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A Simulation Model for the Risk of Fetal Exposure Originated by the Zika Virus (VIZK)

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Abstract

It is set and analyzed a simulation model based on non-linear ordinary differential equations to interpret the dynamics of the microcephaly incidence caused by the Zika virus in a risk group of pregnant women. This one is induced by a population of men in a reproductive age. Also, some parameters of the model were estimated for an average temperature of 23˚C and by using the adjusted functions from references [1] [2]. All system simulations were done with the Maple software and parameters values obtained from several sources (estimated, hypothetic, and form literature). It has been found that the application of contraceptive measures impacts the population of sexually active women. As result, the exposure to congenital abnormalities increases, particularly, microcephaly.

Keywords

Model, Microcephaly, Zika Virus, Basic Reproduction Number, Risk Group, Incidence

1. Introduction

The Zika virus (ZIKV) is transmitted by mosquitoes of the *Flaviviridae* family of the *Flavivirus* gender. These ones are pretty close to the ones that transmit encephalitis, yellow fever, dengue, and virus del Nilo. It was isolated in 1947 from blood of the Rhesus monkey (Macacamulatta) that it was feverish during a study of the yellow fever at the Zika forest in Uganda [3]. Later on, the virus was isolated from an *Aedes africanus* mosquitoes group in 1948 at the same region of the Zika jungle [4]. The natural cycle of

ZIKV implies mosquitoes principally from the genders: *Aedes, Aedes furcifer, Aedes taylori, Aedes luteocephalus,* and *Aedes aegypti.* The last one is considered the main vector for virus transmission [5]-[7]. ZIKV is transmitted by the infected mosquitoes bite maintaining a zoonotic cycle (disease transmission from animals to humans). In this transmission cycle, humans serve as accidental hosts, however, in areas without primates the humans take the role of primary amplifiers [8]. It is suspected that ZIKV uses the primates as principal agents for their reproduction and transmission. Antibodies were detected in other animal species, including: buffaloes, elephants, goats, and hippopotamus among others. This fact suggests the possibility of multi-species transmission. Furthermore, there exists evidence of sexual transmission in humans [5] [9].

ZIKV infection variates in humans, the most common symptoms are: flu, headache, anorexia, eye ache, general discomfort, myalgia, arthralgia, asthenia, edema and diarrhea, that is to say, the symptomatology is unspecific. All this clinical picture may be confused with the other existent diseases, particularly with the most frequent ones, Dengue and Chikungunya [5] [6] [10] [12]. Even some people could be asymptomatic to this disease.

The ZIKV introduces questions about the possible role of the infection with the microcephaly; actually there are only ecological evidences. Microcephaly is defined as the presence of a cranial perimeter less than a couple of standard deviations for the average age, sex, and gestational age [14]. Investigations suggest an increase in the microcephaly in some states where ZIKV was detected, indicating a possible association between events [13]. The maternal-fetal transmission has been demonstrated in several infections as, Dengue and Nilo fever. Also, this disease may cause premature delivery, birth defects and microcephaly [11].

In the last years it has been observed an increase in the infectious diseases, this is due to the known symptoms as well as the reemerging ones that have appeared with a high incidence because of social, economic and health factors. Such is the case of ZIKV, an endemic virus in some countries of Africa and Asia that has been expanded to other zones [8]. From these facts emerges the importance of mathematical models on the risk of exposition to the ZIKV.

Recently, some reports treating this issue have appeared. Daozhou *et al.* (2016), have analyzed a mathematical model for the prevention and control of Zika, including the vectorial and sexual transmission, with data of epidemic outbreaks of Brazil, Colombia and the Salvador. From those studies they conclude that the R_0 is more sensitive to the bite rate and the natural death rate of the mosquitoes as well as the sexual transmission increases the risk of infection, the epidemic size and extends the outbreak [15]. Nishiura *et al.* (2016), have estimated the R_0 of the ZIKV infection, as an indicator of potential transmission, using data from the South Pacific region [16]. On the other hand, Muñoz *et al.* (2016) have formulated and analyzed a mathematical model to treat the risk of microcephaly incidence caused by the ZIKV in a pregnant women group [17].

The model proposed in this paper helps to provide information that may help to elaborate effective control strategies, potential scenarios and transmission mechanisms

of the virus.

2. The Model

It is proposed a simulation model based in non-linear ordinary differential equations to describe the dynamics of pregnant women that are susceptible to get infected by ZIKV and may present fetal microcephaly induced by this virus. The variables of the model are described in Table 1 and the parameters in Table 2.

