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MODELLING THE USE OF *WOLBACHIA* TO CONTROL MALARIA TRANSMISSION

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ABSTRACT: *Experimental Wolbachia infections can reduce Plasmodium number in Anopheles mosquitoe in the laboratory, however, natural Wolbachia infections in field anophelines has never been reported. There is evidence of Wolbachia infections in Anopheles gambaie in Burkina Faso, West Africa. We modify the the malaria transmission model with two delays by including the effect of Wolbachia. By analyzing the characteristic equations of disease free and endemic equilibrium, we obtain the basic reproduction number R_0 and prove the stability of the steady states. We were able to show that careful use of Wolbachia can curtail the spread of malaria in area where R_0 is not higher enough. Otherwise, Wolbachia either eradicates the mosquito population, or has a little effect the spread of malaria. We suggest that the development of Wolbachia-based malaria control method can be a very effective in conjunction with other methods such as reduction of breeding sites.*

KEYWORDS: Malaria;Wolbachia; Cytoplasmic incompatibility; Modelling.

AMS Subject Classification: 92D30

INTRODUCTION

Malaria

Malaria is a mosquito-borne disease caused by Plasmodium parasite,which is transmitted through the bites of an infected mosquito. In 2017, the World Health Organization report reveals estimations of 216 million malaria cases and 445 thousand deaths due to malaria were registered world wide in 2016. However, the most malaria cases and deaths were shared by the WHO Africa region, which account for 90% of cases and 91% death. The most predominant malaria parasite in the WHO Africa region is Plasmodium falciparum, accounting for 99% of malaria cases in 2016 [1]. Malaria is a mosquito-borne disease which is due to four species of the genus plasmodium, namely, *Plasmodium falciparum, Plasmodium vivax, Plasmodium malariae, and Plasmodium ovale*. These parasites are transmitted to the human host through a bite by an infected female anopheles mosquito [12]. Sporozoites are injected into a human host, which are carried through the blood to the liver within 30 min. They invade hepatocytes and undergo a process of asexual replication (exoerythrocytic schizogony) to give rise to 10-40 thousand merozoites per sporozoite. Up to this point, the infection is nonpathogenic and clinically silent. After about 7-9 days, the liver schizonts rupture to release the merozoites into the blood and clinical symptoms, such as fever, pain, chills, and sweat, may develop. Each merozoite invades an erythrocyte and divide to form an erythrocytic schizont containing about 16 daughter merozoites . These merozoites either reinfect fresh erythrocytes, giving rise to cyclical blood-stage infection with a periodicity of 48-72h, depending on the plasmodium species, or differentiate into sexual transmission stages called gametocytes. When a second mosquito bites the infected human, the gametocytes are ingested, giving rise to extracellular

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gametes. In the mosquito midgut, the gametes fuse to form a metile zygote (ookinete), which penetrates the id-gut wall and forms an oocyst, within which meiosis takes place and haploid sporozoites develop. These sporozoites migrate to salivary glands. The incubation period within the mosquito may least 8-22 days. The variation in the length of time is due to the invironmental temperature. For *P. falciparum*, the average time is 12 days. Malaria can also be transmitted through a blood transfusion, organtransplantation and transplacental malaria (i.e. congenital malaria) can also be significant in population which are partially immune to malaria [12]. Current insecticide-based control strategies to stop malaria transmission by targeting the mosquito vector are limited by the rapid spread of insecticide resistance [13]. In addition, these interventions target only indoor feeding and resting populations, with the use of insecticide-treated bednets and the application of indoor residual sprays, respectively. Recent attempts to control transmission have proved unsustainable, so a new approach is needed.

Wolbachia

Wolbachia pipientis is an intracellular maternally inherited bacterial symbiont of invertebrates that is very common in insects, including a number of mosquito species [18,19]. It can manipulate host reproduction in several ways, including cytoplasmic incompatibility (CI), where by certain crosses are rendered effectively sterile. Females that are uninfected produce infertile eggs when they mate with male that carry *Wolbachia*, while there is a 'rescue' effect in *Wolbachia*-infected embryos such that infected females can reproduce successfully with any males. Therefore uninfected females suffer a frequency-dependent reproductive using this powerful mechanism [20,21].

A strain of *Wolbachia* called *wMelPop* has been identified that over-replicates in somatic tissues and roughly halved the lifespan of laboratory *Drosophila melanogaster* [22]. A transinfection of *wMelPop* from *Drosophila* into the mosquito *Aedes aegypti* also leads to a similarly shortened lifespan in the lab, as well as inducing strong CI, which has made it a very promising candidate for the development of a new strategies for controlling mosquito-borne diseases [23]. All mosquito-borne pathogens require an extrinsic incubation period before they can be transmitted that is relatively long (9 days for malaria) compared to mean mosquito lifespan in the field; therefore, a reduction in the number of old individuals in the population will reduce disease transmission [24,25].

Indeed, while *Wolbachia* strains have been detected in many insects, attempts to identify these bacteria in field Anophele have failed, promoting the belief that these mosquitoes are not natural hosts for wolbachia [3]. Taken together with the report in P.*gallinaceum* development in *wMelPop*-infected Ae. aedypti, the data increase the desirability of creating stably *wMelPop* transinfection in important malaria vectors. The potential combination of lifespan shortening and direct inhibition of *Plasmodium* development in the mosquito would represent a very attractive control strategy, since both of these phenotypes are critical components of malaria vectorial capacity. Though lifespan reduction and *Plasmodium* inhibition can each substantially reduce the vectorial capacity of a mosquito population, together they act synergistically to reduce transmission. Depending on the scale of lifespan reduction that would be observed under field conditions, which is as yet unknown, the Plasmodium inhibition effect could dramatically increase the efficacy of the *wMelPop* infection in reducing malaria transmission [5].

Other wolbachia strain might also show malaria inhibition effects, particularly if they reach high somatic densities and/or induce large-scale immune stimulation. Despite *wAlbB* and

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wMelPop suppresing immunity in older *Anophele gambaie* both these strain reduced the levels of the human malaria parasite *Plasmodium falciparum* within the mosquito [4,8]. If other wolbachia strains can be identified which also inhibit Plasmodium transmission, they would represent an attractive alternative to *wMelPop* if they do not shorten lifespan to the same extent, since they are therefore likely to have much lower fitness costs. Only the *wMelPop* strain has to date been found to produce a strong life-shortening phenotype [5]. Several studies present evidence that wolbachia is likely to provide some protection against human malaria plasmodium parasites if stable transinfection of Anopheles is achieved. The effect of the *wMelPop* strain on Plasmodium.*gallinaceum* was tested as this space of malaria parasite is known to be able to infect *Ae. aegypti* mosquitoes in the laboratory. The P. *gallinaceum* oocystload was reduced by 67-88% for *wMelPop* infected *Ae. aegypti* mosquitoes compared to wolbachiauninfected mosquitoes seven day after feeding on an infected chicken (Moreira et al.2009). In *An. gambaie* females transiently infected with *wMelPop* using adult injection, means Plasmodium *berghei* levels were reduced by 75-84% (Kambris et al.2010) although this combination of vector/parasite does not occur in nature, these results do highlight the ability of *Wolbachia* to significantly reduce the level of malaria parasites in A nopheles mosquitoes [2]. There are two ways in which *Wolbachia*-infected mosquitoes may be inferior malaria vectors:

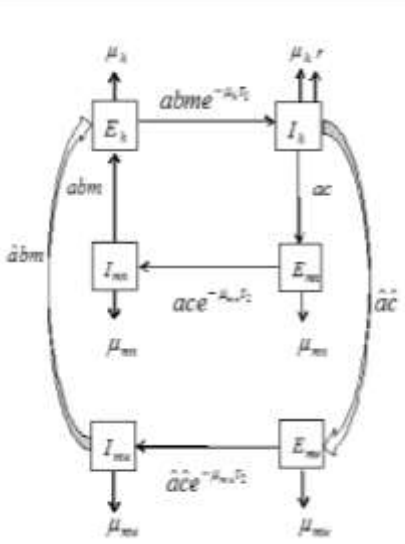
First, Adult mosquitoes experience a high daily mortality rate resulting in only a small parcentage of the total population actually surviving along enough to transmit malaria (Brownstein et al. 2003) therefore a reduction in the daily survival rates is likely to remove a large proportion of the mosquito population capable of transmitting malaria [6].

Second, Recent proof that *Wolbachia* infections of anopheles vectors limit the development of plasmodium parasites that cause malaria [5,6,10] make these bacteria a particularly attractive tool for the control of both endo-and exophagic population of malaria tranmsitting anophelines.

Figure 1: Transfer diagram of the model [2.3]

We shall set up a model that takes account of these changes in vector fitness and transmission potential.

Modelling



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We set up a model to study how introducing *Wolbachia* into *An. gambaie* population might affect the spread of malaria disease. In it, models for *Wolbachia* and malaria infection are superposed on an underlying model for the dynamic of stage structure insect population. In the absence of the density-dependent effect, the insect population may be modelled by

$$\frac{dN}{dt}(t) = \beta e^{-dT_\mu} - \mu N(t) = \beta N(t - T_\mu) - \mu N(t) \quad (2.1)$$

Here, N is the population density of adult female insects, recruitment of offspring to the adult insect population is delayed by the development time T_μ, μ is the per capita death rate of adult mosquitoes, d is the per capita death rate of pre-adult mosquitoes, and B is the per capita birth rate. Hence, β is the per capita recruitment rate, or the rate of production of adult female mosquito for each adult mosquito alive at a time T_μ earlier, taking into account density independent deaths from the pre-adult stage. Density-dependent effects are then assumed to operate at the larval stage, and the model is modified as in Gurney et al.(1980) to give

$$\frac{dN}{dt} = \beta \hat{N} F(\hat{N}) - \mu N(t) \quad (2.2)$$

where $\hat{N}(t) = N(t - T_\mu)$, and F is a decreasing function with $F(0) = 1$, and $F(x) \to 0$ as $x \to \infty$.The model will be parameterised as Dye(1984) did, who took $F(x) = e^{(-hxk)}$, as we shall do when an explicit form is necessary. Note that Dye interpreted N as the size of a population of mosquitoes (in a particular temple complex in Bangkok), whereas we interpret it as a population density; this change will require us to make a correction to Dye's value of h to account for the area of the temple complex.

Based on delayed Ross-Macdonald model of malaria transmission included wolbachia-infected mosquitoes [6] . Now, we first present the model that we will use to study the effect of wolbachia on the malaria transmission. The model is an extension of the four delayed equations model of malaria originally discussed by Macdonald [13] and Anderson and May [16] adapted to include a *Wolbachia*-carrying mosquitoes population complete with the impact of reducing lifespan on the population dynamics. We then analyzed the equilibrium point and their stability for the two cases in which the time delays are zero and time delays are nonzero. We then discuss the method for numerical solution of these equation using Matlab.

We make the following modelling assumption:

-Firstly, We assume that the vector population keeps at a constant number before and after introducing *Wolbachia*. This is because previous experiments show that the hatch rate of mosquitoes depends on the environmental conditions such as climate, amount of breeding sites, and so on. For example, if they were to eliminate all larvae, pupae, and adult *Anophele gambiae* at once from a site, its population could recover two weeks later as a result of egg hatching following rainfall or the addition of water to containers harboring eggs. Therefore we assume that the egg supply is always sufficient but the environmental capacity determines the vector population.

