibly be transmitted directly into the blood through contaminated needles [4]. Viremic patients should be isolated with mosquito netting in areas with potential vectors transmission and until differential diagnoses are eliminated. Although no specific antiviral drugs are available, several compounds with *in vitro* antiviral activity have been described, including ribavirin and interferon- α . However, trials with ribavirin in experimentally infected monkeys have yielded conflicting results [12]. Interferon- γ treatment of monkeys resulted in delayed onset of viremia and illness, but had no effect on survival [2].

2 The Model Equations

Wolbachia is a genus of ***Gram-negative intracellular bacteria*** belonging to the order ***Rickettsiales*** and the family ***Anaplasmataceae***, which infect invertebrate organisms and are found naturally in more than 50% of all arthropod species and in several nematodes. Nevertheless, *wolbachia* is naturally absent from *Aedes aegypti* (*Stegomyia aegypti*), but can be introduced. *Wolbachia*-infected mosquitoes are not considered to be genetically modified as *wolbachia* is a naturally occurring symbiont of invertebrates. Moreover, volunteers that are bitten by *wolbachia*-infected mosquitoes do not show any specific antibody production against *wolbachia*, which probably means that there is no transmission of the bacteria from mosquitoes to human. As *wolbachia* is an obligate intracellular bacterium, it cannot survive in the environment (air, soil, water and leaves), but horizontal transmission between arthropods does occur in nature [7].

The principal transmission route of *wolbachia* is vertically inherited in-vitro of the cytoplasm of the maternal line, in spite of the fact that, horizontal transmission between insect's species also put up to *Wolbachia* prevalence [9]. Since other mechanisms of transmission are uncommon and may be ignored, then we consider the probability of the vertical transmission as one. The main rationale of using *wolbachia* for biological control of disease vectors is formulated on cytoplasmic incompatibility (CI), as a result of its infection in the reproductive organs. Mating between an infected male and an uninfected female leads to abnormality in embryonic development with no or limited numbers of viable progenies. In such a transmission cycle, males are the dead-end host of *wolbachia* and can sterilize the uninfected females.

Mosquitoes with *wolbachia* have a reduced ability to transmit viruses to people, decreasing the risk of Zika, dengue, Chikungunya and yellow fever outbreaks [4, 8].

Since all the three populations i.e., the human, mosquitoes and *wolbachia* continuously varies with time, we therefore used a continuous-time model.

2.1 Assumptions of the Model

The following assumptions were made in constructing the model.

- i. Death induced by an attempt to suck blood for egg fertilization by both the adult female wolbachia-infected and wolbachia-free mosquitoes is neglected.
- ii. The yellow fever virus cannot be transmitted from the wolbachia-infected mosquitoes (I_w) to an adult wolbachia-free mosquitoes (I_m)
- iii. Mosquitoes with wolbachia have a reduced ability to transmit viruses to humans.
- iv. The non-chronic infectious human, i.e., humans within the 1st and the 2nd phase of infection majorly recovered naturally.
- v. Everybody in a given at-risk country cannot be vaccinated
- vi. The yellow fever vaccine does not provide an ageless immunity.
- vii. The yellow fever disease is not contagious, i.e., cannot be spread from human to human through body contact.
- viii. People with weak immune system are considered
- ix. Vaccine induced mortality rate is not considered.

Hence, we obtain the Model equations for the transmission dynamics of yellow fever disease using Wolbachia infected mosquitoes as control as follows:

For the wolbachia-free mosquitoes

$$\frac{dS_m}{dt} = \Lambda_m - \alpha S_m - \delta_1 S_m \quad (1)$$

$$\frac{dE_m}{dt} = \alpha S_m - bE_m - \delta_1 E_m \quad (2)$$

$$\frac{dI_m}{dt} = bE_m - \delta_1 I_m \quad (3)$$

For the wolbachia-infected mosquitoes

$$\frac{dS_w}{dt} = \Lambda_w - \beta S_w - \delta_2 S_w \quad (4)$$

$$\frac{dE_w}{dt} = \beta S_w - \xi E_w - \delta_2 E_w \quad (5)$$

$$\frac{dI_w}{dt} = \xi E_w - \delta_2 I_w \quad (6)$$

For human compartment

$$\frac{dS_h}{dt} = \Lambda_h + \theta S_v + \tau R_h - kS_h - \psi S_h - \mu S_h \quad (7)$$

$$\frac{dS_v}{dt} = kS_h - \theta S_v - \lambda_1 S_v - \mu S_v \quad (8)$$

$$\frac{dS_{uv}}{dt} = \psi S_h - \lambda_2 S_{uv} - \mu S_{uv} \quad (9)$$

$$\frac{dE_h}{dt} = \lambda_1 S_v + \lambda_2 S_{uv} - \phi E_h - \mu E_h \quad (10)$$

$$\frac{dI_h}{dt} = \phi E_h - \rho_1 I_h - \rho_2 I_h - \mu I_h \quad (11)$$

$$\frac{dI_{hN}}{dt} = \rho_1 I_h - \mu I_{hN} - \gamma_1 I_{hN} \quad (12)$$

$$\frac{dI_{hC}}{dt} = \rho_2 I_h - \delta_3 I_{hC} - \mu I_{hC} - \gamma_2 I_{hC} \quad (13)$$

$$\frac{dR_h}{dt} = \gamma_1 I_{hN} + \gamma_2 I_{hC} - \tau R_h - \mu R_h \quad (14)$$

The line of reasoning for the above model is as follows: Wolbachia-infected mothers (S_w) produced the first progeny carrying wolbachia that survived to maturity. Wolbachia-uninfected mothers (S_m) produced the second progenies which are all uninfected. If the female is infected by wolbachia, the possible progenies may be inviable because of cytoplasmic incompatibility (CI).

