The spread of Zika as a vectorial and sexual transmitted disease: a mathematical model analysis

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Abstract

A mathematical model is proposed to explain the contribution of sexual transmission on Zika disease maintenance and spreading. Using the expression obtained for R_0 and reports of Zika in Rio de Janeiro, Brazil during 2015, we show how that a relatively small amount of sexual transmission can increase the basic reproductive number significantly. The model, together with the fact that only transmission from man to woman have been observed, explains the larger prevalence in women than in men reported in [4]. Sexual transmission can explain between 20% to 30% of the increment of R_0, but sensitivity analysis shows that the R_0 value is more sensitive to variations of humans infection period, and vector mortality rate. Although, if the sexual transmission cycle is complete, the Zika infection could be maintained even in the absence of the vector.

Key words: Zika disease, sexual transmission, vector transmission, basic reproductive number, sensitivity analysis

1 Introduction

Zika disease is caused by an arbovirus of the genus *Flavivirus* transmitted by the female of the mosquito *Aedes* (Albopictus and Aegypti), which is the same vector of Dengue and Chikungunya. Many people infected with Zika virus do not show symptoms or they are mild lasting from days to a week. Among

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these symptoms are rash, joint pain, and conjunctivitis. Mortality due to Zika is rare, and because the symptoms of Zika are similar to those of many other diseases, many cases may not have been recognized [21]. However, this disease has been related to several cases of microcephalic newborns [1], and this fact has lead to a world wide alert by World Health Organization.

Zika virus was first isolated in 1947 from a rhesus monkey in the Zika forest, Uganda. The first isolation in humans was done in estearn Nigeria in 1952, but it was not until 2007 that the first epidemic of Zika was reported in the West Pacific island of Yap, followed by a larger epidemic in French Polynesia, with an estimated of 30,000 symptomatic cases [1, 16].

Before 2015, Zika virus disease outbreaks occurred in Africa, Southeast Asia, and the Pacific Islands, but in May 2015 the first case of confirmed Zika virus infection in the Americas was reported in Brazil. Since then, the reports of Zika have been increased, and also the reports of birth defects and Guillain-Barré syndrome in seven countries in the Americas and the Caribbean. The presence of Zika virus in the amniotic fluid of pregnant women that gave birth to microcephalic newborns, as well as epidemiological data favor the hypothesis of a relationship between Zika and microcephaly in newborns. In particular, estimates from Brazil suggest a 20-fold increment in the number of cases of this malformation compared with previous years in areas affected by this disease [1, 16, 20]. Due to these facts, in February of 2016 the World Health Organization declared Zika an International Public Health Emergency [21].

Evidences of sexual transmission of Zika virus by sexual contacts from man to woman, and man to man have been documented by several authors [1, 6, 7, 20]. The first case was reported in 2008 when a scientist became infected in Senegal, and her wife who was at U.S. develped Zika symptoms nine days later. The inconsistency of the time interval with the Zika incubation time (more than 15 days) suggest a sexual transmission of the virus [7]. In [17] was reported the possible persistence of the Zika virus in the genital tract of an infected woman after the disappearance of the virus from her blood and urine samples. These findings suggest to the authors to consider women as possible chronic Zika virus carriers. In the same context, it has been found data that indicate a prolongued presence of virus in semen, which in turn, indicate a higher potential for sexual transmission of Zika virus [2].

The basic reproduction number, R_0, of a disease is the average number of secondary infections derived from a primary infection in a whole susceptible community. R_0 is a very useful tool to measure the severity of a disease, and

to design control policies. Although reports of the basic reproductive number for Zika are not widely avilable, there are several estimates of R_0 for different outbreak of this disease using daily incidence data. In the outbreak of Yap Island reports give estimations of R_0 from 4.3 to 5.8, in contrast to the values of 1.8 to 2.0 in the French Polynesia [12]. In [18] the authors estimated $R_0 = 1.41$, and $R_0 = 4.61$ for Zika outbreaks occurred in the colombian locations of San Andres Island, and Girardot city, respectively. Using notification data of Zika in Rio de Janeiro, Brazil, the basic reproductive number estimated in [3] was of the order of 2.33, and in [5] the authors obtain $R_0 = 1.42$ for Salvador, Brazil.

In [4] the authors found, in the sexually active age group (15-65 years), a significant higher Zika incidence in women than in men, which can not be explained only by social behaviour. They conclude that probably this difference is due to sexual transmission from men to women. Therefore, in order to evaluate the importance of sexual transmission in Zika disease, we propose a general mathematical model involving both vectorial and sexual transmission where human population is divided into men and women to evaluate the difference in prevalence between both genders. The main question to be addressed is how sexual transmission contributes to the spreading of Zika disease and to explain the larger prevalence in woman than in man. For this purpose we deduce from our mathematical model a basic reproductive number which depends explicitly on the vectorial and sexual transmission parameters. Finally, we carry out a sensitivity analysis in order to detect the most relevant parameters for the dispersion of Zika infection.