Table 1. Variables and initial populations of the model.

Variable	Description	Initial populations
x_1	The susceptible and sexually active women's population	$x_1(0) = 400000$
x_2	The susceptible pregnant women's population	$x_2(0) = 10$
x_3	ZIKV positive pregnant women's population	$x_3(0) = 0$
x_4	Infected pregnant women with no development of microcephaly	$x_4(0) = 0$
x_5	Infected women's population	$x_5(0) = 0$
y_1	Susceptible and sexually active men's population	$y_1(0) = 600000$
y_2	ZIKV positive men's population	$y_2(0) = 5$
z_1	The non-carrier *Aedes aegypti* mosquitoes population	$z_1(0) = 100000$
z_2	The virus-carrier *Aedes aegypti* mosquitoes population	$z_2(0) = 20$
N	Total population (men + women)	$N(0) = 1000010$
N_1	Total population of sexually active women	$N_1(0) = 400010$
N_2	Total population of sexually active men	$N_2(0) = 600005$
M	Total population of mosquitoes	$M(0) = 100020$

Table 2. Parameters of the simulation model.

Parameter	Description	Estimated/hypothetic value
Δ	The fraction of women that get into the sexually active population	30
Φ	Men's fraction that get into the sexually active population	20
μ	The natural mortality rate of persons	0.0003
g	Infected pregnant women's fraction that are not developing microcephaly	0.1
$1-g$	Infected pregnant women's fraction that develops microcephaly	0.9
θ	Developing rate of the infection in the pregnant women	0.7
β	Transmission probability to the susceptible women	0.7913
σ	Probability of pregnancy	0.6
α	The infected women recovery rate	0.01
h	Fraction of women that use contraceptive measures	0.3, 0.6, 0.8
δ	Transmission probability to the susceptible men	0.7913
ϕ_1, ϕ_2	Transmission probability to the non-carrier mosquitoes	0.6, 0.35
ϵ	Death rate of the mosquitoes	0.035

In the flux diagrams of the **Figures 1-3**, $\lambda_1(\cdot) = \sigma\left(\dfrac{y_1}{N_2} + \dfrac{y_2}{N_2}\right)$, $\lambda_2(\cdot) = \beta\dfrac{z_2}{M}$, $\lambda_3(\cdot) = \beta\dfrac{z_2}{M}$, $\lambda_4(\cdot) = \gamma\dfrac{z_2}{M}$

$\lambda_5(\cdot) = \phi_1\dfrac{x_3}{N_1} + \phi_2\dfrac{x_4}{N_1} + \phi_1\dfrac{x_5}{N_1} + \phi_1\dfrac{y_2}{N_2}$.

The dynamic system in the sexually active women that get pregnant, susceptible to ZIKV as well as exposed to microcephaly are (according to **Figure 1**):
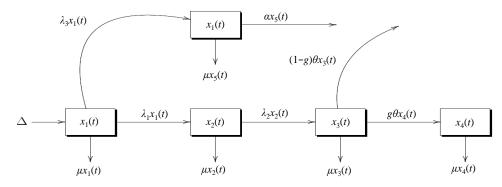
$$\frac{\mathrm{d}x_1(t)}{\mathrm{d}t} = \Delta - \sigma\frac{y_1(t)}{N_2(t)}(1-h)x_1(t) - \sigma\frac{y_2(t)}{N_2(t)}(1-h)x_1(t) - \beta\frac{z_2(t)}{M(t)}x_1(t) - \mu x_1(t) \quad (1)$$
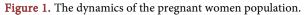
$$\frac{\mathrm{d}x_2(t)}{\mathrm{d}t} = \sigma\frac{y_1(t)}{N_2(t)}(1-h)x_1(t) + \sigma\frac{y_2(t)}{N_2(t)}(1-h)x_1(t) - \beta\frac{z_2(t)}{M(t)}x_2(t) - \mu x_2(t) \quad (2)$$

$$\frac{\mathrm{d}x_3(t)}{\mathrm{d}t} = \beta\frac{z_2(t)}{M(t)}x_2(t) - (\theta + \mu)x_3(t) \quad (3)$$

$$\frac{\mathrm{d}x_4(t)}{\mathrm{d}t} = g\theta x_3(t) - \mu x_4(t) \quad (4)$$

$$\frac{\mathrm{d}x_5(t)}{\mathrm{d}t} = \beta\frac{z_2(t)}{M(t)}x_1(t) - (\alpha + \mu)x_5(t) \quad (5)$$

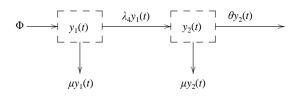**Figure 1.** The dynamics of the pregnant women population.