2.2 Description of the Model Variables and Parameters

Table1: Parameter Description

Parameters	Description
Λ_m	The basic recruitment level for wolbachia-free mosquitoes.
Λ_w	The basic recruitment level for wolbachia-infected mosquitoes.
Λ_h	The basic recruitment level for human
α	The rate at which susceptible wolbachia-free mosquitoes are exposed to flavivirus
b	The rate at which an exposed wolbachia-free mosquitoes are infectious
δ_1	Natural death rate of wolbachia-free mosquitoes
β	The rate at which susceptible wolbachia-infected mosquitoes are exposed to

	flavivirus
ξ	The rate at which an exposed wolbachia-infected mosquitoes are infectious.
δ_2	Natural death rate of wolbachia-infected mosquitoes
K	The rate at which people are vaccinated
ψ	The rate at which people are unvaccinated
λ_1	The force of infection of a susceptible vaccinated human
λ_2	The force of infection of a susceptible unvaccinated human
θ	The rate at which vaccinated humans becomes susceptible.
τ	The rate at which recovered humans become susceptible.
ϕ	The rate at which an exposed humans become infectious.
ρ_1	The rate which an infectious humans progressed to the non-chronic phase of the disease
ρ_2	The rate which an infectious human progressed to the chronic phase of the disease.
γ_1	Natural recovery rate of humans at the non-chronic phase of the disease
γ_2	The recovery rate of humans at the chronic phase of the disease.
μ	The natural death rate of humans
δ_3	Death induced by the disease

Table 2: Variables Description

Variables	Description
S_m	Susceptible class of wolbachia-free mosquitoes
E_m	The class of exposed wolbachia-free mosquitoes
I_m	The class of adult female infectious wolbachia-free mosquitoes
N_m	Total populations of an adult female wolbachia-free mosquitoes, $N_m = S_m + E_m + I_m$
S_w	The susceptible class of an adult wolbachia-infected mosquitoes
E_w	The class of exposed adult wolbachia-infected mosquitoes
I_w	The class of infectious adult wolbachia-infected mosquitoes
N_w	The total populations of an adult wolbachia-infected mosquitoes, $N_w = S_w + E_w + I_w$
S_h	The class of susceptible humans
S_v	The class of vaccinated humans
S_{uv}	The class of unvaccinated humans
E_h	The class of exposed humans to flavivirus
I_h	The class of infectious humans
I_{hN}	The class of infectious humans in the non-chronic phase of the disease
I_{hC}	The class of an infectious humans in the chronic phase of the disease
R_h	The class of humans that recovered from the disease
N_h	The total populations of humans, $N_h = S_h + S_v + S_{uv} + E_h + I_h + I_{hC} + I_{hN} + R_h$

We have that

$$\frac{dN_h}{dt} = \frac{dS_h}{dt} + \frac{dS_v}{dt} + \frac{dS_{uv}}{dt} + \frac{dE_h}{dt} + \frac{dI_h}{dt} + \frac{dI_{hN}}{dt} + \frac{dI_{hC}}{dt} + \frac{dR_h}{dt} \quad (15)$$

$$\frac{dN_m}{dt} = \Lambda_m - \delta_1 N_m \quad (16)$$

$$\frac{dN_w}{dt} = \Lambda_w - \delta_2 N_w \quad (17)$$

3 Analysis of the Model

We investigate the invariant region to determine whether the model is biologically meaningful and that all solutions of our model equations are positive and are attracted in that region.

Lemma 1: The region

$$\text{Let } \Omega_m = (S_m, E_m, I_m), \Omega_w = (S_w, E_w, I_w), \Omega_h = (S_h, S_v, S_{uv}, E_h, I_h, I_{hN}, I_{hC}, R_h)$$

$$\text{So that } \Omega = \Omega_m \times \Omega_w \times \Omega_h$$

Then we have:

$\Omega = (S_m, E_m, I_m, S_w, E_w, I_w, S_h, S_v, S_{uv}, E_h, I_h, I_{hN}, I_{hC}, R_h) \in \mathbb{R}_+^{14}$ to be a relation of the model system with non-negative initial conditions i.e. at $t=0$, we have:

$$S_h > 0, S_v \geq 0, S_{uv} \geq 0, E_h \geq 0, I_h \geq 0, I_{hN} \geq 0, I_{hC} \geq 0, R_h \geq 0,$$

$$S_m \geq 0, E_m \geq 0, I_m \geq 0, S_w > 0, E_w \geq 0, I_w \geq 0.$$

In the absence of the disease (yellow fever) i.e., at disease free equilibrium, we have:

$$S_v = 0, S_{uv} = 0, E_h = 0, I_h = 0, I_{hN} = 0, I_{hC} = 0,$$

then equation (15) becomes:

$$\frac{dN_h}{dt} = \frac{dS_h}{dt}. \quad (*)$$

But from the equation (7) under the human compartment, we now have:

$$\Rightarrow \frac{dS_h}{dt} = \Lambda_h - \mu S_h. \quad (**)$$

This implies that

$$\frac{dN_h}{dt} = \Lambda_h - \mu S_h \Rightarrow \frac{dN_h}{dt} = \Lambda_h - \mu N_h.$$

From the above, we have:

$$\frac{dN_h}{dt} + N_h \mu \leq \Lambda_h \quad (18)$$

Using integrating factor, we solve this to obtain:

$$N_h \leq \frac{\Lambda_h}{\mu} + C e^{-\mu t}.$$

Using initial conditions: $t = 0$, $N_h(0) = N_{h0}$, this then becomes:

$$N_h \leq \frac{\Lambda_h}{\mu} + \left[N_{h0} - \frac{\Lambda_h}{\mu} \right] e^{-\mu t}. \quad (19)$$

$$\text{At } t = 0, \quad N_h \leq \frac{\Lambda_h}{\mu} + N_{h0} - \frac{\Lambda_h}{\mu} \Rightarrow N_h \leq N_{h0}$$

$$\text{Similarly, at } t = \infty, \quad e^{-\mu t} = 0 \text{ so that } N_h \leq \frac{\Lambda_h}{\mu}$$

$$\Rightarrow 0 \leq N_h \leq \frac{\Lambda_h}{\mu} \text{ as } t \rightarrow \infty.$$