2 Formulation of the model

Zika disease is mainly transmitted by the bites of mosquitoes *Aedes*. For this reason we consider in the model the humans, N, and mosquitoes, N_V, populations which are assumed constant. In order to obtain a complete model of Zika transmission, we divide the human population into man and woman denoted by N_M, and N_W, respectively, and we assume that the infection is transmitted among both sub populations via sexual contacts. According to this, the dynamics of the disease is governed by the following system of

ordinary differential equations:

$$\begin{aligned}
\frac{d\bar{S}_M}{dt} &= q\mu N_H - b\beta_V \bar{S}_M \frac{\bar{I}_V}{N_H} - \beta_M \bar{S}_M \frac{\bar{I}_W}{N_H} - \mu \bar{S}_M \\
\frac{d\bar{I}_M}{dt} &= b\beta_V \bar{S}_M \frac{\bar{I}_V}{N_H} + \beta_M \bar{S}_M \frac{\bar{I}_W}{N_H} - (\mu+\gamma)\bar{I}_M \\
\frac{d\bar{S}_W}{dt} &= (1-q)\mu N_H - b\beta_V \bar{S}_W \frac{\bar{I}_V}{N_H} - \beta_W S_W \frac{\bar{I}_M}{N_H} - \mu \bar{S}_W \\
\frac{d\bar{I}_W}{dt} &= b\beta_V \bar{S}_W \frac{\bar{I}_V}{N_H} + \beta_W \bar{S}_W \frac{\bar{I}_M}{N_H} - (\gamma+\mu)\bar{I}_W \\
\frac{d\bar{I}_V}{dt} &= b\alpha(N_V - \bar{I}_V)\frac{I_M}{N_H} + b\alpha(N_V - \bar{I}_V)\frac{\bar{I}_W}{N_H} - \nu \bar{I}_V, \qquad (2.1)
\end{aligned}$$

where $\bar{S}_M, \bar{S}_W$ and $\bar{I}_M, \bar{I}_W$ denote the number of susceptible and infected men and women, respectively, while $\bar{I}_V$ denotes the infected vectors. The parameters β_W, β_M, are the infection rates from an infected men to susceptible women, and an infected woman to a susceptible man, respectively. β_V is the infection rate from mosquitoes to humans, and α the infection rate from humans to mosquitoes. The parameter q denotes the proportion of men, and finally, μ and ν are the per capita mortality rates for human and vector population, respectively, while $1/\gamma$ is the infection period in humans.

We rewrite the variables of system (2.1) in terms of the following proportions

$$S_M = \frac{\bar{S}_M}{N_H}, \quad S_W = \frac{\bar{S}_W}{N_H}, \quad I_M = \frac{\bar{I}_M}{N_H}, \quad I_W = \frac{\bar{I}_W}{N_H}, \quad I_V = \frac{\bar{I}_V}{N_V},$$

in order to compute the disease prevalence as a proportion of the total populations, thus

$$\begin{aligned}
\frac{dS_M}{dt} &= q\mu - bm\beta_V S_M I_V - \beta_M S_M I_W - \mu S_M \\
\frac{dI_M}{dt} &= bm\beta_V S_M I_V + \beta_M S_M I_W - (\mu+\gamma) I_M \\
\frac{dS_W}{dt} &= (1-q)\mu - bm\beta_V S_W I_V - \beta_W S_W I_M - \mu S_W \\
\frac{dI_W}{dt} &= bm\beta_V S_W I_V + \beta_W S_W I_M - (\gamma+\mu) I_W \\
\frac{dI_V}{dt} &= b\alpha(1-I_V) I_M + b\alpha(1-I_V) I_W - \nu I_V, \qquad (2.2)
\end{aligned}$$

where $m = \dfrac{N_v}{N_h}$is the proportion of mosquitoes to humans.

3 Disease-Free Equilibrium and the Basic Reproductive Number

The disease-free equilibrium of system (2.1) is $E_0 = (q, 0, 1-q, 0, 0)$. Linearizing around this equilibrium we obtain the matrix

$$DF(E_0) = \begin{pmatrix} -\mu & 0 & 0 & -\beta_M q & -bm\beta_V q \\ 0 & -(\mu+\gamma) & 0 & \beta_M q & bm\beta_V q \\ 0 & -\beta_W(1-q) & -\mu & 0 & -bm\beta_V(1-q) \\ 0 & \beta_W(1-q) & 0 & -(\mu+\gamma) & bm\beta_V(1-q) \\ 0 & b\alpha & 0 & b\alpha & -\nu \end{pmatrix},$$

where DF denotes the derivative of the vector field F given by the right-hand side of (2.1). The eigenvalues of this matrix are $-\mu_a$ of multiplicity two, and the roots of the cubic polynomial