Figure 2. The dynamics of the sexually active men's population.
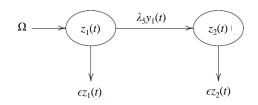

Figure 3. Dynamics of the *Aedes aegypti* mosquitoes population.

In this system $\dfrac{\mathrm{d}x_i(t)}{\mathrm{d}t}; i = 1, \cdots, 5$ indicates the variation of each women population in time, these variations are defined as inflows minus outflows. The equations corresponding to the dynamics of the sexually active men that get infected by the virus-carrier mosquito bite are (according Figure 2):

$$\frac{\mathrm{d}y_1(t)}{\mathrm{d}t} = \Phi - \beta \frac{z_2(t)}{M(t)} y_1(t) - \mu y_1(t) \tag{6}$$

$$\frac{\mathrm{d}y_2(t)}{\mathrm{d}t} = \beta \frac{z_2(t)}{M(t)} y_1(t) - (\theta + \mu) y_2(t) \tag{7}$$

From these equations (6) and (7) $\dfrac{\mathrm{d}y_i(t)}{\mathrm{d}t}; i = 1, 2$, are the variations of each men's population in time, and are the result of inflows minus outflows. Finally, the equations belonging to the infectious process in the non-carrier and virus-carrier mosquitoes are (as shown in Figure 3):

$$\frac{\mathrm{d}z_1(t)}{\mathrm{d}t} = \Omega - \phi_1 \frac{x_3(t)}{N_1(t)} z_1(t) - \phi_2 \frac{x_4(t)}{N_1(t)} z_1(t) - \phi_1 \frac{x_5(t)}{N_1(t)} z_1(t) - \phi_1 \frac{y_2(t)}{N_2(t)} z_1(t) - \epsilon z_1(t) \tag{8}$$

$$\frac{\mathrm{d}z_2(t)}{\mathrm{d}t} = \phi_1 \frac{x_3(t)}{N_1(t)} z_1(t) + \phi_2 \frac{x_4(t)}{N_1(t)} z_1(t) + \phi_1 \frac{x_5(t)}{N_1(t)} z_1(t) + \phi_1 \frac{y_2(t)}{N_2(t)} z_1(t) - \epsilon z_2(t) \tag{9}$$

In a similar way, Equations (8) and (9) are result of inflows and outflows.

The variation in time of each total population $N_1(t), N_2(t), N(t)$ and $M(t)$ is defined by the following differential equations:

$$N_1(t) = \sum_{i=1}^{5} x_i(t)$$
$$\frac{\mathrm{d}N_1(t)}{\mathrm{d}t} = \sum_{i=1}^{5} \frac{\mathrm{d}x_i(t)}{\mathrm{d}t} \tag{10}$$

As well,

$$N_2(t) = \sum_{j=1}^{2} y_j(t)$$
$$\frac{\mathrm{d}N_2(t)}{\mathrm{d}t} = \sum_{j=1}^{2} \frac{\mathrm{d}y_j(t)}{\mathrm{d}t} \tag{11}$$

Then, $N(t) = N_1(t) + N_2(t)$.

Varying with respect to *t*, it is obtained

$$\frac{\mathrm{d}N(t)}{\mathrm{d}t} = \sum_{i=1}^{5} \frac{\mathrm{d}x_i(t)}{\mathrm{d}t} + \sum_{j=1}^{2} \frac{\mathrm{d}y_j(t)}{\mathrm{d}t} \tag{12}$$

In the case of mosquitoes,

$$M(t) = \sum_{k=1}^{2} z_k(t)$$

Varying in function of *t*,

$$\frac{\mathrm{d}M(t)}{\mathrm{d}t} = \sum_{k=1}^{2} \frac{\mathrm{d}z_k(t)}{\mathrm{d}t} \tag{13}$$