-Second, We assume that the proportion of *Wolbachia*-infected mosquitoes in the whole population has arrived to its equilibrium. If it declines to 0, *Wolbachia* has no effect on the vectors, and the case is the same as the model we have in section 3.1. If *Wolbachia* is spread to fixationn^*_{mw} ,from our earlier analysis, we assume the range ofn^*_{mw} is between 0.53 and 1. -*Wolbachia* is a maternally transmitted [3], with transmission probability v; we shall take $v = 1$.

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Other mechanisms of transmission are so rare that they may be neglected. When a *Wolbachia*infected male mosquito fertilizes an uninfected egg, whether it is uninfected because its mother was uninfected or because its mother was infected but vertical transmission failed, there is a certain probability *u* that the zygote dies through cytoplasmic incompatibility [3]; we shall usually take *u* = 1. *Wolbachia* may alter the fecundity , longevity and malaria transmission of it host [6]. Mosquitoes do not become immune to *Wolbachia*; no case of mosquito immunity to *Wolbachia* has been reported.

-Mosquitoes with and without *Wolbachia* are equally likely to become infected with malaria; although they may differ in their ability to transmit it.

-Finally, we denote the mortality rate of *Wolbachia*-infected and *Wolbachia*-free mosquitoes by μ_{mw} and μ_{mn}, respectively; and we assume that its value satisfies μ_{mn} 6 μ_{mw} 6 2μ_{mn}. This assumption is based on laboratory Experiments. However, the laboratory provided a good environment for mosquitoes live, and we expect the life span of mosquitoes in wild to be shorter as a result of limited source of food, existence of predators and so on. Therefore, *Wolbachia* non-carriers have a shorter lifespan than the ones in laboratory, and the life-shortening effect of *Wolbachia* is not as strong as it was observed in lab.

Based on the above assumptions, we separate the mosquito population into two groups: *Wolbachia* carriers and *Wolbachia* non-carriers mosquitoes. We want to look at the dynamics of infectious mosquitoes within each group, and see for different proportions of *Wolbachia*infected mosquitoes, how the infectious human number will change.

The change of exposed and infectious humans depends on the infectious number of both *Wolbachia*-infected and uninfected mosquitoes. We assumed the *Wolbachia* level in mosquitoes has already reached to a fixed numbern^*_{mw}before malaria is introduced into the human population, therefore the factors $n^*_{mw} - e_{mw}(t) - i_{mw}(t$) and (1 $- n^*_{mw}) - e_{mw}(t) - i_{mw}(t$) represent the proportion of *Wolbachia*-infected and non-carriers mosquitoes who do not have the disease(i.e.,who are not infected or infectious) at time t. For simplicity, assume the total populations of humans are constants and denoted by N_h. The mosquitoes are divided in two kinds, *Wolbachia* carriers mosquitoes denoted by $N_{mw}(t)$ and *Wolbachia* no-carriers mosquitoes denoted by N_{mn} given by $N_{mn}(t) = N_m(t) - N_{mw}(t)$. Let $E_h(t)$ and $I_h(t)$ represent the number of exposed and infectious humans. $E_{mw}(t)$ and I_{mw} represent the number of exposed and infectious *Wolbachia*-infected mosquitoes, and $I_{mn}(t)$ and $E_{mn}(t)$ are the corresponding numbers for *Wolbachia* non-carriers. Let *a* and ˆ*a* be the rate of biting on humans by a single *Wolbachia*-free and carrying mosquito (number of bites per unit time), respectively. Then the number of bites on humans per unit time per human is $\frac{a}{N_h}$ ($\frac{\hat{a}}{N_h}$ for *Wolbachia*-carrying mosquito). Let *b* be the proportion of infected bites on humans that produce an infection.

The model contains two time delays for transition from infected to infectious stage in humans (τ_1) and from infected to infectious stage in mosquitoes (τ_2). The equations of the model are:

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$$\begin{cases}
\frac{dE_h}{dt} = (\frac{a}{N_h})b[I_{mn}(t) + I_{mw}(t)][N_h - E_h(t) - I_h(t)] - \mu_h E_h(t) \\
\quad -(\frac{a}{N_h})b[I_{mn}(t-\tau_1) + I_{mw}(t-\tau_1)][N_h - E_h(t-\tau_1) - I_h(t-\tau_1)]e^{-(r+\mu_h)\tau_1} \\
\frac{dI_h}{dt} = (\frac{a}{N_h})b[I_{mn}(t-\tau_1) + I_{mw}(t-\tau_1)][N_h - E_h(t-\tau_1) - I_h(t-\tau_1)]e^{-(r+\mu_h)\tau_1} - \mu_h I_h t - r I_h t \\
\frac{dN_{mn}(t)}{dt} = \beta \hat{Z}_{mn} F(\hat{Z}_{mn} + \hat{Z}_{mw}) - \mu_{mn} N_{mn} \\
\frac{dE_{mn}(t)}{dt} = (\frac{a}{N_h})cI_h(t)[(N_{mn} - N_{mw}) - E_{mn}(t) - I_{mn}(t)] - \mu_{mn} E_{mn}(t) \\
\quad -(\frac{a}{N_h})cI_h(t-\tau_2)[(N_{mn} - N_{mw}) - E_{mn}(t-\tau_2) - I_{mn}(t-\tau_2)]e^{-\mu_{mn}\tau_2} \\
\frac{dI_{mn}(t)}{dt} = (\frac{a}{N_h})cI_h(t-\tau_2)[(N_{mn} - N_{mw}) - E_{mn}(t-\tau_2) - I_{mn}(t-\tau_2)]e^{-\mu_{mn}\tau_2} - \mu_{mn} I_{mn}(t) \\
\frac{dN_{mw}(t)}{dt} = \beta \hat{Z}_{mw} F(\hat{Z}_{mn} + \hat{Z}_{mw}) - \mu_{mw} N_{mw} \\
\frac{dE_{mw}(t)}{dt} = (\frac{\hat{a}}{N_h})\hat{c}I_h(t)[N_{mw} - E_{mw}(t) - I_{mw}(t)] - \mu_{mw} E_{mw}(t) \\
\quad -(\frac{\hat{a}}{N_h})\hat{c}I_h(t-\tau_2)[N_{mw} - E_{mw}(t-\tau_2) - I_{mw}(t-\tau_2)]e^{-\mu_{mw}\tau_2} \\
\frac{dI_{mw}(t)}{dt} = (\frac{\hat{a}}{N_h})\hat{c}I_h(t-\tau_2)[N_{mw} - E_{mw}(t-\tau_2) - I_{mw}(t-\tau_2)]e^{-\mu_{mw}\tau_2} - \mu_{mw} I_{mw}(t)
\end{cases} \tag{2.3}$$

Let μ_h, μ_{mn} and μ_{mw} represent the mortality rate in the human population, the mortality rates in the non-*Wolbachia* and *Wolbachia*-carrying mosquito populations, r is the recovery rate of infectious humans from the disease.

Here, $\beta\hat{Z}_{mn}$ and $\beta\hat{Z}_{mw}$ are equivalent to the term in (2.2), and represent the basic recruitment rate of *Wolbachia*-free and *Wolbachia*-infected adults, in the absence of density-dependent effects. The un-delayed form obtained by keeping track of the number of infected and uninfected offspring are given by

$$Z_{mn} = \frac{N_{mn} + (1-u)N_{mw}}{N_{mn} + N_{mw}}(N_{mn} + (1-v)\phi N_{mw}), \quad Z_{mw} = v\phi N_{mw}. \tag{2.4}$$

The arguments of these are as follows. First, offspring infected by *Wolbachia* are only produced by *Wolbachia*-infected mothers N_{mw} producing offspring that survive to maturity (in the absence of density-dependent effects) at a rate $\beta\hat{}$, of which a fraction v are themselves infected; hence, $\beta Z_{mw} = \beta v N\hat{}_{mw}$, or $Z_{mw} = v\varphi N_{mw}$. Second, offspring uninfected by *Wolbachia* are produced both by *Wolbachia*-uninfected mothers N_{mn} producing offspring at rate β, all of whom are uninfected, and by *Wolbachia*-infected mothers producing offspring at rate $\beta\hat{}$, a fraction $1 - v$ of which are uninfected, which gives potential offspring $\beta Z_{mn} = \beta N_{mn} + \beta(1 - v)N_{mw}$. But we then have to take into account that these potential offspring may be inviable (with probability u) if their father is infected by *Wolbachia*, because CI. Assuming random mating, the probability of invability is therefore $uN_{mw}/(N_{mn} + N_{mw})$, which leads to the first equation of (2.4). The terms in F in system (2.3) represent the competition between all larvae, whether infected either *Wolbachia* or not.

The first equation of the sytem (2.3) represents the rate of change of the infected human population. The uninfected human $N_h - E_h(t) - I_h(t)$ will produce new infectious humans

$$(\frac{a}{N_h})b[I_{mn}(t) + I_{mn}(t)][N_h - E_h(t) - I_h(t)] \text{ at time } t. \text{ The term } (\frac{a}{N_h})b[I_{mn}(t-\tau_1) + I_{mw}(t-\tau_1)][N_h - E_h(t-\tau_1) - I_h(t-\tau_1)]e^{-(r+\mu h)\tau 1}$$

represents the rate at which humans move from the infected to the infectious stage after a latency period of time τ_1. The factor $e^{-\mu h \tau 1}$ allows for the

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death rate of humans during the period τ_1. The term $mu_hE_h(t)$ represents the death rate of infected humans at time *t*.

Second equation of the system represents the rate of change of infectious human population.

The term $(\frac{a}{N_h})b[I_{mn}(t-\tau_1)+I_{mw}(t-\tau_1)][N_h-E_h(t-\tau_1)-I_h(t-\tau_1)]e^{-(r+\mu_h)\tau_1}$ again represents the rate at which infected humans move to the infectious stage after a delay time τ_1. The term $-\mu_hI_ht$ represents the death number of infectious humans at time t and the term $-rI_ht$ represents the recovery number of infectious humans from the disease.

Fourth and seventh equations of the system represents the rate of change of exposed for infected non-*Wolbachia* and *Wolbachia* -carrying mosquitoes population,respectively. In third equation $(\frac{a}{N_h})cI_h(t)[(N_m-N_w)-E_{mn}(t-\tau_2)-I_{mn}(t-\tau_2$)] and in fifth ($\frac{\hat{a}}{N_h})\hat{c}I_h(t)[N_w-E_{mw}(t)-$

$I_{mw}(t)$] represent the rate at which non-*Wolbachia* and *Wolbachia*-caryying mosquitoes, respectively, become exposed by biting an infectious human. The factor $[(N_m-N_w)-E_{mn}(t-)-I_{mn}(t)]$ and $[N_w-E_{mw}(t)-I_{mw}(t)]$ represent the number of the non-*Wolbachia* and *Wolbachia*-carriers , respectively, without disease at time *t*.

The term $-(\frac{a}{N_h})cI_h(t-\tau_2)[(N_m-N_w)-E_{mn}(t-\tau_2)-I_{mn}(t-\tau_2)]e^{-\mu_{mn}\tau_2}$ and $-(\frac{\hat{a}}{N_h})\hat{c}I_h(t-$

$\tau_2)[N_w - E_{mw}(t - \tau_2) - I_{mw}(t - \tau_2)]e^{-\mu mw\tau 2}$ represents the rate at which non-*wolbachia* and *wolbachia*-carriers mosquitoes, respectively, move from the exposed to infectious stage after a latency period τ_2. The factor $e^{-\mu mn\tau 2}$ and $e^{-\mu mw\tau 2}$ allow for the death rate of all both mosquitoes during the period τ_2. The term $-\mu_{mn}E_{mn}(t)$ and $-\mu_{mw}E_{mw}(t)$ represent the death rate of infected non-*Wolbachia* and *Wolbachia*-carrying mosquitoes, respectively, at time *t*.