Therefore, as $t \rightarrow \infty$, the human population (N_h) draw close to:

$$K \leq \frac{\Lambda_h}{\mu} \text{ i.e., } N_h \rightarrow K = \frac{\Lambda_h}{\mu} \text{ as } t \rightarrow \infty.$$

The parameter K is called the carrying capacity. Hence all the viable solution set of the human compartment population model enters the region.

$$\Omega_h = \left\{ (S_h, S_v, S_{uv}, E_h, I_h, I_{hN}, I_{hC}, R_h) \in \mathbf{R}_+^8 : S_h > 0, S_v \geq 0, S_{uv} \geq 0, E_h \geq 0, I_h \geq 0, I_{hN} \geq 0, I_{hC} \geq 0, R_h \geq 0 \right\} N_h \leq \frac{\Lambda_h}{\mu}$$

Similarly, we can show that the viable solutions for the wolbachia-free and the wolbachia-infected mosquito populations enters the region:

$$\Omega_m = \left\{ (S_m, E_m, I_m) \in \mathbf{R}_+^3 : S_m \geq 0, E_m \geq 0, I_m \geq 0 \right\} N_m \leq \frac{\Lambda_m}{\delta_1}$$

$$\Omega_w = \left\{ (S_w, E_w, I_w) \in \mathbf{R}_+^3 : S_w > 0, E_w \geq 0, I_w \geq 0 \right\} N_w \leq \frac{\Lambda_w}{\delta_2}.$$

The solution remains positive for all time t , that is, the domain Ω is positively invariant and the model equation is biologically meaningful and mathematically well posed in the domain. Therefore, meaningful explanation of the disease transmission mechanism can now be carried out.

3.1 Positivity of Solutions

Lemma 3. Let the initial data be:

$$\left\{ S_m(0), S_w(0), S_h(0), \begin{pmatrix} E_m(0), I_m(0), E_w(0), I_w(0), S_v(0), S_{uv}(0), E_h(0), I_h(0), \\ I_{hN}(0), I_{hC}(0) \end{pmatrix} \geq 0 \right\} \in \Omega.$$

Then the solution:

$$\{S_m, E_m, I_m, S_w, E_w, I_w, S_h, S_v, S_{uv}, E_h, I_h, I_{hN}, I_{hC}, R_h(t)\} \text{ of the system is positive for all } t > 0.$$

Proof:

From the wolbachia-free mosquito compartment, we have:

$$\begin{aligned} \frac{dS_m}{dt} &= \Lambda_m - \alpha S_m - \delta_1 S_m \geq -\alpha S_m - \delta_1 S_m \geq -(\alpha + \delta_1) S_m \\ \Rightarrow \frac{dS_m}{dt} &\geq -(\alpha + \delta_1) S_m \end{aligned}$$

Using variable separable method, we have:

$$\frac{1}{S_m} \cdot \frac{dS_m}{dt} \geq -(\alpha + \delta_1) \text{ which on integration yields}$$

$$S_m \geq A e^{-(\alpha + \delta_1)t} \quad \text{where } (A = e^{c_1})$$

$$\text{At } t = 0 \quad S_m(0) = S_{m0} \geq A \Rightarrow S_m \geq S_{m0} e^{-(\alpha + \delta_1)t} \geq 0.$$

Similarly, we can solve for all the other variables to get:

$$S_w \geq S_{w0} e^{-(\beta + \delta_2)t} \geq 0.$$

$$S_h \geq S_{h0} e^{-(K + \psi + \mu)t} \geq 0.$$

Similarly, it can be shown that the human, wolbachia-free and wolbachia-infected mosquito population compartments of the system are all positive for all $t > 0$

We have thus shown that the model is invariant and has positivity of solutions. As such we can then investigate the existence of the disease equilibrium states and possibly the stability of the disease in the population.

3.2 Equilibrium State

Equilibrium analysis of a given disease model enables us to know whether there could be possible disease free or persistent disease presence (Endemic state) in a given population. There are two types of equilibrium usually studied. These are the **disease-free equilibrium (DFE)** and the **endemic disease equilibrium (EE)**.

3.2.1 Disease Free Equilibrium (DFE)

The disease-free equilibrium is defined as the point at which no disease is present in the population. It enables us to know how the model behaves within a short period of time.

Now we consider the disease classes for the wolbachia-free mosquitoes, wolbachia-infected mosquitoes and the human compartment which can be defined as:

$$E_m, I_m, E_w, I_w, E_h, I_h, I_{hN}, I_{hC}.$$

The DFE state of equations (1 - 14) is given by:

$$E^o = (S_m^0, E_m^0, I_m^0, S_w^0, E_w^0, I_w^0, S_h^0, S_v^0, S_{uv}^0, E_h^0, I_h^0, I_{hN}^0, I_{hC}^0).$$

In the absence of the disease or at disease free state, we have:

$$E_h = I_h = E_m = I_m = E_w = I_w = I_{hN} = I_{hC} = 0, \text{ which also implies that:}$$

$$S_v = S_{uv} = R_h = 0.$$

This is to say that, in the absence of the disease, there won't be need for vaccination, infectious rate is trivial and recovery rate is highly immaterial.