$$p(\lambda) = \lambda^3 + a_1\lambda^2 + a_2\lambda + a_3$$

with

$$\begin{aligned} a_1 &= 2(\mu+\gamma) + \nu \\ a_2 &= (\mu+\gamma+2\nu)(\mu+\gamma)\left[1 - \frac{b^2\alpha m\beta_V + (1-q)q\beta_M\beta_W}{(\mu+\gamma+2\nu)(\mu+\gamma)}\right] \\ a_3 &= 1 - R_0, \end{aligned}$$

where the *Basic Reproductive Number,* R_0, is given by

$$R_0 = R_{0_{VHV}} + R_{0_{VWMV}} + R_{0_{VMWV}} + R_{0_{MWM}} \tag{3.3}$$

and

$$\begin{aligned} R_{0_{VHV}} &= \frac{bm\beta_V}{\nu}\frac{b\alpha}{(\gamma+\mu)} \\ R_{0_{VMWV}} &= \frac{bm\beta_V q}{\nu}\frac{(1-q)\beta_W}{(\gamma+\mu)}\frac{b\alpha}{(\gamma+\mu)} \\ R_{0_{VWMV}} &= \frac{bm\beta_V(1-q)}{\nu}\frac{q\beta_M}{(\gamma+\mu)}\frac{b\alpha}{(\gamma+\mu)} \\ R_{0_{MWM}} &= \frac{q\beta_M}{(\gamma+\mu)}\frac{(1-q)\beta_W}{(\gamma+\mu)}. \end{aligned} \tag{3.4}$$

It is well known that the Routh-Hurwitz conditions for a polynomial of degree 3, given by $a_i > 0$, and $a_1 a_2 - a_3 > 0$, imply that the disease free equilibrium is locally asymptotically stable (see [8]). In this case, the conditions are satisfied if and only if $R_0 < 1$.

We observe that R_0 is the sum of the basic reproductive numbers associated with the following four kind of transmissions: i) vector-human-vector, ii) vector-man-woman-vector, iii) vector-woman-man-vector, and iv) man-woman-man (see Figure 1).

Figure 1

4 The Zika outbreak in Rio de Janeiro

In [3] the authors use notification data of Zika in Rio de Janeiro to estimate the basic reproductive number, R_0, of this disease. They found a value of $R_0 = 2.33$, which is higher than the ones obtained from dengue data of epidemics caused by DENV-3 and DEN-4 when these serotypes were introduced by the first time into Rio de Janeiro. The same authors use entomologial data of *Aedes aegypti*, and epidemiological data of dengue transmission to obtain R_0 of Zika under a vectorial-only transmission model, and they found that this value was almost 1.4 times of the dengue R_0 estimated for the 2002 and 2012 epidemics. They conclude that these results suggest that either the knowledge about the vectorial capacity of *Aedes aegypti* is not well known, or other modes of transmission are important in the disease transmission.

In order to understand the difference of sizes between the basic reproductive number of Zika, and dengue disease we use the expression given in (3.4) to measure the importance of sexual transmission in Zika. Because only there are evidences of sexual transmission from men to women we set $\beta_M = 0$, which implies $R_{0_{VWMV}} = R_{0_{MWM}} = 0$. For Zika reproductive number we take $R_0 = 2.33$, and for the vectorial transmission $R_{0_{VH}}$, the values of 1.7 and 1.25, respectively, which correspond to the estimated basic reproductive numbers of the 2002 and 2012 dengue epidemics in Rio de Janeiro [3]. We assume that the proportions of women and men with respect the total human populations are the same (q=0.5), and we assume that the infectious period $1/\gamma$ is around six days ($\gamma = 0.17$ days). If $\beta_M = 0$ the basic reproductive number for Zika becomes

$$R_0 \;=\; R_{0_{VHV}} + R_{0_{VMWV}}. \tag{4.5}$$

Substituting $R_{0_{VHV}} = 1.7$, and the above parameters in (4.5), we obtain $\beta_W \approx 0.25$, which gives the estimation $R_{0_{VMWV}} = 0.64$. Comparing $R_{0_{VMWV}}$ with R_0 we observe that sexual transmission man to woman is involved in around 0.27 of the new Zika cases. Now, if we substitute the 2012 basic reproductive number for dengue, $R_{0_{VHV}} = 1.25$, in (4.5), we obtain $\beta_W \approx 0.55$, and $R_{0_{VMWV}} = 1.1$. In this case the sexual transmission is almost twice that the one obtained for dengue epidemic of 2002, and it is involved in 0.47 of the new infections.

For completeness we now study the hypothetical case of sexual transmission cycle of Zika from man to woman and woman to man. To estimate sexual transmission we propose $\beta_M = \beta_F = \beta$. Substituting the above values in (3.3), and assuming that $R_{0_{VH}} = 1.7$ we obtain $\beta = 0.09$. Substituting this value and the parameters above, we obtain $R_{0_{MWM}} = 0.09$, and $R_{0_{VMWV}} = R_{0_{VMWV}} = 0.25$. Analogously, for $R_{0_{VH}} = 1.25$, we get $\beta = 0.19$, $R_{0_{MW}} = 0.31$, and $R_{0_{VMWV}} = R_{0_{VWMV}} = 0.38$.