The fifth and the eighth equations represents the rate change of the non-*Wolbachia* and *Wolbachia*-carrying infectious mosquito population respectively.The term ($\frac{a}{N_h})c[I_h(t-\tau_2)][(N_m-$

Nw)−*Emn*(*t*−*τ*2)−*Imn*(*t*−*τ*2)]*e*−*μmnτ*2 and ($\frac{\hat{a}}{N_h})\hat{c}I_h(t-\tau_2)[N_w-E_{mw}(t-\tau_2)-I_{mw}(t-\tau_2)]e^{-\mu_{mw}\tau_2}$ again represent the rate at which non-*Wolbachia* and *Wolbachia*-carrying mosquitoes, respectively, move from the infected to infectious stage after a time τ_2. The term $-\mu_{mn}I_{mn}(t)$ and $-\mu_{mw}I_{mw}(t)$ represent the death rate of non-*Wolbachia* and *Wolbachia*-carrying mosquitoes, respectively, at time *t*.

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Table 1: Parameter descriptions and Values for models. The *Wolbachia*- related parameters are for the *wMelpop* strain.

Parameter	Description	Estimated value	Source
m	Ratio of mosquitoes to humans	7.7	[6]
a	Biting rate on human per *Wolbachia*-free mosquito	$0.5day^{-}$	[6]
b	Infected mosquito to human transmission effeciency	0.4	[6]
c	Infected human to *Wolbachia*-free mosquito Efficiency	0.79	[6]
μ_h	Human death rate by Malaria	$0.333day^{-1}$	[14]
μmn	Per capita mortality rate of *Wolbachia*-free mosquito	$0.15day^{-1}$	[6]
$a\hat{}$	Biting rate on human per *Wolbachia*-carrier mosquito	$0.565day^{-1}$	[6]
$c\hat{}$	Infected human to *Wolbachia*-carrier mosquito Efficiency	$0.07day^{-1}$	[6]
$\mu mw = \delta\mu_{mn}$	Per capita mortality rate of *Wolbachia*-carrier mosquito	$0.175day^{-1}$	[6]
r	Per capita human recovery rate	$0.02 - 0.05day^{-1}$	[6]
τ_1	incubation period for P.falciparum in human	$9.5day$	[17]
τ_2	Length of the latent period for mosquito	$12day$	[6]

Analysis

We shall always assume (for a nontrivial problem) that the mosquito population has the potential to survive in the absence of *Wolbachia*, so that its maximum per capita birth rate β exceeds its per capita death rate μ_{mn},$\beta > \mu_{mn}$ then the system (2.3) has a base-line

(malaria and *Wolbachia*-free) steady state given by (E_h,I_h,N_{mn},E_{mn},I_{mn},N_{mn},E_{mw}),I_{mw} = $(N^*_{mn}, 0, 0, 0, 0, 0, 0, 0)$, where $N^*_{mn} = F^{-1}(\mu_{mn}/\beta)$ is uniquely defined and positive since F is a

decreasing function with $F(0) = 1$,$F(x) \to 0$ as $x \to \infty$. Guided by the base line steady state, we non-dimensionalise the variables in the model as follow:

$$n_{mn} = N_{mn}/N^*_{mn}, \quad n_{mw} = N_{mw}/N^*_{mn}, e_h = E_h/N_h, \quad i_h = I_h/N_h,$$

$$zmn = Zmn/Nmn*, \quad emn = Emn/Nmn* \quad imn = Imn/Nmn*, imw = Imw/Nmn*, \quad (3.1)$$
$$zmw = Zmw/Nmn*, \quad , emw = Emw/Nmn*, \quad m = Nmn*/Nh$$

Then $e_h(t)$, $e_{mn}(t)$ and $e_{mw}(t)$ are the proportion of infected but not yet infectious humans, *Wolbachia*-free and *Wolbachia*-carrying mosquitoes at time t, respectively, $i_h(t)$, $i_{mn}(t)$ and $i_{mw}(t)$ are the proportion of infectious humans,*Wolbachia* -free and *Wolbachia*-carrying

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mosquitoes at time *t*, respectively, *m* is the number of female mosquitoes per human ($m = \frac{N^*_{mn}}{N_h}$ where N^*_{mn} is the whole *Wolbachia*-free mosquito population and N_h is the human population) We obtain the following delayed model:

$$\begin{cases} \frac{de_h(t)}{dt} = abm[i_{mn}(t) + i_{mw}(t)][1 - e_h(t) - i_h(t)] - \mu_h e_h(t) \\ \quad -abm[i_{mn}(t-\tau_1) + i_{mw}(t-\tau_1)][1 - e_h(t-\tau_1) - i_h(t-\tau_1)]e^{-(r+\mu_h)\tau_1} \\ \frac{di_h(t)}{dt} = amb[i_{mn}(t-\tau_1) + i_{mw}(t-\tau_1)][1 - e_h(t-\tau_1) - i_h(t-\tau_1)]e^{-(r+\mu_h)\tau_1} - \mu_h i_h(t) - r i_h(t) \\ \frac{dn_{mn}}{dt} = \alpha \hat{z}_{mn} f(\hat{z}_{mn} + \hat{z}_{mw}) - n_{mn} \\ \frac{de_{mn}(t)}{dt} = ac i_h(t)[(1 - n_{mw}) - e_{mn}(t) - i_{mn}(t)] - \mu_{mn} e_{mn}(t) \\ \quad -ac i_h(t-\tau_2)[(1 - n_{mw}) - e_{mn}(t-\tau_2) - i_{mn}(t-\tau_2)]e^{-\mu_{mn}\tau_2} \\ \frac{di_{mn}(t)}{dt} = ac i_h(t-\tau_2)[(1 - n_{mw}) - e_{mn}(t-\tau_2) - i_{mn}(t-\tau_2)]e^{-\mu_{mn}\tau_2} - r i_{mn}(t) - \mu_{mn} i_{mn}(t) \\ \frac{dn_{mw}}{dt} = \alpha \hat{z}_{mw} f(\hat{z}_{mw} + \hat{z}_{mw}) - \delta n_{mw} \\ \frac{de_{mw}(t)}{dt} = \hat{a}\hat{c} i_h(t)[n_{mw} - e_{mw}(t) - i_{mw}(t)] - \mu_{mw} e_{mw}(t) \\ \quad -\hat{a}\hat{c} i_h(t-\tau_2)[n_{mw} - e_{mw}(t-\tau_2) - i_{mw}(t-\tau_2)]e^{-\mu_{mw}\tau_2} \\ \frac{di_{mw}(t)}{dt} = \hat{a}\hat{c} i_h(t-\tau_2)[n_{mw} - e_{mn}(t-\tau_2) - i_{mw}(t-\tau_2)]e^{-\mu_{mw}\tau_2} - r i_{mw}(t) - \mu_{mw} i_{mw}(t) \end{cases} \quad (3.2)$$

where

$$z_{mn} = \frac{(n_{nm} + (1-u)n_{mw})(n_{mn} + (1-v)\phi n_{mw})}{n_{mn} + n_{mw}}, \quad z_{mw} = v\phi n_{mw} \quad (3.3)$$

Now, the model in terms of proportions (3.2) are defined in subset $\Omega^*[0,\infty)$ of $\Re^6_+$ where

$\Omega = \{eh,ih,emn,imn,emw,imw : 0 \leq eh + ih \leq 1, 0 \leq emn + imn \leq nmw \leq 1, 0 \leq emw + imw \leq nmw \leq 1\}$ the hat denote evalution at $t - \tau$, and we have defined the following non-dimensional parameter combinations:

$$\varphi = \beta/\hat{\beta}, \qquad \delta = \mu_{mw}/\mu_{mn}, \quad \alpha = \beta/\mu_{mn}, \qquad \tau = \mu_{mn}T_{\mu mn}. \quad (3.4)$$

The function f defined by $f(x) = F(N^*_{mn}x)$ is monotonic decreasing with $f(0) = 1, f(1) = 1/\alpha$ and $f(x) \to 0$ as $x \to \infty$. The parameter φ and δ represent the birth (fecundity) and death rate of *Wolbachia*-infected compared to uninfected mosquitoes, and so $\varphi \leq 1, \delta \geq 1$ and $\alpha > 1$ is the non-dimensional birth rate for mosquitoes in a *Wolbachia*-free system.

Mosquito-Only System

Since the total densities of both *Wolbachia*-uninfected and *Wolbachia*-infected mosquitoes are independent of any of the other population densities, the system can be decoupled and the equations for the mosquito densities can be studied in isolation. We shall initially neglect delay effects, and return to discuss these later. With these assumptions, the equations become

$$\frac{dn_{mn}}{dt} = \alpha z_{mn} f(z_{mn} + z_{mw}) - n_{mn}, \quad \frac{dn_{mw}}{dt} = \alpha z_{mw} f(z_{mn} + z_{mw}) - \delta n_{mw} \quad (3.5)$$

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where z_{mn} and z_{mw} are given by Eq.(3.3). Here, we consider the special but realistic case $(u,v) = (1,1)$,$\alpha > 1$ (since otherwise the *Wolbachia*-free mosquitoes go to extinction), $\alpha\, phi > \delta$ (so that *Wolbachia*-infected mosquitoes go to extinction), and φ 6 1 6 δ (so that *Wolbachia* has fitness costs in fecundity and survival). The system has steady states $E_0 = (0,0)$ and $E_1 = (1,0)$,$E_2 = (0,k)$, where $k = (1/\varphi)f^{-1}(\delta/\alpha\varphi)$, and $E_3 = k\delta(\varphi,\delta - \varphi)/(\delta(\delta - \varphi) + \varphi)$, a co-existence state in the positive quadrant.The steady state E_0 is unstable, E_1 and E_2 are stable, and E_3 is a saddle point. The system as a whole will therefore lead to bistability whenever cytoplasmic incompatibility and maternal transmission are complete, $(u,v) = (1,1)$. Which equilibrium is reached depends on the initial populations of both types of mosquitoes, with two basins of attraction separated by a separatrix.

Let us now consider the delay terms in equations. Looking for solutions as multiple of $e^{s\tau}$ near the semi-trivial equilibria $E_1 = (1,0)$ and $E_E = (0, n^*_{mw})$, we obtain transcendental equations satisfied by the eigeinvalues s, since the delay terms contribute factors to the equations (Maynard Smith 1974; Britton 2003). The Jacobian matrix J at E_1 is triangular and at E_2 diagonal, so that in both cases the equation for s may immediately be factorised. The eigenvalues at (1,0) satisfy $s = -1 + (1 + \alpha f^0(1))e^{-s\tau}$ or $s = -\delta + \varphi e^{-s\tau}$.

