The role of sexual transmission on the Zika outbreak.

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Abstract

Using an expression for the basic reproductive number R_0, and reports of Zika in Rio de Janeiro, Brazil during 2015, we explain how a relatively small amount of sexual transmission can increase the number of cases of this disease significantly. Our results, 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. 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.

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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 Basic reproductive number for Zika disease

Zika disease is mainly transmitted by the bites of mosquitoes *Aedes*. For this reason we consider in our study the humans, N, and mosquitoes, N_V, populations which are assumed constant. In order to consider sexual transmission we further 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. 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. Due to the vectorial and sexual component observed in Zika infection, we can assume that any of the following forms of transmission can occur: i) vector-human-vector, ii) vector-man-woman-vector. Therefore, the basic reproductive number, R_0, will be equal to the number of secondary infections due to the two kind of transmissions, that is,

$$R_0 = R_{0_{VHV}} + R_{0_{VWMV}} \tag{2.1}$$

where

$$R_{0_{VHV}} = \frac{bm\beta_V}{\nu}\frac{b\alpha}{(\gamma+\mu)} \tag{2.2}$$

$$R_{0_{VHMV}} = \frac{bm\beta_V q}{\nu}\frac{(1-q)\beta_W}{(\gamma+\mu)}\frac{b\alpha}{(\gamma+\mu)} \tag{2.3}$$

In the expressions above $bm\beta_V$ represents the average of infective humans produced by an infectious mosquito by day, and $1/\nu$ the mosquito life expectancy, therefore $\frac{bm\beta_V}{\nu}$ is the number of secondary cases produced by an infected mosquito during its infective period. On the other hand, $\frac{b\alpha}{(\gamma+\mu)}$ is the number of secondary infectives in the mosquito population due to an infected human during the infective period $1/(\gamma+\mu)$. The product of the two quantities, $R_{0_{VHV}}$, is the basic reproductive number due to Zika vector transmission.

Analogously, $\frac{bm\beta_V q}{\nu}$ is the product of the number of secondary infections due to a single mosquito in the man population, $\frac{(1-q)\beta_W}{(\gamma+\mu)}$ the number of secondary infections due to sexual transmission from a single man in the women population , and $\frac{b\alpha}{(\gamma+\mu)}$ the number of secondary infections produced by a single woman in a vector population. The product of the three quantities, $R_{0_{VHMV}}$, is the basic reproduction number associated to the joint effects of vectorial and sexual transmissions.

3 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 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 (2.1) to measure the importance of sexual transmission in Zika. For Zika reproductive number we take $R_0 = 2.33$, and for the vectorial transmission $R_{0_{VH}} = 1.25$ which correspond to the estimated basic reproductive number of the 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).

Substituting $R_{0_{VHV}} = 1.25$, in (2.1), we obtain $\beta_W \approx 0.55$, and $R_{0_{VMWV}} = 1.1$. Then, the sexual transmission is involved in $100\dfrac{R_{0_{VMWV}}}{R_0} = 47\%$ of the new infections.

4 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 give an expression for the basic reproductive number in which both kind of transmissions are coupled (See 2.1). 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 (2.1) 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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