We further calculate the ratios β_W/β for $R_{0_{VH}} = 1.7$, and $R_{0_{VH}} = 1.25$, respectively, and the average between both quantities gives approximately 2.6. This number indicates that the probability of sexual transmission increases almost three times when it is only from man to woman. This behaviour also can be observed in the numerical simulation of the model given in Figure 2a-c, which illustrate the temporal course of the infected women and men using the parameters above. In Figures 2a-b it is assumed that sexual transmission is only from man to woman, while in Figure 2c the same transmission is in

both directions. In the first two figures there are quantitatively differences between the proportion of infectious men and women. In particular, in Figure 2b we observe that maximal prevalence of infective women is 1.6 times bigger than the maximal prevalence of infected men. In contrast, in Figure 2c the proportion of infective woman and man is practically the same.

Figures 2a, 2b and 2c

5 Sensitivity Analysis

The objective of the sensitivity analysis is quantify how input uncertainty impacts model outcome. There are a lot of different approaches and the perform of each one depends the proposed model. In this section, following [13, 19], we carry out a global sensitivity analysis to quantify the impact of the variations of the parameters $m\beta_V, \beta, \alpha, \gamma, \nu$ on the numerical simulations of model (2.2), using the basic reproductive number R_0 as the response function. For this end, we first sample the space of the input values using the latin hypercube sampling (LHS) with $m\beta_V \sim Unif(0.1, 0.4)$, $\beta \sim Unif(0.05, 0.25)$, $\alpha \sim Unif(0.5, 1.1)$, $\gamma \sim Unif(0.08, 0.38)$, and $\nu \sim Unif(0.07, 0.43)$ where $Unif$ means an uniform probability distribution. In LHS, each parameter probability distribution is divided into N equal intervals, and sampling from each interval exactly once guarantees that the entire parameter space is explored.

A Monte Carlo simulation was done by drawing $N = 10000$ independent parameters set, $X_i = (m\beta_V, \beta, \alpha, \gamma, \nu)$ with $i = 1, ..., N$, and evaluating $Y_i = R_0$ for each parameter set using equation (3.3). Assuming that the relation between output and input is linear, a regression model of the form $\bar{R_0} = b_0 + b_1(m\beta_V) + b_2\beta + b_3\alpha + b_4\gamma + b_5\nu$ can be used to assess the R_0 sensitivity to each parameter. It is known that the standardized regression coefficients $\eta_{m\beta_V} = (\sigma_{m\beta_V}/\sigma_{\bar{R_0}})b_1$, $\eta_\beta = (\sigma_\beta/\sigma_{\bar{R_0}})b_2$, $\eta_\alpha = (\sigma_\alpha/\sigma_{\bar{R_0}})b_3$, $\eta_\gamma = (\sigma_\gamma/\sigma_{\bar{R_0}})b_4$, $\eta_\nu = (\sigma_\nu/\sigma_{\bar{R_0}})b_5$ where σ_k is the standard deviation with $k \in \{m\beta_V, \beta, \alpha, \gamma, \nu, R_0\}$ satisfy $\eta^2_{m\beta_V} + \eta^2_\beta + \eta^2_\alpha + \eta^2_\gamma + \eta^2_\nu = 1$, if the parameters are independent and the model is linear. The deviation from linearity is measured by

$$R^2 = \sum_{i=1}^{N} = \frac{\bar{R_0}^{\,i} - \mu_{R_0}}{R_0^i - \mu_{R_0}},$$

where $R_0, \bar{R_0}$ and μ_{R_0} are respectively the simulation results, the values provided by the regression model and the mean value of R_0. When $R^2 \geq 0.7$ the standardized regression coefficients can be used for sensitivity analysis. Transforming both the input and output sample vectors to ranks can improvement the performance of the regression-based approach because rank transformation can substantially linearized a nonlinear, albeit monotonic, function [13, 19].

Scatter plots of R_0 versus each one of the parameters were done to examine the assumption of the monotonic relationships between outputs and inputs (see Figure 3).

Figures 3a, 3b, 3c, 3d

Figure 4 shows the standard regression coefficients (SCR) obtained from the data. In this case, $R^2 = 0.63$. The sensitivity based on the SCR can capture 95% of the variation on R_0 ($\eta^2_{m\beta_V} + \eta^2_\beta + \eta^2_\alpha + \eta^2_\gamma + \eta^2_\nu = 0.95$). The parameters γ accounts for 49% of this variation ($\eta^2_\gamma = 0.49$). Increasing γ or ν promotes the decreasing of R_0. This relation is not true for the others parameters, since in this case, a decrement of the transmission rates α, β or $m\beta_V$ leads to a decrease of R_0, corresponding to the vectorial transmission, $m\beta_V$, the highest variation. The order of importance related to the contribution of each parameters to R_0 is $\gamma, \nu, m\beta_V, \alpha$ and β. Using the rank-transformed data we obtained $R^2 = 0.93$, with $\eta_{m\beta_V} = 0.4, \eta_\beta = 0.2, \eta_\alpha = 0.2$, $\eta_\gamma = -0.7$, and $\nu = -0.5$.