For each of these equations, we shall consider how solutions s move in the complex plane as τ increase from zero, where $s = \alpha f^0(1) < 0$ for the first and $s = -\delta + \varphi < 0$ for the second. Because of the exponential terms, each equation will define multiple branches of s as τ increases, and we wish to determine whether any branch crosses the imaginary axis. If so, then instability occurs for some sufficiently large τ, but if not, then instability does not occur for any τ. For the second equation, $s = 0$ is not a solution for any τ, so a branch of solution can only cross the imaginary axis away from the origin. Let $s = u + iv$; then $u = -\delta + \varphi e^{-u\tau} cos v\tau$, $v = \varphi e^{-u\tau} sin v\tau$, so $(u + \delta)^2 + v^2 = \varphi^2 e^{-2u\tau}$, and there is no solution $s = u + iv$ with $u > 0$ if $\varphi^2 < \delta^2 + v^2$, which is true in the biologically realistic case $\varphi < \delta$. A similar argument for the first equation shows that instability is only possible if $\alpha|f^0(1)| > 2$, or $\beta_{mn} N^*_{mn} |F'(N^*_{mn})| > 2\mu_{mn}$ in dimensional variables. For $(0,n^*_{mw})$, eigenvalues are given by $s = -1$ and the roots of

$$s = -\delta + (\delta + \alpha\phi n^*_{mw} f'(n^*_{mw}))e^{-s\tau}, \text{ and instability is only possible if } \alpha\phi n^* mw |f'(n^*_{mw})| > 2\delta,$$

or $\beta_{mw} N^*_{mw} |F'(N^*_{mw})| > 2\mu_{mw}$ in dimensional variables. A calculation with Dye's parameter values(Dye 1984), and with his function $F(x) = exp(-hx^k)$, show that neither $(N^*_{mn}, 0)$ nor

$(0, N^*_{mw})$ is destabilised by the delay terms whatever the value of $T_{\mu mn}$, so that these are the stable states of the mosquito-only subsystem.

It follows that the only stable (and therefore biologically interesting)spatially uniform steady states of the system a whole must involve either *Wolbachia*-infected or uninfected mosquitoes, but not both. In the spatially uniform case it is therefore justifiable to proceed by studying two four-dimensional subcases of the complete system (3.2): the system obtained at the *Wolbachia*free equilibrium and the system obtained at the completely *Wolbachia*-infected equilibrium. The spatially non-uniform case may be analysed by adding diffusion terms to the system (3.5),

$$\frac{\partial n_{mn}}{\partial t} = \alpha z_{mn} f(z_{mn} + z_{mw}) - n_{mn} + D\nabla^2 n_{mn},$$
$$\frac{\partial n_{mw}}{\partial t} = \alpha z_{mw} f(z_{mn} + z_{mw}) - \delta n_{mw} + D\nabla^2 n_{mw},$$

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where D is mosquito diffusion coefficient and solving the resulting partial differential equations numerically (using *pdepe*, MATLAB's built-in solver for parabolic and elliptic PDEs).

Wolbachia-free System

The set of equations with the mosquito population at the *Wolbachia*-free equilibrium is given by

$$\begin{cases} \frac{de_h(t)}{dt} = abmi_{mn}(t)(1-e_h(t)-i_h(t)) - \mu_h(t)e_h(t) \\ \qquad -abmi_{mn}(t-\tau_1)(1-e_h(t-\tau_1)-i_h(t-\tau_1))e^{-(r+\mu_h)\tau_1} \\ \frac{di_h(t)}{dt} = abmi_{mn}(t-\tau_1)(1-e_h(t-\tau_1)-i_h(t-\tau_1))e^{-(r+\mu_h)\tau_1} - ri_h(t) - \mu_h i_h(t) \\ \frac{de_{mn}(t)}{dt} = aci_h(t)(1-e_{mn}(t)-i_{mn}(t)) - \mu_{mn}e_{mn}(t) \\ \qquad -aci_h(t-\tau_2)(1-e_{mn}(t-\tau_2)-i_{mn}(t-\tau_2))e^{-\mu_{mn}\tau_2} \\ \frac{di_{mn}(t)}{dt} = aci_h(t-\tau_2)(1-e_{mn}(t-\tau_2)-i_{mn}(t-\tau_2))e^{-\mu_{mn}\tau_2} - \mu_{mn}i_{mn}(t) \end{cases} \quad (3.6)$$

To deduce the threshold for the disease to establish in the human, we have to analyze the existence of equilibria and their stability for model (3.6). Find the basic reproduction R_0 which may be read as the average number caused by a single infectious subject in a wholly susceptible population. At the beginning of the epidemics, to have malaria spread in both vector and human population, the number of infectious hosts and vectors need to increase. If either of them fails, the disease cannot persist in the population.

From the system (3.6), when an epidemic occur, we have

$$\begin{cases} \frac{ds_h(t)}{dt}|_{t=0} > 0 \\ \frac{di_{mn}(t)}{dt}|_{t=0} > 0 \end{cases} \quad (3.7)$$

or

$$abmimn(t-\tau 1)(1-eh(t-\tau 1)-ih(t-\tau 1))e-(r+\mu h)\tau 1 - rih(t) - \mu hih(t)|t=0 > 0$$

$$(3.8) -\mu mn^{\tau}2\ aci_h(t-\tau_2)(1-e_{mn}(t-\tau_2)-i_{mn}(t-\tau_2))e \quad -\mu_{mn}i_{mn}(t)|_{t=0} > 0$$

At the beginning of an epidemic, the number of non-susceptible hosts and vectors can be assumed negligible and

$N_h - E_h(0) - I_h(0) \approx N_h \Longrightarrow 1 - e_h(0) - i_h(0) \approx 1$ and

$N_m - E_{mn}(0) - I_{mn}(0) \approx N_m \Longrightarrow 1 - e_{mn}(0) - i_{mn}(0) \approx 1,$

Also the number of infectious hosts at time t and $t-\tau_1$ is almost the same, so is the number of infectious vectors at time t and $t-\tau_2$

$I_h(t) \approx I_h(t-\tau_1) \Longrightarrow i_h(t) \Longrightarrow i_h(t-\tau_1)$ and

$I_{mn}(t) \Longrightarrow I_{mn}(t-\tau_2) \Longrightarrow 1_{mn}(t) \approx i_{mn}(t-\tau_2)$

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Then the system (3.8) becomes

$$(abmi_{mn}(t)e^{-(r+\mu h)\tau 1} > (r+\mu h)ih(t)$$
$$acih(t)e^{-\mu mn\tau 2} > \mu mnimn(t) \quad (3.9)$$

Multiplying the two inequalities, we have

$$a2bcmimn(t)ih(t)e^{-(r+\mu h)\tau 1-\mu mn\tau 2} > \mu mn(r+\mu h)ih(t)imn(t) \quad (3.10)$$

Equivalent to

$$\frac{a^2bcme^{(-(r+\mu_h)\tau_1-\mu_{mn}\tau_2)}}{\mu_{mn}(r+\mu_h)} > 1 \quad (3.11)$$

The above inequality is the condition for the disease to spread. So the expression of the basic reproduction number has the form:

$$R_0 = \frac{a^2bcme^{(-(r+\mu_h)\tau_1-\mu_{mn}\tau_2)}}{\mu_{mn}(r+\mu_h)} \quad (3.12)$$

An heuristic derivation is as follows. Take a primary case with a recovery rate of r, the average time spend in an infection state is $1/r$. During this time, since the incubation period in humans has duration τ_1, the average number of mosquito bites received from m susceptible mosquitoes each with a biting rate a give a total of $acme^{-(r+\mu h)\tau 1}/r+\mu_h$ mosquitoes infected by the primary human case. Each of these mosquitoes survives for an average time $1/\mu_{mn}$and with another incubation period $\tau_2$in mosquitoes, makes a total of $abe^{-\mu mn\tau 2}/\mu_{mn}$ infectious bites.

The total number of secondary cases is thus $a^2bcme^{-(r+\mu h)\tau 1-\mu mn\tau 2}/\mu_{mn}(r+\mu_h)$, which is the basic reproduction number R_o. Notice that a appear twice in the expression since the mosquito biting rate controls transmission from humans to mosquitoes and from mosquitoes to humans. Then we have the following results on the existence of equilibria.

Lemma 3.2.1 *In the first quadrant,(3.6) has at most two equilibria. More precisely,*

(i) If $R_0 < 1$, *then system (3.6) has a unique trivial equilibrium* $E_1(0,0,0,0)$*;*

(ii)If $R_0 > 1$, *then the system (3.6) has two equilibria, the trivial equilibria* $E_1(0,0,0,0)$ *and the positive equilibrium* $\mathcal{E}_2(\epsilon_h^*, i_h^*, e_{mn}^*, i_{mn}^*)$, *where*

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$$
\begin{aligned}
e_h^* &= \frac{(e^{(r+\mu_h)\tau_1}-1)(r+\mu_h)(a^2bcm - r\mu_{mn}e^{(r+\mu_h)\tau_1}e^{\mu_{mn}\tau_2} - \mu_h\mu_{mn}e^{(r+\mu_h)\tau_1}e^{\mu_{mn}\tau_2})}{ac(\mu_h^2e^{(r+\mu_h)\tau_1}e^{\mu_{mn}\tau_2} - abmr + r\mu_he^{(r+\mu_h)\tau_1}e^{\mu_{mn}\tau_2} + abmre^{(r+\mu_h)\tau_1} + abm\mu_he^{(r+\mu_h)\tau_1})} \\
&= \frac{(e^{(r+\mu_h)\tau_1}-1)(r+\mu_h)(R_0-1)}{ac\frac{\mu_h}{\mu_{mn}} + (e^{(r+\mu_h)\tau_1}-1)rR_0 + R_0\mu_he^{(r+\mu_h)\tau_1}}, \\
i_h^* &= \frac{(a^2bcm\mu_h - r\mu_h\mu_{mn}e^{(r+\mu_h)\tau_1}e^{\mu_{mn}\tau_2} - \mu_h^2\mu_{mn}e^{(r+\mu_h)\tau_1}e^{\mu_{mn}\tau_2})}{ac(\mu_h^2e^{(r+\mu_h)\tau_1}e^{\mu^{mn}\tau_2} - abmr + r\mu_he^{(r+\mu_h)\tau_1}e^{\mu_{mn}\tau_2} + abmre^{(r+\mu_h)\tau_1} + abm\mu_he^{(r+\mu_h)\tau_1})} \\
&= \frac{\mu_h(R_0-1)}{ac\frac{\mu_h}{\mu_{mn}} + (e^{(r+\mu_h)\tau_1}-1)rR_0 + R_0\mu_he^{(r+\mu_h)\tau_1}}, \\
e_{mn}^* &= \frac{(e^{(r+\mu_h)\tau_1}-1)(a^2bcm - r\mu_{mn}e^{(r+\mu_h)\tau_1}e^{\mu_{mn}\tau_2} - \mu_h\mu_{mn}e^{(r+\mu_h)\tau_1}e^{\mu_{mn}\tau_2})}{a^2bcm\mu_he^{\mu_{mn}\tau_2} - abmr\mu_{mn}e^{\mu_{mn}\tau_2} + abmr\mu_{mn}e^{(r+\mu_h)\tau_1}e^{\mu_{mn}\tau_2} + abm\mu_h\mu_{mn}e^{(r+\mu_h)\tau_1}e^{\mu_{mn}\tau_2}} \\
&= \frac{\mu_h\mu_{mn}(r+\mu_h)(e^{\mu_{mn}\tau_2}-1)(R_0-1)}{a^2bcm\mu_he^{(}-(r+\mu_h)\tau_1) + abmr\mu_{mn}(1-e^{-(r+\mu_h)\tau_1}) + abm\mu_h\mu_{mn}}, \\
i_{mn}^* &= \frac{(a^2bcm - r\mu_h\mu_{mn}e^{(r+\mu_h)\tau_1}e^{\mu_{mn}\tau_2} - \mu_h^2\mu_{mn}e^{(r+\mu_h)\tau_1}e^{\mu_{mn}\tau_2})}{a^2bcm\mu_he^{\mu_{mn}\tau_2} - abmr\mu_{mn}e^{\mu_{mn}\tau_2} + abmr\mu_{mn}e^{(r+\mu_h)\tau_1}e^{\mu_{mn}\tau_2} + abm\mu_h\mu_{mn}e^{(r+\mu_h)\tau_1}e^{\mu_{mn}\tau_2}} \\
&= \frac{\mu_h\mu_{mn}(r+\mu_h)(R_0-1)}{a^2bcm\mu_he^{(}-(r+\mu_h)\tau_1) + abmr\mu_{mn}(1-e^{-(r+\mu_h)\tau_1}) + abm\mu_h\mu_{mn}}
\end{aligned}
\tag{3.13}
$$