Considering the *wolbachia-free mosquito's compartment* and setting the equations to zero, we have:

$$\Lambda_m - \alpha S_m^0 - \delta_1 S_m^0 = 0 \quad (i)$$

$$\alpha S_m^0 - b E_m^0 - \delta_1 E_m^0 = 0 \quad (ii)$$

$$b E_m^0 - \delta_1 I_m^0 = 0 \quad (iii)$$

Recall that $E_m = I_m = 0$

Then, from equation (i) we have:

$$(S_m^0, E_m^0, I_m^0) = \left(\frac{\Lambda_m}{\alpha + \delta_1}, 0, 0 \right) \quad [A]$$

Similarly we can obtain those of the wolbachia-infected mosquitoes and the humans as:

$$(S_w^0, E_w^0, I_w^0) = \left(\frac{\Lambda_w}{\beta + \delta_2}, 0, 0 \right) \quad [B]$$

$$(S_h^0, S_v^0, S_{uv}^0, E_h^0, I_h^0, I_{hN}^0, I_{hC}^0, R_h^0) = \left(\frac{\Lambda_h}{\mu}, 0, 0, 0, 0, 0, 0 \right) \quad [C]$$

From equation A,B,C we have:

$$S_m^0 = \frac{\Lambda_m}{\alpha + \delta_1} \quad (20)$$

$$S_w^0 = \frac{\Lambda_w}{\beta + \delta_2} \quad (21)$$

$$S_h^0 = \frac{\Lambda_h}{\mu} \quad (22)$$

The above **equations (20 - 22)** represents the rate at which there is no infection in the society. Therefore, the disease-free equilibrium state of the model **equation (1- 14)** is given by:

$$\begin{aligned} E^0 &= (S_m^0, E_m^0, I_m^0, S_w^0, E_w^0, I_w^0, S_h^0, S_v^0, S_{uv}^0, E_h^0, I_h^0, I_{hN}^0, I_{hC}^0, R_h^0) \\ &= \left(\frac{\Lambda_m}{\alpha + \delta_1}, 0, 0, \frac{\Lambda_w}{\beta + \delta_2}, 0, 0, \frac{\Lambda_h}{\mu}, 0, 0, 0, 0, 0, 0, 0 \right). \end{aligned}$$

3.2.2 Endemic Equilibrium State

From the Wolbachia-free mosquitoes' compartment, we solve for the endemic point(s). However, note that in the endemic case, the derivatives on the left-hand side of equations (1 – 14) are still zero but since the disease is endemic, at least some(all) of the disease compartments are non-zero. Thus, we solve the equations to obtain the following:

$$S_m^* = \frac{\Lambda_m}{\alpha + \delta_1} \quad (23)$$

$$E_m^* = \frac{\alpha \Lambda_m}{\alpha b + \delta_1(b + \alpha + \delta_1)} \quad (24)$$

$$I_m^* = \frac{\alpha b \Lambda_m}{\delta_1 [\alpha b + b \delta_1 + \alpha \delta_1 + \delta_1^2]} \quad (26)$$

$$S_w^* = \frac{\Lambda_w}{\beta + \delta_2} \quad (27)$$

$$E_w^* = \frac{\beta S_w^*}{\xi + \delta_2} \quad (28)$$

$$E_w^* = \frac{\beta \Lambda_w}{\xi \beta + \delta_2(\xi + \beta + \delta_2)} \quad (29)$$

$$I_w^* = \frac{\xi \beta \Lambda_w}{\delta_2 [\xi \beta + \xi \delta_2 + \delta_2^2]} \quad (30)$$

$$S_v^* = \frac{k(\Lambda_h + \tau R_h^*)}{\theta(\psi + \mu) + (\lambda_1 + \mu)(k + \psi + \mu)} \quad (31)$$

$$S_{uv}^* = \frac{\psi [(\Lambda_h + \tau R_h^*)(\theta(\psi + \mu) + (\lambda_1 + \mu)(k + \psi + \mu) + k\theta)]}{(\lambda_2 + \mu)(k + \psi + \mu)[\theta(\psi + \mu) + (\lambda_1 + \mu)(k + \psi + \mu)]} \quad (32)$$

$$E_h^* = \frac{(\Lambda_h + \tau R_h^*) [\lambda_1 k(\lambda_2 + \mu)(k + \psi + \mu) + \lambda_2 \psi(k\theta + \theta(\psi + \mu))] + \lambda_2 \psi[(\lambda_1 + \mu)(k + \psi + \mu)]}{(\theta + \mu)(\lambda_2 + \mu)(k + \psi + \mu)[\theta(\psi + \mu) + (\lambda_1 + \mu)(k + \psi + \mu)]} \quad (33)$$

$$I_h^* = \frac{\theta(\Lambda_h + \tau R_h^*)[\lambda_1 k(\lambda_2 + \mu)(k + \psi + \mu)] + \lambda_2 \psi(k\theta + \theta(\psi + \mu)) + \lambda_2 \psi \theta[(\lambda_1 + \mu)(k + \psi + \mu)]}{(\rho_1 + \rho_2 + \mu)(\theta + \mu)(\lambda_2 + \mu)(k + \psi + \mu)[\theta(\psi + \mu) + (\lambda_1 + \mu)(k + \psi + \mu)]} \quad (34)$$

$$I_{hN}^* = \frac{\rho_1 \theta(\Lambda_h + \tau R_h^*)[\lambda_1 k(\lambda_2 + \mu)(k + \psi + \mu)] + \lambda_2 \psi(k\theta + \theta(\psi + \mu)) + \rho_1 \lambda_2 \psi \theta[(\lambda_1 + \mu)(k + \psi + \mu)]}{(\mu + \gamma_1)(\rho_1 + \rho_2 + \mu)(\theta + \mu)(\lambda_2 + \mu)(k + \psi + \mu)[\theta(\psi + \mu) + (\lambda_1 + \mu)(k + \psi + \mu)]} \quad (35)$$