Figure 4

In Figure 5 we changed the range of the parameter β, and instead, we assume $\beta \sim Unif(0.2, 0.7)$, which corresponds to the case without sexual transmission from women to men. Here, $R^2 = 0.60$ and $\eta^2_{m\beta_V} + \eta^2_\beta + \eta^2_\alpha + \eta^2_\gamma + \eta^2_\nu = 0.96$. It is interesting to note that the contribution of β to the model outputs was reduced from 4% to 2.2%, i.e., almost two times. Using the rank-transformed data we obtained $R^2 = 0.94$, with $\eta_{m\beta_V} = 0.4, \eta_\beta = 0.1, \eta_\alpha = 0.2$, $\eta_\gamma = -0.6$. and $\nu = -0.5$.

Figure 5

6 Discussion

The recent outbreaks of Zika in South America have had a very high prevalence which contrasts with outbreaks of other infections transmitted by *Aedes* mosquitoes as dengue and chikungunya. There are comparative studies among the outbreaks of all of these infections during 2016, which show notable differences among the respective basic reproductive numbers [3]. A remarkable aspect of Zika is that recent cases of this disease occurred in the Americas are due to sexual transmission from men to women [1, 6, 7, 20].

Although, recently it has been found that woman could also be an important chronic Zika virus carriers [17], the evidences until now suggest that sexual transmission occurs only from men to women. In the past, Zika sexual transmission has been basically ignored because it is assumed that the proportion of this kind of transmission is very small, and its cycle is not complete due to the lack of evidence of contagion from women to men.

In this work we carried out an analysis of the effect of sexual transmission on the dynamics of Zika propagation. For this, we formulated an ODE model for the evolution of the dynamics of this infection taking into account both sexual and vectorial transmission. This model gives an expression for the basic reproductive number in which both kind of transmissions are coupled (See 3.3). Since this coupling is given by the product of terms measuring the vectorial and sexual transmission, even a moderate sexual transmission can be significant if the vectorial transmission is large enough. In fact, with data from the outbreak of Rio de Janeiro, we show that a relatively small amount of sexual transmission from man to woman can increase the basic reproductive number between 20% and 30%, which could explain the high prevalence in the Zika outbreaks. We also showed that, even if the sexual transmission cycle is not complete, it can increase significantly the basic reproductive number of the disease. This is due to the fact that the sexual transmission couples to the vector transmission, that is, sexually infected women transmit the infection to men through the vector.

As was mention in the Introduction, in [4] the authors found that for the human reproductive ages, Zika incidence in woman is much higher than in man. In fact, they found in women an incidence that is almost 90% larger than in men. Using data of Dengue disease, they argued that at most thirty percent of the difference is due to the fact that women visit more often the medical services, and they suggest that rest (60%) could be explained by sexual transmission. We want to notice that the simulations of our model

are in agreement with these data and the authors conclusion. This can be seen in Figure 2b where the maximal prevalence in woman is 76% higher that the maximal prevalence in men. It is also worth to mention that the values obtained for the sexual transmission β_F in our work are in the range observed for sexual transmitted diseases such as gonorrhea $(0.19 - 0.65)$ [10], HIV $(0.05 - 0.5)$ [14], and Hepatitis B $(0.18 - 0.44)$ [11].

For completeness we also studied the case where the sexual transmission cycle is closed, and there is also infection from woman to man. Using the basic reproductive number of dengue epidemics of 2002, $R_0 = 1.7$, the basic reproductive number involving Zika vectorial transmission is $R_{0_{VHV}} + R_{0_{VMWV}} + R_{0_{VWMV}} = 2.2$, while the basic reproductive number only for sexual transmission is $R_{0_{MWM}} = 0.1$. These results are consistent with the corresponding basic reproductive numbers $R_{0_{VH}} = 1.96$, and $R_{0_{HH}} = 0.14$, obtained in [9] adjusting data of Zika epidemics occurred in Brazil, Colombia and El Salvador during 2015-2016 with a model considering sexual transmission in both directions. It is interesting to notice, that in the case where sexual cycle is closed, the disease can be sustained even in the absence of the vector, as can be seen from (3.3) if $R_{0_{MWM}} > 1$.

