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Mathematical model of Zika virus transmission and control measures

Dewey Taylor

ABSTRACT. Zika virus (ZIKV) is an emerging mosquito-borne flavivirus capable of infecting humans through mosquito bites as well as through sexual contact between humans. ZIKV mitigation has traditionally focused on the reduction of the presence and abundance of mosquitoes. As the mosquitoes adapt to pesticides, the use of personal preventive measures will have to play a crucial role in controlling the spread of ZIKV. To evaluate different kinds of preventions, we consider a new mathematical model for ZIKV dynamics that incorporates four control measures, including two separate prevention measures, one for mosquito bite prevention and one for sexual transmission prevention. We study the model both analytically and numerically. We show that the mosquito bite control measure is more important for disease elimination and mitigation than the sexual transmission prevention.

1. Introduction

Zika virus (ZIKV) is an emerging mosquito-borne flavivirus, of the Flaviviridae family, that is closely related to the Spondweni serocomplex (Hamel et al., 2015). ZIKV was first isolated in 1947 from a febrile rhesus macaque monkey in the Zika Forest of Uganda and later identified in *Aedes africanus* mosquitoes from the same forest (Dick et al., 1952). The first cases of human infection were reported in 1954 in Nigeria (Macnamara, 1954). ZIKV is transmitted to humans through the bites of infected *Aedes* mosquitoes, including *A. aegypti, A. africanus, A. apicoargenteus, A. furcifer, A. hensilli, A. luteocephalus* and *A. vitattus* (Agusto et al., 2017a; Giovanetti et al., 2016). Recent studies show that ZIKV can be transmitted between humans via sexual contact (Foy et al., 2011).

Historically, symptomatic ZIKV infections were limited to sporadic cases or small clusters of patients (Plourde and Bloch, 2016). The climate changes may be behind the recent rise of *Aedes*-borne infections (Robert et al., 2020, 2019, 2016). The first major outbreak of ZIKV infection occurred in Yap Island in 2007 Duffy et al. (2009) and since then ZIKV infections have spread rapidly (Musso et al., 2014; Marcondes et al., 2016; Fauci and Morens, 2016). Serosurveillance studies in humans suggest that ZIKV is widespread throughout Africa, Asia, Oceania and Latin America (Plourde and Bloch, 2016; Wikan and Smith, 2017; Wikan et al., 2016). However, these studies may overestimate the virus's true prevalence, given serologic overlap between ZIKV and related flaviviruses (Korhonen et al., 2016; Plourde and Bloch, 2016).

ZIKV infection is predominantly a mild or asymptomatic denguelike disease (Fauci and Morens, 2016) with symptoms that include fever, rash, joint pain, conjunctivitis, muscle pain, and headache (Duffy et al., 2009; Petersen et al., 2016; Wahid et al., 2018). However, it has also been linked to

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Guillain-Barré Syndrome (Sejvar et al., 2011; Oehler et al., 2014) and severe birth defects, including microcephaly (Mlakar et al., 2016; Cauchemez et al., 2016). No vaccine, specific treatment, or fast diagnostic test is available to prevent, treat, or diagnose the ZIKV infection at this time (Gao et al., 2016). The year 2017 saw a marked decline in reported ZIKV cases and its severe disease manifestations (WHO, 2017). This decline has been widely attributed to the build-up of immunity against ZIKV in the wider human population (Ferguson et al., 2016), although it remains unknown how many people have been infected (O'Reilly et al., 2018).

ZIKV mitigation is closely associated with the reduction of the presence and abundance of *A. aegypti* (Basso et al., 2017). Controlling the mosquito population is a very challenging problem since mosquitoes can adapt to pesticides (Lima et al., 2011; Yakob and Walker, 2016). Moreover, mosquito control tools must be feasible and practical; community engagement was found to be an important element of integrated public health strategies (Sommerfeld and Kroeger, 2012).

Mathematical modeling is now a crucial tool in designing prevention of infectious diseases (Anderson et al., 1992; Keeling and Rohani, 2011) and many math models have been used to describe various aspects of ZIKV outbreaks, transmission dynamics and controls (Ding et al., 2016; Kucharski et al., 2016; Tang et al., 2016; Padmanabhan et al., 2017; Agusto et al., 2017b; Maxian et al., 2017; Agusto et al., 2017a; Lee et al., 2017; Bonyah et al., 2017; Amoah-Mensah et al., 2018; Dantas et al., 2018; Bonyah et al., 2019; Amoah-Mensah et al., 2019).