$$I_{hC}^* = \frac{\rho_2 \theta(\Lambda_h + \tau R_h^*)[\lambda_1 k(\lambda_2 + \mu)(k + \psi + \mu)] + \lambda_2 \psi(k\theta + \theta(\psi + \mu)) + \lambda_2 \psi \theta[(\lambda_1 + \mu)(k + \psi + \mu)]}{(\delta_3 + \mu + \gamma_2)(\rho_1 + \rho_2 + \mu)(\theta + \mu)(\lambda_2 + \mu)(k + \psi + \mu)[\theta(\psi + \mu) + (\lambda_1 + \mu)(k + \psi + \mu)]} \quad (36)$$

$$R_h^* = \frac{(\Lambda_h[\lambda_1 k(\lambda_2 + \mu)(k + \psi + \mu) + \lambda_2 \psi(k\theta + \theta(\psi + \mu))] + \{(\lambda_2 \psi)(\lambda_1 + \mu)(k + \psi + \mu)\})\{(\delta_3 + \mu + \gamma_2)(\rho_1 \gamma_1 \theta) + (\mu + \gamma_1)(\rho_2 \gamma_2 \theta)\}}{[(\tau + \mu)(\mu + \gamma_1)(\delta_3 + \mu + \gamma_2)(\rho_1 + \rho_2 + \mu)(\theta + \mu)(\lambda_2 + \mu)(k + \psi + \mu)[\theta(\psi + \mu) + (\lambda_1 + \mu)(k + \psi + \mu)]]} \quad (37)$$

$$S_h^* = \frac{\Lambda_h[(\theta k + \theta(\psi + \mu) + (\lambda_1 + \mu)(k + \psi + \mu))]}{(k + \psi + \mu)[\theta(\psi + \mu) + (\lambda_1 + \mu)(k + \psi + \mu)]} + \frac{\tau(\theta k + [\theta(\psi + \mu) + (\lambda_1 + \mu)(k + \psi + \mu)])}{(k + \psi + \mu)[\theta(\psi + \mu) + (\lambda_1 + \mu)(k + \psi + \mu)]} \times \frac{(\Lambda_h[\lambda_1 k(\lambda_2 + \mu)(k + \psi + \mu) + \lambda_2 \psi(k\theta + \theta(\psi + \mu))] + \{(\lambda_2 \psi)(\lambda_1 + \mu)(k + \psi + \mu)\})\{(\delta_3 + \mu + \gamma_2)(\rho_1 \gamma_1 \theta) + (\mu + \gamma_1)(\rho_2 \gamma_2 \theta)\}}{[(\tau + \mu)(\mu + \gamma_1)(\delta_3 + \mu + \gamma_2)(\rho_1 + \rho_2 + \mu)(\theta + \mu)(\lambda_2 + \mu)(k + \psi + \mu)[\theta(\psi + \mu) + (\lambda_1 + \mu)(k + \psi + \mu)]]} \quad (39)$$

From these computations, we can write the endemic equilibrium state as:

$$E^* = (S_m^*, I_m^*, E_m^*, I_w^*, S_w^*, E_w^*, I_v^*, S_v^*, S_{uv}^*, E_h^*, I_h^*, I_{hN}^*, I_{hC}^*, R_h^*), \quad (40)$$

with the values of the variables as obtained above.

4 Stability Analyses

Stability analysis is a basic analysis of a dynamical system which is used to study and predict the variability or instability characteristics of the system. It can also be defined as an analysis indicating how a model reacts to perturbation or changes in any of the compartments of the disease population such as the infectious compartments or in the interaction or contact rate of the susceptible and the infectious classes. We shall consider stability at the disease-free equilibrium and endemic equilibrium respectively.

4.1 Local Stability of Disease-Free Equilibrium

The local stability of a disease-free equilibrium enables us to study the short-term dynamics of the disease. The disease-free equilibrium (DFE) is locally asymptotically stable (LAS) if $R_0 < 1$ and unstable if $R_0 > 1$. The above theorem simply implies that: if $R_0 < 1$, then on the average, an infected individual produces less than one new infected individual over the course of its infectious period,

and the infection cannot grow. Conversely, if $R_0 > 1$, then each infected individual produces on the average, more than one new infection, and the disease can invade the population.

However, to carry out the analysis this local stability of the disease-free equilibrium, we shall use the Jacobian matrix method. Thus, we obtain from the model equations (1 - 14)) as shown below:

$$J^0 = \begin{bmatrix} -\delta_1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & -(b + \delta_1) & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & b & -\delta_1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & -\delta_2 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & -(\xi + \delta_2) & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & \xi & -\delta_2 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & -(k + \psi + \mu) & \theta & 0 & 0 & 0 & 0 & 0 & \tau \\ 0 & 0 & 0 & 0 & 0 & 0 & k & -(\theta + \mu) & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & \psi & 0 & -\mu & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & -(\theta + \mu) & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & \theta & -(\rho_1 + \rho_2 + \mu) & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & \rho_1 & -(\gamma_1 + \mu) & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & \rho_2 & 0 & -(\delta_3 + \mu + \gamma_2) & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & \gamma_1 & \gamma_2 & -(\tau + \mu) \end{bmatrix}$$

From the above, we have $|J^0 - \lambda I| = 0$, and using rows and column transformation, the above matrix is reduced to obtain the following eigen values:

$$\lambda_1 = \lambda_2 = -\delta_1, \lambda_3 = -(b + \delta_1), \lambda_4 = \lambda_5 = -\delta_2, \lambda_6 = -(\xi + \delta_2), \lambda_7 = -\mu.$$

After the reduction of the matrix, MAPLE is further used to obtain the remaining eigenvalues as shown below:

$$\lambda_8 = -(\theta + \mu), \lambda_9 = -(\rho_1 + \rho_2 + \mu), \lambda_{10} = -(\gamma_1 + \mu), \lambda_{11} = -(\delta_3 + \mu + \gamma_2), \lambda_{12} = -(\tau + \mu),$$

$$\lambda_{13} = -\left(\frac{\theta}{2} + \mu - \frac{k}{2} + \frac{\psi}{2} - \sqrt{(k^2 + 2k\psi + 2k\theta - 2\psi\theta + \theta^2)}\right),$$

$$\lambda_{14} = -\left(\frac{\theta}{2} + \mu - \frac{k}{2} + \frac{\psi}{2} + \sqrt{(k^2 + 2k\psi + 2k\theta - 2\psi\theta + \theta^2)}\right).$$

Since all the eigen values are negative, we conclude that the disease-free equilibrium (DFE) is locally stable.