The sensitivity analysis carried out in the last section reveals the relevance of each model parameters on R_0 prediction. The results shown that γ and ν, respectively the inverse of the infection period in humans and the per capita mortality rates of the vector, together explain 60% to 75% of the variation of R_0. Increasing in one of these parameters promotes the decreasing of R_0. The infection rates α and β, respectively from humans to mosquitoes and from man to woman (or woman to man), explain between 5% to 8% of the variation of R_0. Lastly, $m\beta_V$ explains 16% of the variation of R_0. Control measures applied to mosquito population can decrease the value of $m\beta_V$ and increase the value of ν. On the other hand, control measures applied to human population (protected sex behaviour) can decrease the value of β. Since the first two parameters are the main drivers of Zika transmission (R_0 value) we can conclude that the control efforts applied to mosquito population still being the more effective way to control Zika infection because the sexual transmission men to women is not closed.

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Figure Captions

Figure 1.Transmission chains of model (2.1).

Figure 2. Zika infectious proportions of women and men. In all the simulations the basic reproductive number of Zika is $R_0 = 2.33$. a) Sexual transmission only from man to woman assuming vectorial transmission $R_{0_{VHV}} = 1.7$. b) Sexual transmission from man to woman assuming vectorial transmission $R_{0_{VHV}} = 1.25$. c) Sexual transmission from man to woman and woman to man assuming $R_{0_{VHV}} = 1.7$. The values of the parameters in Figure 2a are $\beta_W = 0.25$, $\beta_M = 0$, $m\beta_V = 0.37$, $b = 0.5$, $\alpha = 0.77$, $\gamma = 0.17$ day^{-1}, $\mu_V = 0.25$ day^{-1}, and $\mu_H = 0.00004$ day^{-1}. In Figure 2b, $\beta_W = 0.55, \beta_M = 0$, $m\beta_V = 0.27$, and the other parameters are as in Figure 2a. In Figure 2c, $\beta_W = \beta_M = 0.1$, $m\beta_V = 0.37$, and the other parameters are as in Figure 2a.

Figure 3. Scatter plots of R_0 versus a) γ, b) α, c) β, d) $m\beta_V$, and e) ν. $N = 1000$ parameters sets were used to generate each plot. The Pearson correlation coefficients are $-0.52, 0.22, 0.14, 0.27$ and -0.41 respectively.

Figure 4. Sensitivity analysis results for model (2.2) using $R_0 = R_{0_{VH}} + R_{0_{WMV}} + R_{0_{MWV}} + R_{0_{MW}}$ as the response function. The latin hypercube sampling (LHS) was done from $m\beta_V \sim Unif(0.1, 0.4)$, $\beta \sim Unif(0.05, 0.25)$, $\alpha \sim Unif(0.5, 1.1)$, $\gamma \sim Unif(0.08, 0.38)$, and $\nu \sim Unif(0.07, 0.43)$, where $Unif$ means an uniform probability distribution.

Figure 5. Sensitivity analysis results for model (2.2) using $R_0 = R_{0_{VH}} + R_{0_{MWV}}$ as the response function. In this case it is assumed that there is no sexual transmission from women to men. The latin hypercube sampling (LHS) was done from $m\beta_V \sim Unif(0.1, 0.4)$, $\beta \sim Unif(0.2, 0.7)$, $\alpha \sim Unif(0.5, 1.1)$, $\gamma \sim Unif(0.08, 0.38)$, and $\nu \sim Unif(0.07, 0.43)$, where $Unif$ means an uniform probability distribution.