The endemic equilibrium E_2 is only biologically meaningful for $R_0 \geq 1$. It coincide with the disease-free equilibrium E_1 at $R_0 = 1$, and this is therefore a bifurcation point. Since R_0 defined by (3.12) and the steady state values given in (3.13) are all delayed dependent, increasing the delay values will decrease to make it equal to 1 and will make the positive steady state to coincide with the trivial equilibrium. Thus, Hopf bifurcation does not occur when the delay increases as there are no bifurcating periodic solution due to the increase of the delays value. Next we discuss the stability of $E_1(0,0,0,0)$ and $E_2(e_h^*, i_h^*, e_{mn}^*, i_{mn}^*)$. First we consider the linearized system of (3.4) at $E_1(0,0,0,0)$:

$$
\begin{cases}
\frac{de_h(t)}{dt} = -\mu_he_h(t) + abmi_{mn}(t) - abmi_{mn}(t-\tau_1)e^{-(r+\mu_h)\tau_1} \\
\frac{di_h(t)}{dt} = (-r-\mu_h)i_h(t) + abmi_{mn}(t-\tau_1)e^{-(r+\mu_h)\tau_1} \\
\frac{de_{mn}(t)}{dt} = aci_h(t) - \mu_{mn}e_h(t) - aci_h(t-\tau_2)e^{-\mu_{mn}\tau_2} \\
\frac{di_{mn}(t)}{dt} = -\mu_{mn}i_h(t) + aci_h(t-\tau_2)e^{-\mu_{mn}\tau_2}
\end{cases}
\tag{3.14}
$$

The characteristics equation associated with system (3.14) takes the form

$$
\begin{aligned}
&\lambda 3 + (r + 2\mu h + \mu mn)\lambda 2 + (\mu 2h + r\mu h + r\mu mn + 2\mu h\mu mn \\
&- a2_{bcme}{-}(r{+}\mu h)\tau^1{-}\mu^{mn}\tau^2_e{-}(\tau^1{+}\tau^2)\lambda)\lambda \\
&+ \mu_h(r\mu_{mn} + \mu_h\mu_{mn} - a2bcme{-}(r{+}\mu^h)\tau^1{-}\mu^{mn}\tau^2e{-}(\tau^1{+}\tau^2)\lambda) = 0
\end{aligned}
\tag{3.15}
$$

Let

$$
\begin{aligned}
&G(\lambda,\tau_1,\tau_2) = \lambda^3 + (r + 2\mu_h + \mu_{mn})\lambda^2 \\
&+ (\mu 2h + r\mu h + r\mu mn + 2\mu h\mu mn - a2bcme{-}(r{+}\mu h)\tau 1{-}\mu mn\tau 2e{-}(\tau 1{+}\tau 2)\lambda)\lambda \\
&+ \mu_h(r\mu_{mn} + \mu_h\mu_{mn} - a2bcme{-}(r{+}\mu^h)\tau^1{-}\mu^{mn}\tau^2e{-}(\tau^1{+}\tau^2)\lambda)
\end{aligned}
\tag{3.16}
$$

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It is clear that $G(\lambda,\tau_1,\tau_2)$ is an analytic function. $G(0,\tau_1,\tau_2) = \mu_h\mu_{mn}(r + \mu_h)(1 - R_0)$, and

$$G(\lambda,0,0) = \lambda^3 + (r + 2\mu_h + \mu_{mn})\lambda^2 + (\mu^2{}_h + r\mu_h + r\mu_{mn} + 2\mu_h\mu_{mn} - a^2bcm)\lambda \quad (3.17)$$

$$+ \mu_h(r\mu_{mn} + \mu_h\mu_{mn} - a^2bcm)$$

To discuss the distribution of the roots of the transcendental (3.15, we consider three cases.

(i) If $R_0 < 1$, then $G(0,\tau_1,\tau_2) > 1$ and $G_\lambda{}^0(\lambda,\tau_1,\tau_2) > 0$ for all positive λ,τ_1 and τ_2. Hence,(3.15) has no zero root for positive τ_1 and τ_2. Now, we claim that (3.15) has a pair of purely imaginary roots $\pm\omega i,\omega > 0$ for some τ_1 and τ_2 . Then ω must be a positive root of $\omega 6 + (r + 2r\mu h + 2\mu 2h + \mu 2mn)\omega 4 + (\mu 4h + 2r\mu 3h + r2\mu 2mn + r2\mu 2h + 2r\mu h\mu mn2 + 2\mu 2h\mu 2mn - (r+\mu h)\tau 1-\mu mn\tau 2)2)\omega 2 + \mu 2h((r\mu mn + \mu h\mu mn)2 - (a2bcme-(r+\mu h)\tau 1-\mu mn\tau 2)2) = 0(3.18) - (a2bcme$

However, it is easy to see that (3.18) does not have nonnegative real roots when $R_0 < 0$. Hence, (3.15) doesn't have any purely imaginary roots. On the other hand, One can easily get that the roots of $G(\lambda,0,0)$ all have negative real parts roots when $R_0 < 1$. By the implicit function theorem and the continuity of $G(\lambda,\tau_1,\tau_2)$, we know that all roots of (3.15) have negative real parts for positive and, which implies that $E_1(0,0,0,0)$ is stable.

(ii) If $R_0 = 1$, then $G(0,\tau_1,\tau_2)$ and $G^0{}_\lambda(\lambda,\tau_1,\tau_2)$ for $\lambda \geq 0,\tau_1 > 0$ and $\tau_2 > 0$. Hence, (3.15) has a simple zero root τ_1 and τ_2 and non positive real root for all positive and. Using a similar argument as in (*i*), we can obtain that except a zero root, all roots of (3.15) have negative real parts for positive τ_1 and τ_2. Thus, $E_1(0,0,0,0)$ is a degenerate equilibrium of codimension one and is stable except in one dimension.

(iii) If $R_0 > 1$, then $G(0,\tau_1,\tau_2) < 0$ and $G^0{}_\lambda(\lambda,\tau_1,\tau_2) > 0$ for $\lambda \geq 0,\tau_1 > 0$ and $\tau_2 > 0$. Hence, (3.15) has a positive real root for all positive τ_1 and τ_1. On the other hand,$G(\lambda,0,0)$ has at least one negative real root λ . From the implicit function theorem, (3.15) has a root with negative real part for small τ_1 and τ_2. Therefore, $E_1(0,0,0,0)$ has both stable and unstable manifold for some τ_1 and τ_2. To determine the unstable manifold of (0,0,0,0) when $R_0 > 1$, we discuss the stability of the other equilibrium $E_2(e_h^*, i_h^*, e_{mn}^*, i_{mn}^*)$ when $R_0 > 1$.

Remark 3.2.2 *We would like to point out, as suggested by one the referees, that the stability of the trivial equilirium* $E_1(0,0,0,0)$ *can also be analyzed via the real eigenvalues of its Jacobian matrix by using a theorem on page 92 in Smith* (1995).

The the linearized system of (3.4) at $E_2(e_h^*, i_h^*, e_{mn}^*, i_{mn}^*)$:

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$$\begin{cases} \frac{de_h}{dt} = (-abmi^*_{mn} - \mu_h)e^*_h - abmi^*_{mn}i_h(t) + amb(1 - e^*_h - i^*_h)i_{mn}(t) + abmi^*_{mn}e_h(t-\tau_1) \\ \quad +abmi^*_{mn}e^{-(r+\mu_h)\tau_1}i_h(t-\tau_1) - abm(1 - e^*_h - i^*_h)e^{-(r+\mu_h)\tau_1}i_{mn}(t-\tau_1) \\ \frac{di_h}{dt} = -\mu_h i_h(t) - ri_h(t) - abmi^*_{mn}e_h(t-\tau_1) - abmi^*_{mn}i_h(t-\tau_1) \\ \quad +amb(1 - e^*_h - i^*_h)e^{-(r+\mu_h)\tau_1}i_{mn}(t-\tau_1) \\ \frac{e_{mn}}{dt} = ac(1 - e^*_{mn} - i^*_{mn})i_h(t) - (aci^*_h + \mu_{mn})e_{mn}(t) - aci^*_h i_{mn}(t) \\ \quad -ac(1 - e^*_{mn} - i^*_{mn})e^{-\mu_{mn}\tau_2}e_h(t-\tau_2) \\ \quad +aci^*_h e^{\mu_{mn}\tau_2}e_{mn}(t-\tau_2) + aci^*_h e^{-\mu_{mn}\tau_2}i_{mn}(t-\tau_2) \\ \frac{i_{mn}}{dt} = -\mu_{mn}i_{mn}(t) + ac(1 - e^*_{mn} - i^*_{mn})e^{-\mu_{mn}\tau_2}e_h(t-\tau_2) \\ \quad +aci^*_h(1 - e^*_{mn} - i^*_{mn})e^{-\mu_{mn}\tau_2}i_h(t-\tau_2) \end{cases}$$

(3.19)

From the above system we change variables in term $Q = abmi^*_{mn}$,

$$Q_1 = abm(1 - e^*_h - i^*_h),\ Q_3 = ac(1 - e^*_{mn} - i^*_{mn}),\ Q_3 = aci^*_{mn}.$$

The characteristic equation associated with system (3.19) takes the form

$$\lambda^4 + A_1\lambda^3 + A_2\lambda^2 + A_3\lambda + A_4 = 0 \quad (3.20)$$

where

$A_1 = r + 2\mu_h + 2\mu_{mn} + Q_3 + Q,$

$A2 = \mu 2h + \mu 2mn + r\mu h + 2r\mu mn + 4\mu h\mu mn + Q3(r + \mu h + \mu mn) + Q(2\mu mn + r - re^{-(r+\mu h)\tau 1}e^{-\lambda\tau 1})$

$+ QQ_3 - Q_1Q_{2e}e^{-((r+\mu^h)\tau^1+\mu^{mn}\tau^2)_e-\lambda(\tau^1+\tau^2)},$

$A3 = r\mu 2mn + 2\mu h\mu 2mn + 2\mu 2h\mu mn + 2r\mu h\mu mn + Q3(\mu 2h + r\mu h + r\mu mn + 2\mu h\mu mn)$

$-((r+\mu h)\tau 1+\mu mn\tau 2)e^{-\lambda(\tau 1+\tau 2)}) + QQ3(r + \mu h + \mu mn$ (3.21) $+ Q(\mu 2mn + 2r\mu mn + 2\mu h\mu mn - 2r\mu mne$

$- {}_{re}e^{-((r+\mu_h)\tau 1+\mu mn\tau 2)_e-\lambda(\tau 1+\tau 2))} - Q_1Q_{2e}e^{-((r+\mu_h)\tau 1+\mu mn\tau 2)_e-\lambda(\tau 1+\tau 2)},$

$A4 = \mu 2hmu2mn - r\mu hmu2mn + Q3(\mu h2mumn + \mu hmumn) + Q(r\mu 2mn + \mu hmu2mn - r\mu 2mne(r+\mu h)\tau 1e^{-\lambda\tau 1})$

$+ QQ_3(r\mu_{mn} + \mu_h mu_{mn} - r\mu_{mn})e^{-(r+\mu^h)\tau^1}e^{-\lambda\tau^1} - Q_1Q_2\mu_h mu_{mn}e^{-((r+\mu^h)\tau^1+\mu^{mn}\tau^2)e-\lambda(\tau^1+\tau^2)}$ For any non negative τ_1 and τ_2, we have the following proposition.