4.2 Local Stability of Endemic Equilibrium (EEP)

The local stability of an endemic equilibrium enables us to study the long-term dynamics of the disease.

To analyse the local stability of the endemic equilibrium, we consider the Jacobian matrix of the model equations (1- 14) above, we use the Jacobian matrix method to obtain:

$$J' = \begin{bmatrix} -(\alpha + \delta_1) & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ \alpha & -(b + \delta_1) & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & b & -\delta_1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & -(\beta + \delta_2) & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & \beta & -(\xi + \delta_2) & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & \xi & -\delta_2 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & -(k + \psi + \mu) & \theta & 0 & 0 & 0 & 0 & 0 & \tau \\ 0 & 0 & 0 & 0 & 0 & 0 & k & -(\theta + \lambda_1 + \mu) & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & \psi & -(\lambda_2 + \mu) & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & \lambda_1 & -(\theta + \mu) & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & \theta & -(\rho_1 + \rho_2 + \mu) & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & \rho_1 & -(\gamma_1 + \mu) & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & \rho_2 & 0 & -(\delta_3 + \mu + \gamma_2) & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & \gamma_1 & \gamma_2 & -(\tau + \mu) & 0 & 0 \end{bmatrix}$$

and by row and column transformation, we have the following eigenvalues thereby reducing the matrix to 8 by 8 matrix as shown below:

$$\lambda_1 = -(\alpha + \delta_1), \lambda_2 = -(b + \delta_1), \lambda_3 = -\delta_1, \lambda_4 = -\delta_2, \lambda_5 = -(\xi + \delta_2), \lambda_6 = -(\beta + \delta_2)$$

$$\begin{bmatrix} -(k + \psi + \mu) & \theta & 0 & 0 & 0 & 0 & 0 & \tau \\ k & -(\theta + \lambda_1 + \mu) & 0 & 0 & 0 & 0 & 0 & 0 \\ \psi & 0 & -(\lambda_2 + \mu) & 0 & 0 & 0 & 0 & 0 \\ 0 & \lambda_1 & \lambda_2 & -(\theta + \mu) & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & \theta & -(\rho_1 + \rho_2 + \mu) & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & \rho_1 & -(\gamma_1 + \mu) & 0 & 0 \\ 0 & 0 & 0 & 0 & \rho_2 & 0 & -(\delta_3 + \mu + \gamma_2) & 0 \\ 0 & 0 & 0 & 0 & 0 & \gamma_1 & \gamma_2 & -(\tau + \mu) \end{bmatrix}$$

Simplifying the above matrix using MAPLE, the following eigenvalues were obtained:

$$\lambda_7 = -(\rho_1 + \rho_2 + \mu), \lambda_8 = -(\lambda_2 + \mu), \lambda_9 = -(\delta_3 + \mu + \gamma_2), \lambda_{10} = -(\theta + \mu), \lambda_{11} = -(\gamma_1 + \mu), \\ \lambda_{12} = -(\tau + \mu),$$

$$\begin{aligned}
\lambda_{13} &= -\frac{k}{2} - \mu - \frac{\psi}{2} - \frac{\theta}{2} - \frac{\lambda_1}{2} \\
&\quad + \frac{1}{2} \sqrt{(k^2 + 2k\psi + 2k\theta - 2k\lambda_1 + \psi^2 - 2\psi\theta - 2\psi\lambda_1 + \theta^2 + 2\theta\lambda_1 + \lambda_1^2)} \\
&= -\left[\frac{k}{2} + \mu + \frac{\psi}{2} + \frac{\theta}{2} + \frac{\lambda_1}{2} - \right. \\
&\quad \left. \frac{1}{2} \sqrt{(k^2 + 2k\psi + 2k\theta - 2k\lambda_1 + \psi^2 - 2\psi\theta - 2\psi\lambda_1 + \theta^2 + 2\theta\lambda_1 + \lambda_1^2)} \right], \\
\lambda_{14} &= -\frac{k}{2} - \mu - \frac{\psi}{2} - \frac{\theta}{2} - \frac{\lambda_1}{2} \\
&\quad - \frac{1}{2} \sqrt{(k^2 + 2k\psi + 2k\theta - 2k\lambda_1 + \psi^2 - 2\psi\theta - 2\psi\lambda_1 + \theta^2 + 2\theta\lambda_1 + \lambda_1^2)} \\
&= -\left[\frac{k}{2} + \mu + \frac{\psi}{2} + \frac{\theta}{2} + \frac{\lambda_1}{2} + \right. \\
&\quad \left. \frac{1}{2} \sqrt{(k^2 + 2k\psi + 2k\theta - 2k\lambda_1 + \psi^2 - 2\psi\theta - 2\psi\lambda_1 + \theta^2 + 2\theta\lambda_1 + \lambda_1^2)} \right].
\end{aligned}$$

If all the eigenvalues are negative, we conclude that the endemic equilibrium is locally stable and unstable if otherwise.

5 Simulation of the Model Equations

A numerical simulation of the model equations is conducted using Runge-kutta method of order 4 in MATLAB and MAPPLE software in order to find out the dynamics of the disease in both human, wolbachia-free and wolbachia-infected mosquitoes' populations.