In Bonyah and Okosun (2016), the authors developed a mathematical model of the ZIKV dynamics incorporating three control measures, namely mosquito control, treatment control and prevention control. The prevention limited all transmission rates, mosquitoes-to-humans, humans-to-mosquitoes and humans-to-humans simultaneously. In this article, we build on the work in Bonyah and Okosun (2016) and extend their model by considering two separate prevention controls: a mosquito bite control that limits transmission between mosquitoes and humans and a contact control that limits human-to-human transmissions. Understanding the role of limiting human-to-human transmission is important since ZIKV has little impact on sexual activity (Hills, 2016).

We present the mathematical model in Section 2. We analyze the model in Section 3 where we derive the basic reproduction number, $\mathcal{R}_0$, and show that the disease-free equilibrium is locally asymptotically stable if $\mathcal{R}_0 < 1$ while the endemic equilibrium is stable, and unique, if $\mathcal{R}_0 > 1$. We parameterize the model and perform numerical simulations in Section 4. Our analysis and numerical simulations indicate that controlling mosquito bites is more important than controlling human-to-human transmissions. We conclude the paper with a discussion in Section 5.

2. Model

We present a simple SIR-SI compartmental ODE model of ZIKV dynamics that extends the model shown in Bonyah and Okosun (2016). The total human population size at time t, denoted by $N_h(t)$, is partitioned into susceptible individuals, $S_h(t)$, infectious individuals, $I_h(t)$, and recovered individuals, $R_h(t)$.

The basic model, without any control measures, is as follows. The human recruitment rate is Λ_h. We assume no vertical transmission thus all newly recruited individuals are susceptible. We also assume that individuals die at a rate of μ_h and that infectious individuals naturally recover at a rate of γ. Recovered individuals are assumed to have acquired permanent immunity. The susceptible individuals can be infected in one of the following ways: (1) directly through contact with an infected individual which happens at rate β_{hh}, or (2) through a bite by an infected mosquito, the effective mosquito-to-human transmission rate will be denoted β_{vh}. The mosquito population of

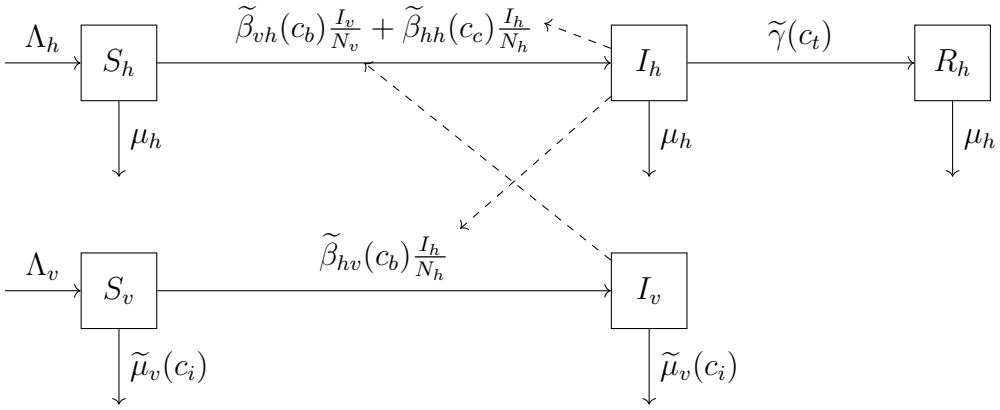

FIGURE 2.1. Scheme of the ODE model for ZIKV transmission.

size $N_v(t)$ is divided into susceptible, $S_v(t)$, and infectious, $I_v(t)$. The mosquito recruitment rate is Λ_v and we again assume that there is no vertical transmission, all mosquitoes are born susceptible. The mosquito natural death rate is μ_v. Mosquitoes are infected via contact with infected humans at a rate of β_{hv}.