Proposition 3.2.3 *For any endemic equilibrium* $E_2(e^*_h, i^*_h, e^*_{mn}, i^*_{mn})$ *of the system with characteristic equation (3.20), one always has*

$$A_1 > 0; A_2 > 0; A_3 > 0; A_4 > 0; A_1A_2 - A_3 > 0;$$

$$A_3(A_1A_2 - A_3) - A_1^2A_4 > 0 \quad (3.22)$$

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It is clear that $A_1 > 0$, and known conditions, according to Routh-Hurwitz criteria [11], the proof of the proposition is staightforward.

Case 1. When $\tau_1 = \tau_2 = 0$, as a results of proposition 1 and Hurwitz criterion, all roots of the characteristic equation (3.20) have negative real parts and the endemic equilibrium E_2^* of the (3.6) is stable when $\tau_1 = \tau_2 = 0$.

Case 2. When $\tau_1 > 0, \tau_2 = 0$, the characteristic equation (3.20) becomes

$$\lambda 4 + A01\lambda 3 + A11\lambda 2 + A21\lambda + A31 = e{-}\lambda\tau 1(T11\lambda 2 + T21\lambda + T31 \quad (3.23)$$

Where

$$A01 = r + 2\mu h + 2\mu mn + aci{*}{+}abmi{*}mn,$$

$$A11 = \mu 2h + \mu 2mn + r\mu h + 2r\mu mn + 4\mu h\mu mn + acrih{*} + ac\mu hih{*} + ac\mu mni{*}h + abmri{*}mnabm\mu hi{*}mn + 2abm\mu mni{*}mn + a2bcmi{*}hi{*}mn,$$

$$A21 = r\mu 2mn + 2\mu h\mu 2mn + 2\mu 2h\mu mn + 2r\mu h\mu mn + acih{*}\mu 2h + aci{*}hr\mu h + aci{*}hr\mu mn + 2aci{*}h\mu h\mu mn$$

$$+ abmi{*}mn\mu 2mn + 2abmi{*}mnr\mu mn + 2abm\mu h\mu mni{*}mn + a2bcmi{*}hi{*}mn + a2bcm\mu mnih{*}i{*}mn,$$

$$A31 = \mu 2h\mu 2mnr\mu h\mu 2mn + ac\mu 2h\mu mnih{*} + ac\mu h\mu mni{*}h + abmr\mu 2mni{*}mn + abm\mu h\mu mn2i{*}mn$$

$$+ a2bcmr\mu mni{*}hi{*}mn + a2bcm\mu h\mu mni{*}hi{*}mn, \quad (3.24)$$

$$T11 = (abmri{*}mn + a2bcm - a2bcm(e{*}h(1 - imn{*}) + ih{*}(1 - i{*}mn) + e{*}mn(1 - i{*}h)$$

$$+ i{*}mn(1 - e{*}h))e{-}(r{+}\mu h)\tau 1,$$

$$T21 = (2abmr\mu mni{*}mn + a2bcmri{*}hi{*}mn + a2bmc\mu h + a2bcm\mu mn - (a2bmc\mu h + a2bcm\mu mn)$$

$$(e{*}h(1 - i{*}mn) + i{*}h(1 - i{*}mn) + e{*}mn(1 - ih{*}) + imn{*}(1 - e{*}h))e{-}(r{+}\mu h)\tau 1,$$

$$T31 = abmr\mu 2mni{*}mn + a2bcmr\mu mni{*}hi{*}mn + a2bcm\mu h\mu mn - a2bcm\mu h\mu mn(e{*}h(1 - imn{*}) + i{*}h(1 - i{*}mn)$$

$$+ e{*}mn(1 - i{*}h) + i{*}mn(1 - e{*}h))e{-}(r{+}\mu h)\tau 1$$

By the implicit function theorem and the continuity of the left-hand side function of (3.20), all roots (3.23) have negative real parts for small τ_1. Notice that the condition $R_0 > 1$ is equivalent to

$$\tau_1 < \tau_1^* = \frac{1}{(r + \mu_h)} ln \frac{a^2 bcm}{\mu_{mn}(\mu_h + r)} \quad (3.25)$$

Furthermore, we claim that (3.23) does not have any non negative real roots for any $\tau_1 > 0$. Rewrite (3.23) by moving the positive terms from the right-side to the left-hand side. The rewritten (3.23) takes the form

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$$\lambda 4 + A01\lambda 3 + Ag11\lambda 2 + Ag21\lambda + Ag31 = e{-}\lambda\tau 1(Tf11\lambda 2 + Tf21\lambda + Tf31) \quad (3.26)$$

where

$$Ag11 = A11 - (abmri{*}mn + a2bcm)e{-}(r{+}\mu h)\tau 1,$$

$$Ag21 = A21 - (2abmr\mu mni{*}mn + a2bcmri{*}hi{*}mn + a2bcm\mu h + a2bcm\mu mn)e{-}(r{+}\mu h)\tau 1e{-}\lambda\tau 1, \quad (3.27)$$

$$Ag31 = A31 - (abmr\mu 2mni{*}mn + a2bcmr\mu mni{*}hi{*}mn + a2bcm\mu h\mu mn)e{-}(r{+}\mu h)\tau 1e{-}\lambda\tau 1$$

It is easy to see that $\widetilde{A_{11}} > 0, \widetilde{A_{21}} > 0$ and $\widetilde{A_{31}} > 0$ for all $\lambda > 0$ and $\tau_1 \in (0, \tau_1^*)$. Consequently the left- hand side in (3.26) is positive for all $\lambda \geq 0$ while the right-hand side is negative for all $\lambda \geq 0$ and the two cannot be equal for any $\lambda \geq 0$. Therefore, (3.23)does not have any non negative real roots for any $\tau_1 \in (0, \tau_1^*)$. Now we want to show that all roots of (3.23) have negative real parts for is $\tau_1 \in (0, \tau_1^*)$. To do so , we show that (3.23) does not have any purely imaginary roots for all $\tau_1 \in (0, \tau_1^*)$. We assume that $\lambda = i\omega$ with $\omega > 0$ being root of (3.23).

Then ω must satisfy the following system:

$$\omega^4 - A_{11}\omega^2 + A_{31} = (T_{31} - T_{11}\omega)\cos(\omega\tau_1) + T_{21}\omega \sin(\omega\tau_1),$$

$$A_{01}\omega - A_{21}\omega^3 = T_{21}\omega \cos(\omega\tau_1) + (T_{11}\omega^2 - T_{31})\sin(\omega\tau_1), \quad (3.28)$$

Thus ω must be a a positive root of

$$\omega 8 + B1\omega 6 + B2\omega 4 + B3\omega 2 + B4 = 0 \quad (3.29)$$

where

$$B_1 = A_{21}^2 - 2A_{11},$$

$$B2 = A211 + 2A31 - 2A01A21 - T112 , \quad (3.30)$$
$$B3 = A201 - A11A31 + 2T31T11 - T212 , B4 = A231 - T312$$

Let $z = \omega^2$, then (3.25)

$$z^4 + B_1z^4 + B_2z^2 + B_3z + B_4 = 0 \quad (3.31)$$

Clearly if $B_1 > 0, B_2 > 0, B_3 > 0$ and $B_4 > 0$, then (3.31) has no positive real roots. Therefore, (3.23) does not have any purely imaginary roots for all so that all roots of the characteristic equation (3.23) have negative real real parts and the endemic equilibrium E_2^* is stable.

Case 3. When ,$\tau_2 > 0, \tau_1 = 0$ the characteristic equation (3.20) becomes

$$\lambda 4 + A02\lambda 3 + A12\lambda 2 + A22\lambda + A32 = e{-}\lambda\tau 2(T12\lambda 2 + T22\lambda + T32) \quad (3.32)$$

where

$$A02 = r + 2\mu h + 2\mu mn + aci{*}h + abmi{*}mn,$$

$$A12 = \mu 2h + \mu 2mn + r\mu h + 2r\mu mn + 4\mu h\mu mn + acrih{*} + ac\mu hih{*} + ac\mu mni{*}h + abmri{*}mn$$

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$+ abm\mu hi*mn + 2abm\mu mni*mn + a2bcmi*hi*mn,$

$A22 = r\mu 2mn + 2\mu h\mu 2mn + 2\mu 2h\mu mn + 2r\mu h\mu mn + aci*h\mu 2h + aci*hr\mu h + aci*hr\mu mn + 2aci*h\mu h\mu mn$

$+ abmi*mn\mu 2mn + 2abmimn* r\mu mn + 2abm\mu h\mu mnimn* + a2bcmri*hi*mn + a2bcm\mu mni*hi*mn,$

$A32 = \mu 2h\mu 2mn + r\mu h\mu 2mn + ac\mu 2h\mu mni*h + ac\mu h\mu mni*h + abmr\mu mni*h + abm\mu h\mu 2mni*mn$ (3.33)

$+ a2bcmr\mu mni*hi*mn + a2bcm\mu h\mu mni*hi*mn,$

$T12 = a2bcm(1 - (e*h(1 - i*mn) + i*h(1 - i*mn) + e*mn(1 - ih*) + i*mn(1 - e*h))e-\mu mn\tau 2,$
$T22 = (a2bmc\mu h + a2bcm\mu mn)(1 - (e*h(1 - imn*) + ih*(1 - i*mn) + e*mn(1 - i*h)$

$+ i*mn(1 - e*h))e-\mu mn\tau 2,$

$T32 = a2bcm\mu h\mu mn(1 - (e*h(1 - i*mn) + ih*(1 - imn*) + e*mn(1 - i*h) + i*mn(1 - eh*))e-\mu mn\tau 2$ The condition $R_0 > 1$is equivalent to

$$\tau_2 < \tau_2^* = \frac{1}{\mu_{mn}} ln \frac{a^2bcm}{\mu_{mn}(\mu_h + r)} \quad (3.34)$$

Using a similar as in case 2, we know that all roots of (3.32) have negative real parts for $\tau_2 \in (0, \tau_2^*)$ when $C \geq 0, C_2 \geq 0, C_3 \geq 0$ and $C_4 \geq 0$, where

$$C1 = A222 - 2A12,$$

$$C2 = A212 + 2A32 - 2A02A22 - T122 ,$$

$$C3 = A202 - A12A32 + 2T32T12 - T222 , C4 = A232 - T322 \quad (3.35)$$

Case 4. When $\tau_1 > 1, \tau_2 > 1$, the condition $R_0 > 1$ is equivalent to

$$\tau_2 < \tau_2^* = \frac{1}{\mu_{mn}} ln \frac{a^2bcm}{\mu_{mn}(\mu_h + r)} e^{-(r+\mu_h)\tau_1} \quad (3.36)$$

From cases 1, and 2 the roots of (3.20) only have negative real parts for $\tau_1 \in (0, \tau_1^*)$ and $\tau_2 = 0$ the left-hand side function (3.20), there is a $\tau_2(\tau_1)$ satisfying $0 < \overline{\tau_2}(\tau_1) \geq \overline{\tau_2^*}(\tau_1)$, such that all roots of (3.20) have negative real parts for $0 < \tau_2 < \tau_2(\tau_1)$. We show that $\overline{\tau_2}(\tau_1) = \overline{\tau_2^*}(\tau_1)$

when $B_i \geq 0$ and $C_i \geq 0, i = 1,2,3$. Suppose that $0 < \overline{\tau_2}(\tau_1) \geq \tau_2^*(\tau_1 \_\_)$ for $\tau_1 \in [0, \tau_1^*)$, then there must be at $\tilde{\tau}_2(\tau_1), \tau_2(\tau_1) < \tilde{\tau}_2(\tau_1) < \tau_2^*(\tau_1 \_\_)$, such that one root of (3.20) has non negative real part for $\tau_2 = \tilde{\tau}_2(\tau_1)$. As a result of the continuity of τ_2 in τ_1, we have $\tilde{\tau}_2(0) < \tau_2^*(0) = \tau_2^*$. However, from the argument in case 3, we know that all the roots of (3.20) have negative real parts for $\tau_1 = 0$ and $\tau_2 \in [0, \tau_2^*)$ contradict. Thus $\overline{\tau_2}(\tau_1) = \tau_2^*(\tau_1)$ which implies that the endemic equilibrium E_2 is stable when $\tau_1 \in [0, \tau_1^*), \tau_2 \in [0, \tau_2^*(\tau_1)), B_i \geq 0$ and $C_i \geq 0, i = 1,2,3$.