From the dynamic systems, replacing the equations (1)-(7) in (10)-(13), it is obtained the dynamic system of the populations,

$$\frac{\mathrm{d}N_1(t)}{\mathrm{d}t} = \Delta - \mu N_1(t) - \theta x_3(t) - \alpha x_5(t) + g\theta x_3(t)$$

$$\frac{\mathrm{d}N_2(t)}{\mathrm{d}t} = \phi - \mu N_2(t) - \theta y_2(t)$$

$$\frac{\mathrm{d}N(t)}{\mathrm{d}t} = \Delta + \phi - \mu N(t) - \theta x_3(t) - \alpha x_5(t) - \theta y_2(t) + g\theta x_3(t)$$

$$\frac{\mathrm{d}M(t)}{\mathrm{d}t} = \Omega - \epsilon M(t)$$

3. Simulations and Results

The dynamic systems (1)-(5), (6)-(9) were simulated using the Maple software, with the values of Table 1 and Table 2.

In Figure 4 it is indicated that with an 80% of women under contraceptive protection, the populations of susceptible pregnant women, the infected ones and men infected with ZIKV tend to stabilize in an average time of 40 days. These populations have a maximum point in an average of 10 days and having a lower number of infections through time. Moreover, the infected pregnant women with no microcephaly present a significant increase and tend to rise slowly through the time. This can be explained through a recent report by Cauchemez *et al.* (2016) [18] where they have estimated that the risk of microcephaly increase approximately 1\% when the pregnant women are infected by ZIKV in the first trimester. According to this fact, it is possible to corroborate the increase of infected women that do not develop microcephaly, associating the ZIKV with a low fetal risk. Figure 5 depicts different levels of h (women's
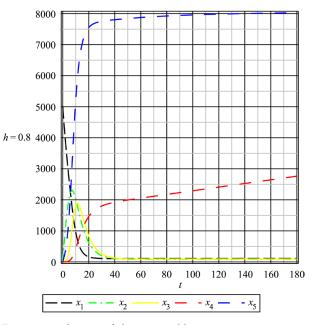

Figure 4. Behavior of the susceptible pregnant women, infected pregnant women, infected women without microcephaly development, and ZIKV infected men.
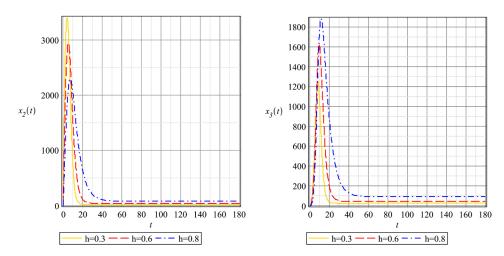
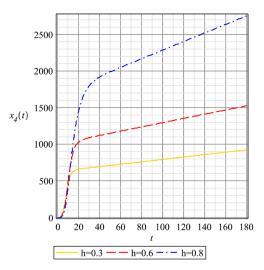**Figure 5.** The susceptible x₂ and infected x₃ pregnant women's behavior.

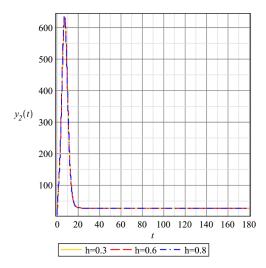**Figure 6.** Infected pregnant women that do not develop microcephaly.

Figure 7. ZIKV infected men's population.

fraction under contraceptive protection). The behavior of the susceptible pregnant women population rise showing a maximum point that is each time smaller as h increases, namely, with the contraceptive measures, the susceptible women population decreases. A similar behavior is presented by the infected pregnant women. Both populations tend to stabilize in an average of 35 days.

The pregnant women's population that develops microcephaly have a quick growth till almost 25 days, after that, the population tends to have a linear-like growth through time as h increases. However, this population has a maximum point when $h = 0.8$ see Figure 6.

Figure 7 shows that the infected men's population rises quickly in an average of 10 days, after 20 days decreases and tends to stabilize. This population does not change through time when the fraction of women that are under contraceptive treatments rises.

4. Conclusions

The behavior of the simulations shows that the susceptible pregnant women's population is sensitive to the women's fraction under birth control. This is an expected result if we account for an 80% of this fraction, were the susceptible women, infected pregnant women and women without microcephaly development population's decrease. With this model it is possible to make predictions and analysis to design more effective strategies in the future.

ZIKV has a little known natural history, then, it is primordial to generate new mathematical studies to gain a better understanding of this disease and propose effective control strategies.

The proposed model in this paper can be applied (with the respective adjustments) in the study of other viral infections transmitted by vectors that generate risk of other pathological complications.

Acknowledgements

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