There are four control measures:

(1) The bite control, c_b, such as using insecticide treated nets. This control limits the human-to-mosquito and mosquito-to-human contact rate and causes the effective transmission rates to be $\widetilde{\beta}_{hv}(c_b) = (1 - c_b)\beta_{hv}$ and $\widetilde{\beta}_{vh}(c_b) = (1 - c_b)\beta_{vh}$, respectively.
(2) The human-to-human contact control, c_c, such as the use of condoms. This control causes the effective human-to-human transmission rate to be $\widetilde{\beta}_{hh}(c_c) = (1 - c_c)\beta_{hh}$.
(3) The treatment control, c_t, which causes recovery to progress at a faster rate $\widetilde{\gamma}(c_t) = \gamma + c_t\gamma_{h,t}$.
(4) The insecticide control, c_i, which increases the mosquito death rate to $\widetilde{\mu}_v(c_i) = \mu_v + c_i\mu_{v,i}$.

For simplicity, all control measures are assumed to be constants and in the interval $[0, 1]$.

The dynamics of the compartmental ODE model are summarized in Figure 2.1. See Table 2.1 for a summary of the notation along with its meaning.

The model in Figure 2.1, which is a special case of a system considered in Wei et al. (2008), yields the following differential equations.

$$\frac{dS_h}{dt} = \Lambda_h - \left(\widetilde{\beta}_{vh}(c_b)\frac{I_v}{N_v} + \widetilde{\beta}_{hh}(c_c)\frac{I_h}{N_h} + \mu_h\right) S_h \tag{2.1}$$

$$\frac{dI_h}{dt} = \left(\widetilde{\beta}_{vh}(c_b)\frac{I_v}{N_v} + \widetilde{\beta}_{hh}(c_c)\frac{I_h}{N_h}\right) S_h - (\mu_h + \widetilde{\gamma}(c_t))I_h \tag{2.2}$$

$$\frac{dR_h}{dt} = \widetilde{\gamma}(c_t)I_h - \mu_h R_h \tag{2.3}$$

$$\frac{dS_v}{dt} = \Lambda_v - \left(\widetilde{\beta}_{hv}(c_b)\frac{I_h}{N_h} + \widetilde{\mu}_v(c_i)\right) S_v \tag{2.4}$$

$$\frac{dI_v}{dt} = \widetilde{\beta}_{hv}(c_b)\frac{I_h}{N_h}S_v - \widetilde{\mu}_v(c_i)I_v \tag{2.5}$$

TABLE 2.1. Model parameters and notation. All rates are per capita per day.

Notation	Meaning	Base value	Reference(s)
Λ_h	Human recruitment rate	$\frac{0.01392}{365}$	World Bank (2020)
Λ_v	Mosquito recruitment rate	3000	Andraud et al. (2012)
μ_h	Human natural death rate	$\frac{1}{74 \cdot 365}$	CIA (2020)
μ_v	Mosquito natural death rate	$\frac{1}{11}$	Otero et al. (2006)
γ	Natural recovery rate	$\frac{1}{7.9}$	Lessler et al. (2016); Ferguson et al. (2016)
$\gamma_{h,t}$	Treatment recovery rate	$\frac{1}{5}$	Gao et al. (2016)
$\mu_{v,i}$	Insecticide related death rate	1	Momoh and Fügenschuh (2018)
β_{vh}	Mosquito-to-human transmission rate (without control)	$\frac{1}{11.3}$	Dantas et al. (2018); Ferguson et al. (2016)
β_{hv}	Human-to-mosquito transmission rate (without control)	$\frac{1}{8.6}$	Dantas et al. (2018); Ferguson et al. (2016)
β_{hh}	Human-to-human transmission rate (without control)	$\frac{1}{20}$	Gao et al. (2016)
c_b	Mosquito bite control	variable	
c_c	Contact control	variable	
c_t	Treatment control	variable	
c_i	Insecticide control	variable	
$\widetilde{\beta}_{vh}(c_b)$	Mosquito-to-human transmission rate with control	$(1-c_b)\beta_{vh}$	
$\widetilde{\beta}_{hv}(c_b)$	Human-to-mosquito transmission rate with control	$(1-c_b)\beta_{hv}$	
$\widetilde{\beta}_{hh}(c_c)$	Human-to-human transmission rate with control	$(1-c_c)\beta_{hh}$	
$\widetilde{\gamma}(c_t)$	Recovery rate with treatment control	$\gamma + c_t\gamma_{h,t}$	
$\widetilde{\mu}_v(c_i)$	Mosquito death rate with insecticide control	$\mu_v + c_i\mu_{v,i}$	