The initial conditions for the three populations are:

$$\begin{aligned}
&\mathbf{S}_{h(0)} = 4200, \mathbf{S}_{v(0)} = 3200, \mathbf{S}_{uv(0)} = 2000, \mathbf{E}_{h(0)} = 1000, \mathbf{I}_{h(0)} = 1070, \mathbf{I}_{hN(0)} = 1200, \mathbf{I}_{hC(0)} = 450, \\
&\mathbf{S}_{m(0)} = 300, \mathbf{E}_{m(0)} = 5000, \mathbf{I}_{m(0)} = 4000, \mathbf{S}_{w(0)} = 600, \mathbf{E}_{w(0)} = 4000, \mathbf{I}_{w(0)} = 3000, \mathbf{R}_{h(0)} = 300.
\end{aligned}$$

Table3: Parameter values for model

Parameter	Description	Base Value	Source
Λ_m	The basic recruitment level for wolbachia-free mosquitoes.	3000	Assumed
Λ_w	The basic recruitment level for wolbachia-infected mosquitoes.	1500	Assumed

Λ_h	The basic recruitment level for human	2000	Assumed
α	The rate at which susceptible wolbachia-free mosquitoes are exposed to flavivirus	0.02	[8]
b	The rate at which an exposed wolbachia-free mosquitoes are infectious	0.1000	[8]
δ_1	Natural death rate of wolbachia-free mosquitoes	0.061	[15]
β	The rate at which susceptible wolbachia-infected mosquitoes are exposed to flavivirus	0.004	Assumed
ξ	The rate at which an exposed wolbachia-infected mosquitoes are infectious.	0.51	
δ_2	Natural death rate of wolbachia-infected mosquitoes	0.068	[24]
k	The rate at which people are vaccinated	0.01	[32]
ψ	The rate at which people are unvaccinated	0.99	[32]
λ_1	The force of infection of a susceptible vaccinated humans	0.05	[27]
λ_2	The force of infection of a susceptible unvaccinated human	0.2	Assumed
θ	The rate at which vaccinated humans becomes susceptible.	0.005	Assumed
τ	The rate at which recovered humans become susceptible.	0.89	Assumed
ϕ	The rate at which an exposed humans become infectious.	0.31	[27]
ρ_1	The rate at which infectious humans progress to the non-chronic phase of the disease	0.85	[27]
ρ_2	The rate at which infectious humans progress to	0.25	[27]

	the chronic phase of the disease.		
γ_1	Natural recovery rate of humans at the non-chronic phase of the disease	0.9	Assumed
γ_2	The recovery rate of humans at the chronic phase of the disease.	0.143	[21]
μ	The natural death rate of humans	0.000035	[21]
δ_3	Death induced by the disease	0.068	[21]
u_1	The rate of contact between an infectious wolbachia-free mosquitos and vaccinated human	0.05	Assumed
u_2	The rate of contact between an infectious wolbachia-free mosquitos and unvaccinated human	0.04	Assumed
v_1	The rate of contact of an infectious wolbachia-infected mosquitoes and vaccinated human	0.003	Assumed
v_2	The rate of contact of an infectious wolbachia-infected mosquitoes and unvaccinated human	0.002	Assumed
m_1	The rate of contact of a non chronic infectious human and a susceptible wolbachia-free mosquitoes	0.00025	Assumed
m_2	The rate of contact of a chronic infectious human and a susceptible wolbachia-free mosquitoes	0.00031	Assumed
n_1	The rate of contact of a non chronic infectious human and a susceptible wolbachia-infected mosquitoes	0.000011	Assumed
n_2	The rate of contact of a chronic infectious human and a susceptible wolbachia-infected mosquitoes	0.00021	Assumed

Here, the effect of interaction between human, Wolbachia-free and Wolbachia-infected mosquitoes were investigated. Since interaction occurs on a faster timescale, the dynamics of an outbreak can be affected. Thus, we present the following graphical results:

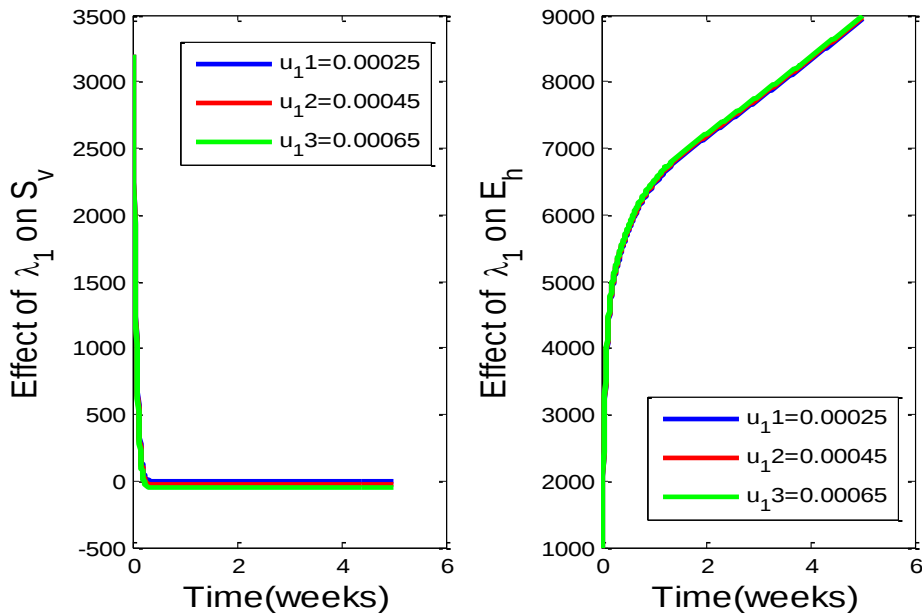


Figure 1.