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The above analysis can be summarized into the following theorem.

Theorem 3.2.4 *If* $R_0 > 1$, $B_i \geq 0$ *and* $C_i \geq 0, i = 1,2,3$, *the unique endemic equilibrium* E_2 *of system (3.6) is stable.*

Completely Wolbachia-infected system

A very similar analysis can be performed for the case when all of the mosquitoes are infected by *Wolbachia*. In this case, the system is given by

$$\begin{cases} \frac{de_h(t)}{dt} = \hat{a}bmi_{mw}(t)(1-e_h(t)-i_h(t)) - \mu_h(t)e_h(t) \\ \qquad -\hat{a}bmi_{mw}(t-\tau_1)(1-e_h(t-\tau_1)-i_h(t-\tau_1))e^{-(r+\mu_h)\tau_1} \\ \frac{di_h(t)}{dt} = \hat{a}bmi_{mw}(t-\tau_1)(1-e_h(t-\tau_1)-i_h(t-\tau_1))e^{-(r+\mu_h)\tau_1} - ri_h(t) - \mu_h i_h(t) \\ \frac{de_{mw}(t)}{dt} = \hat{a}\hat{c}i_h(t)(n^*_{mw}-e_{mw}(t)-i_{mw}(t)) - \mu_{mw}e_{mw}(t) \\ \qquad -\hat{a}\hat{c}i_h(t-\tau_2)(n^*_{mw}-e_{mw}(t-\tau_2)-i_{mw}(t-\tau_2))e^{-\mu_{mw}\tau_2} \\ \frac{di_{mw}(t)}{dt} = \hat{a}\hat{c}i_h(t-\tau_2)(n^*_{mw}-e_{mw}(t-\tau_2)-i_{mw}(t-\tau_2))e^{-\mu_{mw}\tau_2} - \mu_{mw}i_{mw}(t) \end{cases} \quad (3.37)$$

This is just a scaled version of Eqs.(3.6) (With e_{mn} replaced by e_{mw}/n^*_{mw}, i_{mn} by i_{mw}/n^*_{mw} and b, e_h and i_h unchanged). Doing the same deduction as in 3.7 the basic reproduction number R'_0 is given by

$$R'_0 = \frac{\hat{a}^2 bm\hat{c}n^*_{mw}e^{-(r+\mu_h)\tau_1}e^{-\mu_{mn}\tau_2}}{\mu_{mw}(\mu_h+r)} \quad (3.38)$$

Again they may be one or two equilibria, the disease-free equilibrium $E'_1(0,0,0,0)$ and the endemic equilibrium $E'_2(e'^*_h, i'^*_h, e^*_{mw}, i^*_{mw})$.

$$\begin{aligned} e'^*_h &= \frac{(e^{(r+\mu_h)\tau_1}-1)(r+\mu_h)(\hat{a}^2b\hat{c}mn^*_{mw} - r\mu_{mw}e^{(r+\mu_h)\tau_1}e^{\mu_{mw}\tau_2} - \mu_h\mu_{mw}e^{(r+\mu_h)\tau_1}e^{\mu_{mw}\tau_2}}{ac(\mu_h^2e^{(r+\mu_h)\tau_1}e^{\mu^{mw}\tau_2} - abmn^*_{mw}r + r\mu_he^{(r+\mu_h)\tau_1}e^{\mu_{mw}\tau_2} + abmn^*_{mw}re^{(r+\mu_h)\tau_1} + abmn^*_{mw}\mu_he^{(r+\mu_h)\tau_1})} \\ &= \frac{(e^{(r+\mu_h)\tau_1}-1)(r+\mu_h)(R'_0-1)}{ac\frac{\mu_h}{\mu_{mw}} + (e^{(r+\mu_h)\tau_1}-1)rR'_0 + R'_0\mu_he^{(r+\mu_h)\tau_1}}, \\ i'^*_h &= \frac{(\hat{a}^2b\hat{c}mn^*_{mw}\mu_h - r\mu_{mw}\mu_he^{(r+\mu_h)\tau_1}e^{\mu_{mn}\tau_2} - \mu_h^2\mu_{mw}e^{(r+\mu_h)\tau_1}e^{\mu_{mn}\tau_2})}{ac(\mu_h^2e^{(r+\mu_h)\tau_1}e^{\mu^{mn}\tau_2} - \hat{a}bmn^*_{mw}r + r\mu_he^{(r+\mu_h)\tau_1}e^{\mu_{mw}\tau_2} + \hat{a}bmn^*_{mw}re^{(r+\mu_h)\tau_1} + abmn^*_{mw}\mu_he^{(r+\mu_h)\tau_1})} \\ &= \frac{\mu_h(R'_0-1)}{\hat{a}\hat{c}\frac{\mu_h}{\mu_{mw}} + (e^{(r+\mu_h)\tau_1}-1)rR\prime_0 + R\prime_0\mu_he^{(r+\mu_h)\tau_1}}, \\ e^*_{mw} &= \frac{(e^{(r+\mu_h)\tau_1}-1)(\hat{a}^2b\hat{c}mn^*_{mw}\mu_h - r\mu_h\mu_{mw}e^{(r+\mu_h)\tau_1}e^{\mu_{mw}\tau_2} - \mu_h^2\mu_{mw}e^{(r+\mu_h)\tau_1}e^{\mu_{mw}\tau_2})}{\hat{a}^2b\hat{c}m\mu_he^{(\mu_{mw}\tau_2} - \hat{a}bmr\mu_{mw}e^{\mu_{mw}\tau_2} + \hat{a}bmr\mu_{mw}e^{(r+\mu_h)\tau_1}e^{\mu_{mw}\tau_2} + \hat{a}bm\mu_h\mu_{mw}e^{(r+\mu_h)\tau_1}e^{\mu_{mw}\tau_2}} \\ &= \frac{\mu_h\mu_{mw}(e^{\mu_{mw}\tau_2}-1)(r+\mu_h)(R'_0-1)}{\hat{a}^2b\hat{c}m\mu_he^{-(r+\mu_h)\tau_1} + \hat{a}bmr\mu_{mw}(1-e^{-(r+\mu_h)\tau_1})\hat{a}bm\mu_h\mu_{mw}}, \\ i^*_{mw} &= \frac{(\hat{a}^2b\hat{c}mn^*_{mw}\mu_h - r\mu_h\mu_{mw}e^{(r+\mu_h)\tau_1}e^{\mu_{mw}\tau_2} - \mu_h^2\mu_{mw}e^{(r+\mu_h)\tau_1}e^{\mu_{mw}\tau_2})}{\hat{a}^2b\hat{c}m\mu_he^{\mu_{mw}\tau_2} - \hat{a}bmr\mu_{mw}e^{\mu_{mw}\tau_2} + \hat{a}bmr\mu_{mw}e^{(r+\mu_h)\tau_1}e^{\mu_{mw}\tau_2} + \hat{a}bm\mu_h\mu_{mw}e^{(r+\mu_h)\tau_1}e^{\mu_{mw}\tau_2}} \\ &= \frac{\mu_h\mu_{mw}(r+\mu_h)(R'_0-1)}{\hat{a}^2b\hat{c}m\mu_he^{\mu_{mw}\tau_2} - \hat{a}bmr\mu_{mw}e^{\mu_{mw}\tau_2} + \hat{a}bmr\mu_{mw}e^{(r+\mu_h)\tau_1}e^{\mu_{mw}\tau_2} + \hat{a}bm\mu_h\mu_{mw}e^{(r+\mu_h)\tau_1}e^{\mu_{mw}\tau_2}} \end{aligned} \quad (3.39)$$

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With the endemic equilibrium only being biologically meaningful for $R_0' > 1$. As in *Wolbachia*-free case, a similar argument shows that Since R_0' defined by (3.38) and the steady state values given in (3.39) are all delayed dependent, increasing the delay values will decrease R_0' to make it equal to 1 and will make the positive steady state to coincide with the trivial equilibrium. Thus, Hopf bifurcation does not occur when the delay increases as there are no bifurcating periodic solution due to the increase of the delays value.

RESULTS AND DISCUSSION

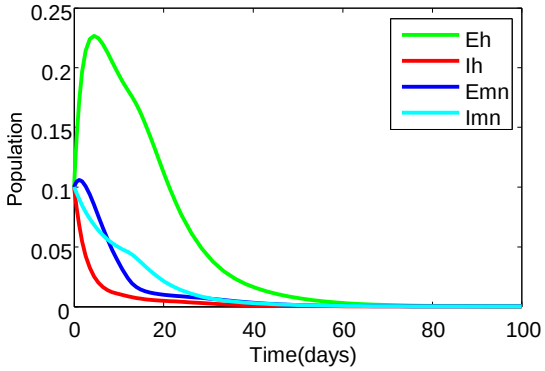
In this section, we present some numerical results of system (2.3), (3.6)and (3.37) that support and extend our theoretical research for some particular values of the parameters.

Numerical simulations

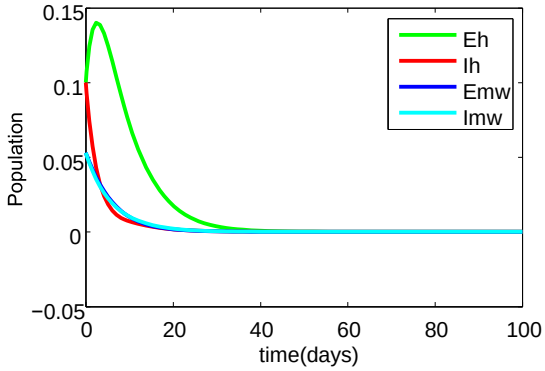
To investigate the effect of introducing *Wolbachia* to the dynamics of infectious humans, we choose various *Wolbachia* levels in the mosquito population: $n_{mw}^* = 0, 0.53, 0.85$, and 1. We perform all simulations and graphs with *MATLABR*2014*a*.

To numerically illustrate the results, we need to choose some parameter value (see table 1); The incubation period of *Plasmodium falciparum* in human was reported between 9 and 10 days with a mean of 9.5days (Molineaux and Gramicia (1980)) [17]. Before introducing *Wolbachia*, for a *Wolbachia*-free system (3.6) we have the following parameters: $a = 0.5day^{-1}$, $b = 0.4$, $c = 0.79$,$m = 7.7$, $r = 0.05day^{-1}$, $\mu_h = 0.333day^{-1}$, $\mu_{mn} = 0.15day^{-1}$, $\tau_1 = 9.5days$, $\tau_2 = 12days$. We can see that the basic reproduction number $R_0 = 0.0460 < 1$ and in two months the solution approaching the trivial equilibrium (0,0,0,0) **(see Fig.2(a)**.