3. Analysis

There are two equilibria of the differential equations given in (2.1)-(2.5). We find those equilibria by solving the following system of algebraic equations.

$$0 = \Lambda_h - \left(\widetilde{\beta}_{vh}(c_b)\frac{I_v}{N_v} + \widetilde{\beta}_{hh}(c_c)\frac{I_h}{N_h} + \mu_h\right) S_h \tag{3.1}$$

$$0 = \left(\widetilde{\beta}_{vh}(c_b)\frac{I_v}{N_v} + \widetilde{\beta}_{hh}(c_c)\frac{I_h}{N_h}\right) S_h - (\mu_h + \widetilde{\gamma}(c_t))I_h \tag{3.2}$$

$$0 = \widetilde{\gamma}(c_t)I_h - \mu_h R_h \tag{3.3}$$

$$0 = \Lambda_v - \left(\widetilde{\beta}_{hv}(c_b)\frac{I_h}{N_h} + \widetilde{\mu}_v(c_i)\right) S_v \tag{3.4}$$

$$0 = \widetilde{\beta}_{hv}(c_b)\frac{I_h}{N_h}S_v - \widetilde{\mu}_v(c_i)I_v \tag{3.5}$$

By adding (3.1)-(3.3) we see that

$$N_h = \frac{\Lambda_h}{\mu_h}. \tag{3.6}$$

Moreover, adding (3.4)-(3.5) yields

$$N_v = \frac{\Lambda_v}{\widetilde{\mu}_v(c_i)}. \tag{3.7}$$

3.1. Disease-free equilibrium

We will denote the disease-free equilibrium by $E^0 = (S_h^0, I_h^0, R_h^0, S_v^0, I_v^0)$. In the disease-free equilibrium we assume that $I_h^0 = 0$. By (3.1) we see that $S_h^0 = \frac{\Lambda_h}{\mu_h}$. It follows immediately from (3.5) and (3.3) that $I_v^0 = 0$ and $R_h^0 = 0$. Finally, by (3.4) we have $S_v^0 = \frac{\Lambda_v}{\widetilde{\mu}_v(c_i)}$. Hence we see that the disease free equilibrium is given by

$$E^0 = \left(\frac{\Lambda_h}{\mu_h}, 0, 0, \frac{\Lambda_v}{\widetilde{\mu}_v(c_i)}, 0\right). \tag{3.8}$$

The basic reproduction number, $\mathcal{R}_0$, is given by

$$\mathcal{R}_0 = \frac{1}{\mu_h + \widetilde{\gamma}(c_t)} \cdot \left(\widetilde{\beta}_{hh}(c_c) + \frac{\widetilde{\beta}_{hv}(c_b)\widetilde{\beta}_{vh}(c_b)}{\widetilde{\mu}_v(c_i)}\right). \tag{3.9}$$

This formula for the basic reproduction number can be derived using the next generation matrix method (van den Driessche and Watmough, 2002), but can also be derived as follows. A single infectious individual stays infected for a period $\frac{1}{\mu_h + \widetilde{\gamma}(c_t)}$. During that time, that individual directly infects other individuals at a rate of $\widetilde{\beta}_{hh}(c_c)$ and directly infects mosquitoes at rate of $N_v\frac{\widetilde{\beta}_{hv}(c_b)}{N_h}$. Each of the infected mosquitoes stays infected for a time $\frac{1}{\widetilde{\mu}_v(c_i)}$. One infected mosquito infects humans at the rate $\frac{\widetilde{\beta}_{vh}(c_b)}{N_v}N_h$.