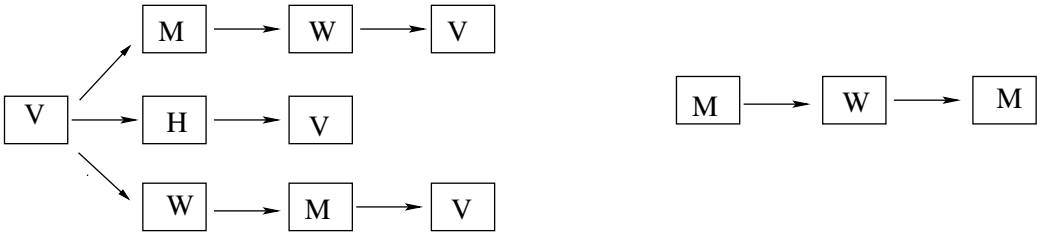

Figure 1

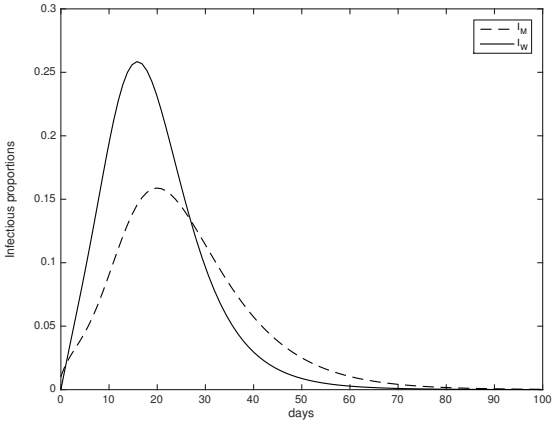

Figure 2a

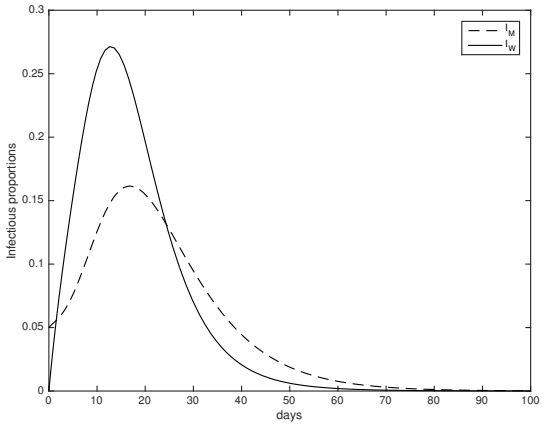

Figure 2b

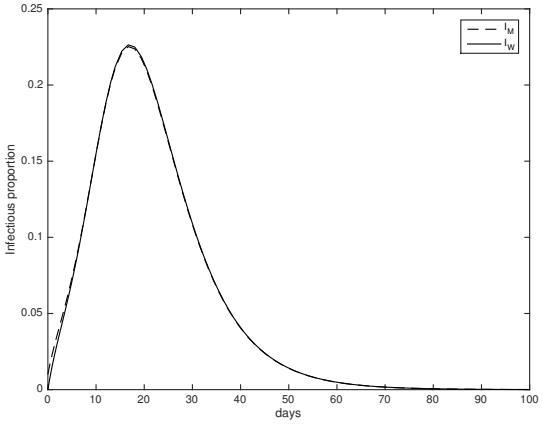
0.25
0.2
0.15
0.1
0.05
0
Infectious proportion
0
10
20
30
40
50
60
70
80
90
100
days
I_M
I_W