After introducing *Wolbachia*,a completely *Wolbachia* infected system (3.37) the mortality rate of mosquitoes is increased to $mu_{mw} = 1.16\mu_{mn}$, biting rate increase to $\hat{a} = 1.13a$ and susceptibility decrease to $\hat{c} = c/11$ [6]. For a typical parameter valuesn_{mw}^* is about 0.53. Then the basic reproduction number is reduced to $R_0' = 0.0018 < 1$. This reduction depends on N_{mn} since n_{mw} does. Prevalence level in both human host and mosquito decrease and in one month the solution are approaching the trivial equilibrium (0,0,0,0). clearly in *Wolbachia* infected system almost one month before a disease die out compare to *Wolbachia*-free system **(see Fig.2(b))**.



(a)



(b)

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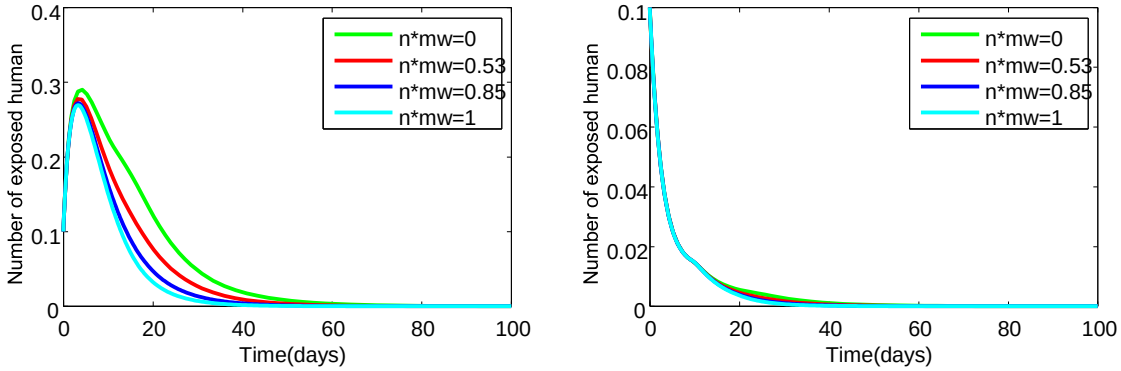
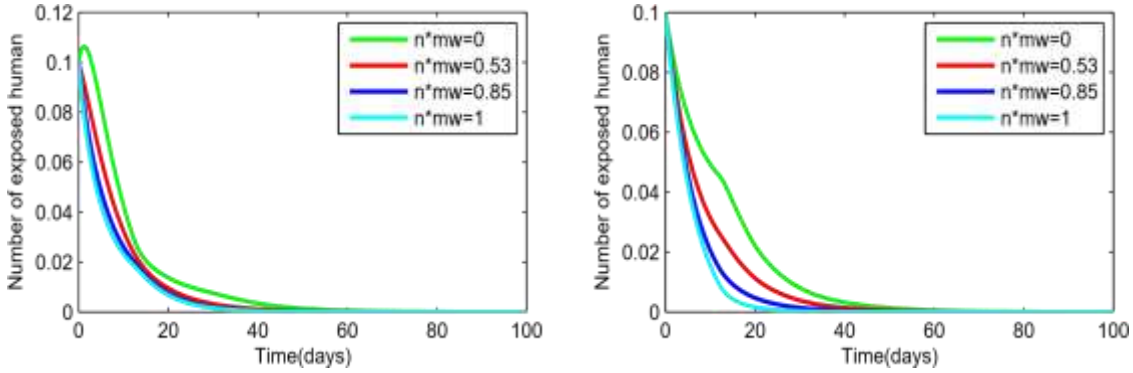
Fig. 2: The density of infected and infectious mosquitoes and human over a 100-day period. The initial values used were $e_h = 0.1$, $i_h = 0.1$, $e_{mn} = 0.1$, with $i_{mn} = 0.1$ and $n_{mn} = 1$ for (**a**) and $n_{mw} = n^*_{mw}$, $e_{mw} = 0.1n^*_{mw}$ and $i_{mw} = 0.1n^*_{mw}$ for (**b**), and the parameter values were were $a = 0.5$, $b = 0.4$, $c = 0.79$, $r = 0.05$, $\mu_h = 0.333$, $\mu_{mn} = 0.15$, $\tau_1 = 9.5$ and $\tau_2 = 12$, and in (**b**) $a\hat{} = 0.565$, $\hat{}c = 0.07$ and $\mu_{mw} = 0.175$, relevant to the *wMelpop* strain. Fig(**a**) show the situation when the entire *Anophele gambaie* population is *Wolbachia*-free. In (**b**) the entire *Anophele gambaie* population is exposed with *Wolbachia*. In (*b*), the density tends to zero as $t \to \infty$. the value for n^*_{mw} is 0.53.

Fig.3 shows the dynamics of exposed, infectious humans and vectors when n^*_{mw} changes. In **Fig.3(b)**,all the curves have a similar behavior. They increase to a peak and decay, then oscillate around and eventually approach to an equilibrium. Moreover, as n^*_{mw} increase, the first peak becomes smaller and more delayed, and the equilibrium also decreases. A *Wolbachia* level that is less than 1 is sufficient to lower infection to 0.



(a) Dynamics of exposed humans (b) Dynamics of Infectious humans



(c) Dynamics of exposed vectors (d) Dynamics of Infectious vectors

Fig. 3: Numerical simulation of dynamics of (a) exposed humans, (b) infectious humans, (c) exposed vectors,

(d) infectious vectors for different *Wolbachia* levels in vector population. The initial condition is $e_h = 0.1$, $i_h = 0.1$, $e_{mn} = 0.1$, $i_{mn} = 0.1$. The parameter value of this simulation:$a = 0.5$, $b = 0.4$, $c = 0.79$, $\tau_1 =$

9.5, $\tau_2 = 12, \mu_h = 0.333$, $\mu_{mn} = 0.15$, $a\hat{} = 0.565$, $c\hat{} = 0.07$, $\mu_{mw} = 0.175$ (see table 1).

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Reproduction Number

At which level is *Wolbachia* high enough to eliminate the malaria spread? The easiest way to see it is to calculate reproduction number. At the beginning of an endemic, non-susceptible humans or vectors are negligible, so $1-e_h(0)-i_h(0) \approx 1$, $(1-n^*_{mw})-e_{mn}(0)-i_{mn}(0)) \approx (1-n^*_{mw})$ and $n^*_{mw} - e_{mw}(0) - i_{mw}(0)) \approx n^*_{mw}$. The same as the deduction in system (3.6), we find that

Malaria will spread if and only if

$$abm[imn(t) + imw(t)]e^{-(r+\mu h)\tau 1} > (r + \mu h)ih(t),$$

$$acih(t)(1 - n*mw)e^{-\mu mn\tau 2} > \mu mnimn(t), \quad (4.1)$$

$$a\hat{c}i\hat{h}(t)n*mwe^{-\mu mw\tau 2} > \mu mwimw(t)$$

Dividing the second and the third inequalities by μ_{mn} and μ_{mw} on both sides respectively, summing them up, and multiplying by the first inequality, we have

$$abme^{-(r+\mu_h)\tau_1}\left(\frac{ac}{\mu_{mn}}(1-n^*_{mw})e^{-\mu_{mn}\tau_2} + \frac{\hat{a}\hat{c}}{\mu_{mw}}n^*_{mw}e^{-\mu_{mw}\tau_2}\right) > r + \mu_h \quad (4.2)$$

and

$$\frac{abme^{-(r+\mu_h)\tau_1}\left(\frac{ac}{\mu_{mn}}(1-n^*_{mw})e^{-\mu_{mn}\tau_2} + \frac{\hat{a}\hat{c}}{\mu_{mw}}n^*_{mw}e^{-\mu_{mw}\tau_2}\right)}{r+\mu_h} > 1 \quad (4.3)$$

Therefore, the new basic reproduction number after introducing *Wolbachia* is

$$R = \frac{abme^{-(r+\mu_h)\tau_1}\left(\frac{ac}{\mu_{mn}}(1-n^*_{mw})e^{-\mu_{mn}\tau_2} + \frac{\hat{a}\hat{c}}{\mu_{mw}}n^*_{mw}e^{-\mu_{mw}\tau_2}\right)}{r+\mu_h} \quad (4.4)$$

To study how the *Wolbachia* level n^*_{mw} will affect *R*, with our data in table (1) it is easy to verify that reproduction number $R < 1$, but if we choose death rate for human caused by malaria $\mu_h = 0.000093 day^{-1}$(which is $0.0028 month^{-1}$) from the work of (Bakary Traore et al.,(2017)) [34], and pick other parameter values in table (1), this makes $R > 1$ for small values of n^*_{mw}. **Fig.4** shows the relationship betweenn^*_{mw} and *R*. The basic reproduction number decreases as n^*_{mw} increases,and arrives to 1 when $n^*_{mw} = 0.90$ In other words, when the proportion of

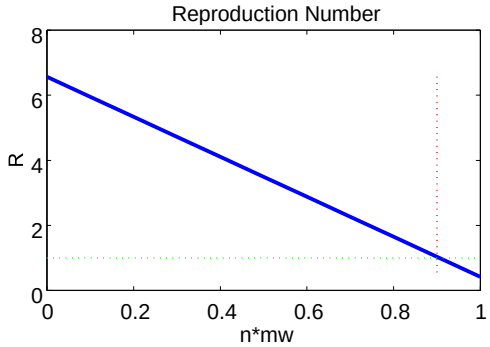

Fig. 4: The basic reproduction number with *Wolbachia*vs. *Wolbachia* level. The intercept of the curve and $R = 1$ is at$n^*_{mw} = 0.90$

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Wolbachia-carriers is greater than 90%, the malaria infection can be eliminated from the populations based on our current parameter values. Which means that under our assumptions, using *Wolbachia* to fight malaria has a high success rate. But when the reproduction number is high enough, even all mosquitoes are infected with *Wolbachia* malaria disease will persist in human population.

CONCLUSION

We have analyzed a model for *wolbachia* and malaria infection superposed on an underlying data-based model for *Anophele gambiae* population dynamics. There are three possible outcomes for the system as a whole, with or without *Wolbachia* and with malaria. Which one is reached depends first on whether the chosen *Wolbachia* strain is able to establish itself and then on what the corresponding reproduction number of malaria infection is. If both *Wolbachia* and malaria persist, then there is a reduction in endemic level of malaria and the size of malaria epidemics, depending on the properties of the strain of *Wolbachia*.

Key questions remains are the use of *Wolbachia* for malaria control will require stably infected lines of major malaria vector such as *Anophele gambiae* s.l. (Africa), *Anophele Stephansi* (India) and *Anophele darlingi* (central and South America) and a comprehensive assessment of the protective effect against human malaria parasites such as P.falciparum/ and *P.vivax*. The applied use of *Wolbachia* for malaria control would also require significant characterization of *Wolbachia*'s phenotypic effect in diverse genetic background of these anopheles vector species. In reality, widespread control of malaria using *Wolbachia*-based methods is not achievable. For example, the difficulties of colonizing *An.darlingi* (and therefore transinfecting this spacies with *Wolbachia*) would prevent the applied use of *Wolbachia* for control malaria in parts of the Amazonian region. In that case, transinfection of colonisable spacies such as *Anopheles aquasalis* (Dasilva et al. 2006) would provide applicability in areas where this spacies has vectorial importance. Lastly, one has to be aware that the complexity of malaria vector population (Lanzaro et al,.1998, Donelly et al.2002) would be a major complicating factor in the use of *Wolbachia* for malaria control. However, this novel approach may provide an effective mechanism of malaria control in some malaria endemic areas in which a single, vector species is present.

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