Theorem 3.1. *The disease-free equilibrium is locally asymptotically stable if $\mathcal{R}_0 < 1$. It is unstable if $\mathcal{R}_0 > 1$. If $\mathcal{R}_0 \leq 1$, it is globally asymptotically stable.*

Proof. The statement follows from Theorems 2.1.1 and 2.1.2 of Wei et al. (2008). □

3.2. Endemic equilibrium

In this section we assume $\mathcal{R}_0 > 1$. The endemic equilibrium is given by $E^* = (S_h^*, I_h^*, R_h^*, S_v^*, I_v^*)$ where I_h^* is a positive solution of

$$a(I_h^*)^2 + bI_h^* + c = 0 \tag{3.10}$$

where

$$a = \left(\frac{\widetilde{\gamma}(c_t) + \mu_h}{\mu_h}\right)\left(\frac{\widetilde{\beta}_{hh}(c_c)\widetilde{\beta}_{hv}(c_b)}{N_h^2}\right) \tag{3.11}$$

$$b = \frac{\widetilde{\gamma}(c_t) + \mu_h}{\mu_h}\left(\frac{\widetilde{\beta}_{vh}(c_b)\widetilde{\beta}_{hv}(c_b)}{N_h} + \frac{\widetilde{\beta}_{hh}(c_c)}{N_h}\widetilde{\mu}_v(c_i) + \frac{\widetilde{\beta}_{hv}(c_b)}{N_h}\mu_h\right) - \frac{\widetilde{\beta}_{hh}(c_c)\widetilde{\beta}_{hv}(c_b)}{N_h} \tag{3.12}$$

$$c = \widetilde{\mu}_v(c_i)\big(\widetilde{\gamma}(c_t) + \mu_h - \widetilde{\beta}_{hh}(c_c)\big) - \widetilde{\beta}_{vh}(c_b)\widetilde{\beta}_{hv}(c_b) \tag{3.13}$$

and

$$S_h^* = \frac{\Lambda_h}{\mu_h} - \frac{(\widetilde{\gamma}(c_t) + \mu_h)I_h^*}{\mu_h} \tag{3.14}$$

$$R_h^* = \frac{\widetilde{\gamma}(c_t)}{\mu_h}I_h^* \tag{3.15}$$

$$I_v^* = \frac{\Lambda_v}{\widetilde{\mu}_v(c_i)} \cdot \frac{\widetilde{\beta}_{hv}(c_b)\frac{I_h^*}{N_h}}{\widetilde{\beta}_{hv}(c_b)\frac{I_h^*}{N_h} + \widetilde{\mu}_v(c_i)} \tag{3.16}$$

$$S_v^* = \frac{\Lambda_v}{\widetilde{\mu}_v(c_i)} - I_v^*. \tag{3.17}$$

Indeed, by (3.3),

$$R_h^* = \frac{\widetilde{\gamma}(c_t)}{\mu_h}I_h^*. \tag{3.18}$$

By (3.6),

$$S_h^* = N_h - I_h^* - R_h^* = \frac{\Lambda_h - (\widetilde{\gamma}(c_t) + \mu_h)I_h^*}{\mu_h}. \tag{3.19}$$

By (3.5) and (3.7), we get

$$0 = \widetilde{\beta}_{hv}(c_b)\frac{I_h^*}{N_h}(N_v - I_v^*) - \widetilde{\mu}_v(c_i)I_v^* \tag{3.20}$$

and thus

$$I_v^* = N_v\frac{\widetilde{\beta}_{hv}(c_b)\frac{I_h^*}{N_h}}{\widetilde{\beta}_{hv}(c_b)\frac{I_h^*}{N_h} + \widetilde{\mu}_v(c_i)}. \tag{3.21}$$

By (3.1), (3.19), and (3.21) we get

$$0 = \Lambda_h - S_h^* \widetilde{\beta}_{vh}(c_b) \frac{\widetilde{\beta}_{hv}(c_b)\frac{I_h^*}{N_h}}{\widetilde{\beta}_{hv}(c_b)\frac{I_h^*}{N_h} + \widetilde{\mu}_v(c_i)} - S_h^* \widetilde{\beta}_{hh}(c_c)\frac{I_h^*}{N_h} - \mu_h \frac{\Lambda_h - (\widetilde{\gamma}(c_t) + \mu_h) I_h^*}{\mu_h} \tag{3.22}$$

which yields

$$0 = -S_h^* \widetilde{\beta}_{vh}(c_b) \frac{\widetilde{\beta}_{hv}(c_b)\frac{1}{N_h}}{\widetilde{\beta}_{hv}(c_b)\frac{I_h^*}{N_h} + \widetilde{\mu}_v(c_i)} - S_h^* \frac{\widetilde{\beta}_{hh}(c_c)}{N_h} + \big(\widetilde{\gamma}(c_t) + \mu_h\big) \tag{3.23}$$