Figure 1 above shows that, the increasing biting rate of the wolbachia-free infectious mosquitoes on vaccinated human, does not in any way change the trend of the infection in the population since the susceptible is protected against the disease. We can equally see that the population of the exposed persons does not change irrespective of the level of contact of the Wolbachia-free mosquito with susceptible human population. This now confirm the fact in our assumption of this model that **“the population of the vaccinated humans only decreases as the average daily biting rate of the mosquito increases if the vaccination effect wanes with time in the susceptible.**

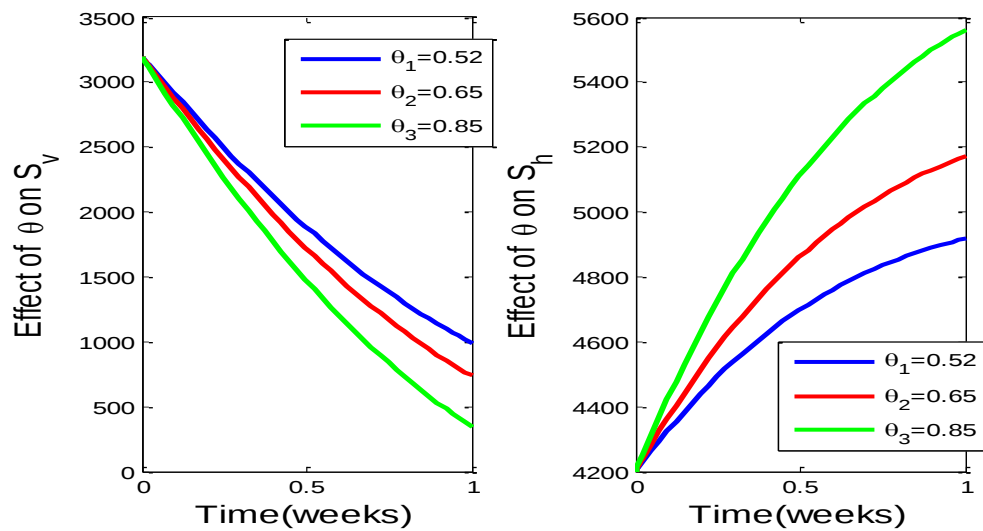


Figure 2.

From Figure 2, we can see that as more vaccinated persons loose their immunity, the population of vaccinated compartment reduces while the population of the exposed class increases. What this shows is that as we loose immunity due to the wanning of the vaccine, people become more exposed to the disease because they are no longer protwcted. This is the reason for asking persons even though vaccinated, to be careful about exposing oneself to yellow fever by carefully avoided any interactions with yellow-fever infectious individuals.

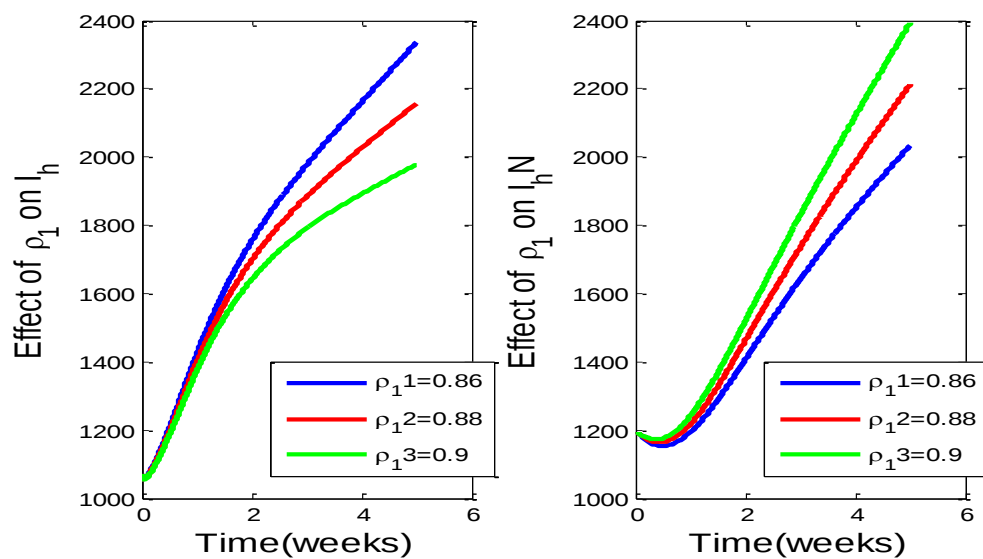


Figure 3.

Figure 3 above clearly shows that if there is increment in the rate at which infectious persons move to the remission stage, that is the non-chronic stage, then the population of the infectious compartment reduces while that of the non-chronic compartment increases. A look at the second graph shows that the population decreased first before increasing. Practically, this explains that it takes more time for infectious individual to remain in the non-chronic stage than for the non-chronic persons to remain in the non-chronic stage. This implies that the domicility time in this stage is transient, that is very small, and so people must have moved more to the chronic stage before the mass movement from the infectious class dominates the movement from the non-chronic stage or compartment and so the cause of the increment in the population of the non-chronic compartment.

6 Conclusion

This work is basically centered on a mathematical model consisting of three compartmental populations i.e. the human population, wolbachia-free mosquitoes and wolbachia-infected mosquito populations. The dynamical system was studied using a classical fourth order Runge-Kutta method in MATLAB for the ordinary differential equation model. We investigated the stability analysis of both disease free and endemic equilibrium states and found that its locally and asymptotically stable. Numerical simulations were presented for various values of parameters which aid us in sensitivity analysis. From these analyses we found that in order to completely eradicate yellow fever disease, there is need for vaccination against the disease. Furthermore, we needed to ensure that the rate at which people move from infectious class to the non-chronic stage must be effectively controlled if the yellow fever disease has to be eradicated. This means that appropriate and early detection and treatment of yellow fever disease must be handled appropriately, timely and efficiently.

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