Figure 2c

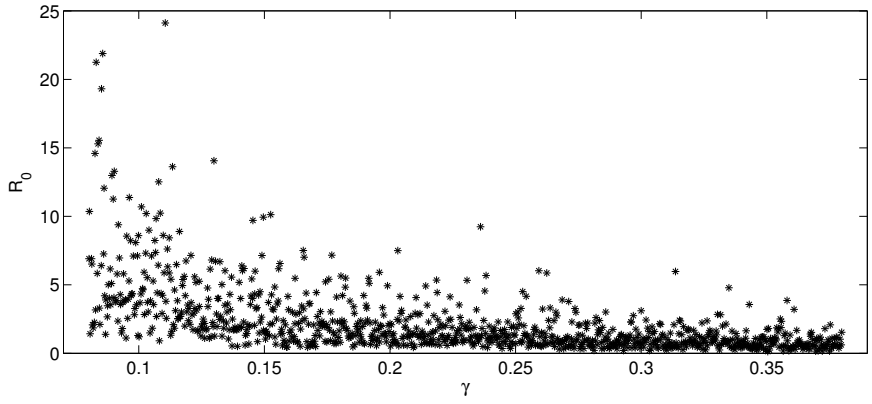

Figure 3a

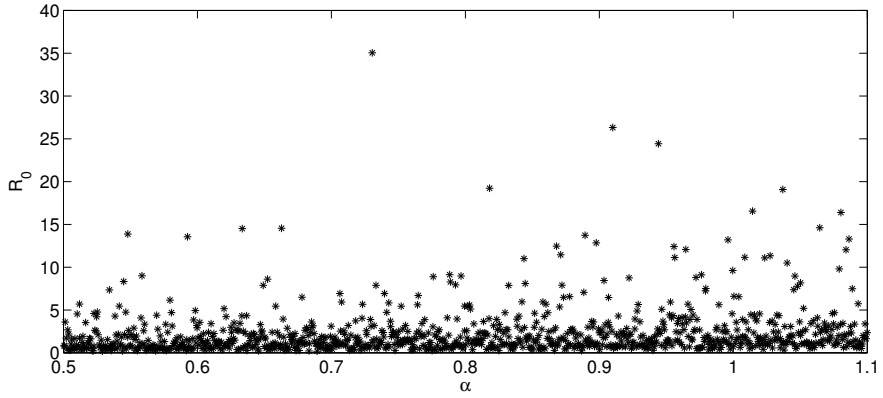

Figure 3b

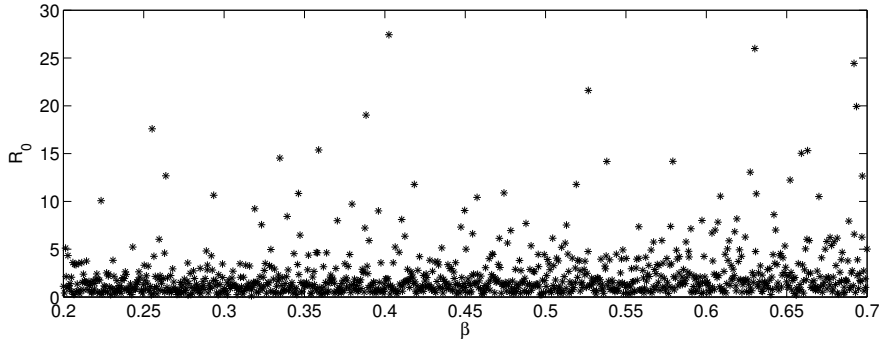

Figure 3c

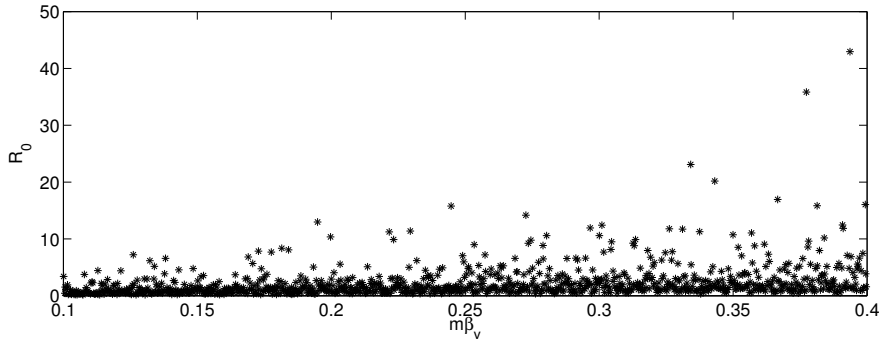

Figure 3d

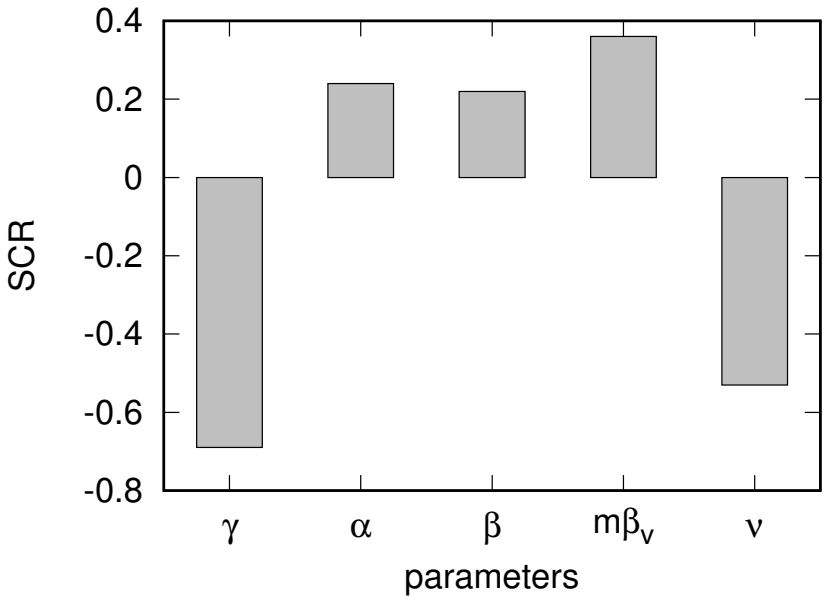

Figure 4

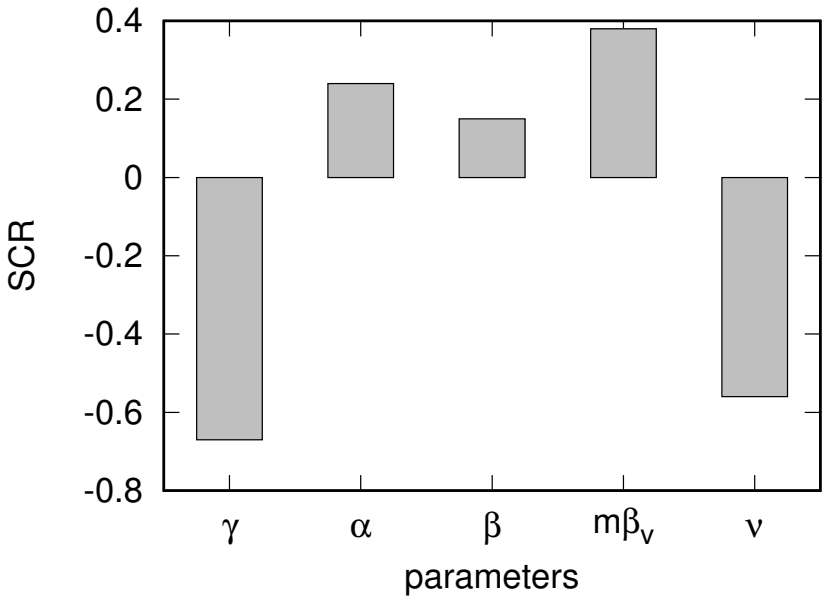

Figure 5