and thus

$$\left(N_h - \frac{\widetilde{\gamma}(c_t) + \mu_h}{\mu_h} I_h^*\right) \cdot \left[\frac{\widetilde{\beta}_{vh}(c_b)\widetilde{\beta}_{hv}(c_b)\frac{1}{N_h}}{\widetilde{\beta}_{hv}(c_b)\frac{I_h^*}{N_h} + \widetilde{\mu}_v(c_i)} + \frac{\widetilde{\beta}_{hh}(c_c)}{N_h}\right] = (\widetilde{\gamma}(c_t) + \mu_h). \tag{3.24}$$

The last equation yields a quadratic equation (3.10) for I_h^*.

Theorem 3.2. *If $\mathcal{R}_0 > 1$, the endemic equilibrium is unique.*

Proof. If $\mathcal{R}_0 > 1$, then $c < 0$, where $c = \widetilde{\mu}_v(c_i)\big(\widetilde{\gamma}(c_t) + \mu_h - \widetilde{\beta}_{hh}(c_c)\big) - \widetilde{\beta}_{vh}(c_b)\widetilde{\beta}_{hv}(c_b)$ is as in (3.13). Since $a > 0$, there is only one positive root of (3.10). □

Theorem 3.3. *If $\mathcal{R}_0 > 1$, the endemic equilibrium is locally asymptotically stable.*

Proof. Follows from Wei et al. (2008), Theorem 2.2.1. □

4. Numerical simulations

4.1. Parameter estimation

We follow the general parameter estimation presented in Dantas et al. (2018) which fits the ZIKV transmission model to data from Brazil.

The birth rate in Brazil is 13.92 per year per 1000 people (World Bank, 2020). The life expectancy, μ_h^{-1}, in Brazil is 74 years (CIA, 2020). An individual stays infectious for $\gamma^{-1} = 7.9$ days; this estimate was derived in Dantas et al. (2018) from the fact that it takes on average 9.9 days for the infected individual to have no detectable virus in the blood (Lessler et al., 2016) and the infectiousness in ZIKV infection ends 1.5–2 days before the virus becomes undetectable (Ferguson et al., 2016). The recovery rate, if treated, was estimated by $\frac{1}{5}$ as the reciprocal of the duration of the acute ZIKV phase considered in Gao et al. (2016).

About 1000-5000 mosquitoes are born a day, with an average of 3000 a day (Andraud et al., 2012). The mosquito life span μ_v^{-1} is assumed to be 11 days (Otero et al., 2006). This is consistent with the usual life expectancy for the mosquito in Rio de Janeiro, Brazil (Maciel-De-Freitas et al., 2007), and close to the average of 2–3 weeks considered in biological studies (Nelson, 1986).

The time between a mosquito being infected and it infecting a human, β_{vh}^{-1}, and the time between a human infection and a mosquito taking an infectious blood meal, β_{hv}^{-1}, are estimated as an average of 11.3 days and 8.6 days, respectively (Dantas et al., 2018; Ferguson et al., 2016). The human-to-human transmission rate was estimated by $\frac{1}{20}$ as in Gao et al. (2016).

We assumed the insecticide related death rate, $\mu_{v,i}$ is 1, about 10 times the natural mosquito mortality rate, which is in line with the estimates done in Momoh and Fügenschuh (2018).

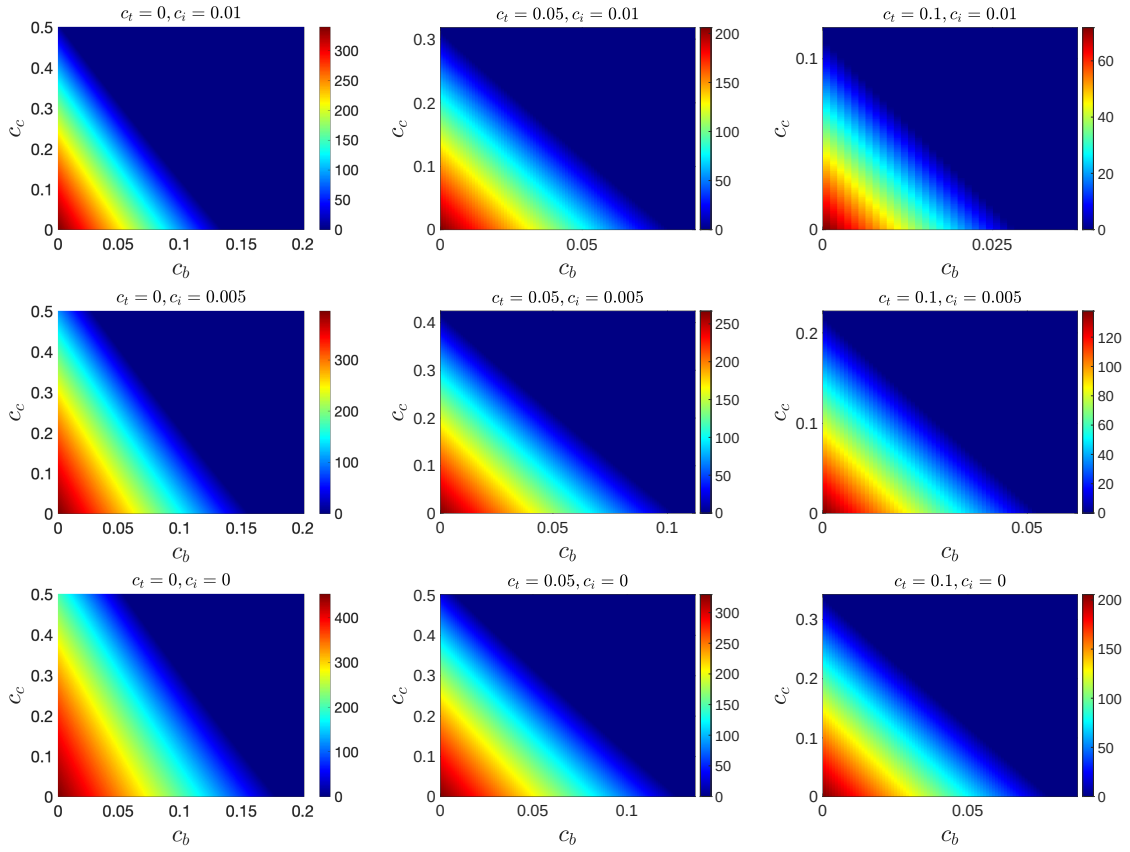

FIGURE 4.1. Annual incidence rates when the treatment control, c_t and insecticide control c_i are as specified.

4.2. Incidence rates

Figure 4.1 shows incidence rates for varying control measures. We note that during 2018, the incidence rate of suspected cases in Brazil was about 9.1/100,000 population, in Panama it was 66/100,000 population and in Bolivia 15/100,000 population (WHO, 2019).

It follows that the bite control measure c_b is much more important than the contact control measure c_c. We can also see that the incidence rate rapidly decreases with the insecticide control c_i and the treatment control c_t.

5. Conclusions and discussion

We considered a new mathematical model for ZIKV dynamics that incorporates mosquito transmission as well as sexual transmission. Our model incorporates four control measures and extends a model developed in Bonyah and Okosun (2016). We explicitly split the personal protection control measure considered in Bonyah and Okosun (2016) into bite control (preventing mosquito bites) and contact control (preventing transmission between humans).

We studied the model both analytically and numerically. We derived the basic reproduction number, R_0 as a function of the control measures. Through numerical simulations, we were able to see that the bite control measure is more important for the disease elimination and mitigation than the contact control measure.

We saw that, in theory, ZIKV can be effectively mitigated and perhaps eliminated with the use of insecticide control. However, controlling the mosquito population is a very challenging problem since mosquitoes can adapt to pesticides (Padmanabhan et al., 2017; Lima et al., 2011; Yakob and Walker, 2016). Consequently, the use of personal protections and effective bite control measures will have to play a crucial role in controlling the spread of ZIKV.

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(D. Taylor) Department of Mathematics and Applied Mathematics, Virginia Commonwealth University, Richmond, VA 23284, USA

Email address, Corresponding author: `dttaylor2@vcu.edu`