Higher incidence of Zika in adult women than adult men in Rio de Janeiro suggests a significant contribution of sexual transmission from men to women

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SUMMARY

Objectives: The recent emergence of Zika in Brazil and its association with an increased rate of congenital malformations has raised concerns over its impact on the birth rate in the country. Using data on the incidence of Zika in 2015–2016 and dengue in 2013 and 2015–2016 for the city of Rio de Janeiro (population 6.4 million), a massive increase of Zika in women compared to men was documented.
Methods: The age-adjusted incidence was compared between men and women. A negative binomial Poisson generalized linear model was fitted to the Zika incidence data to determine the significance of sexual transmission statistically.
Results: Even after correcting for the bias due to the systematic testing of pregnant women for Zika, there were found to be 90% more registered cases per 100 000 women than men in the sexually active age group (15–65 years); this was not the case for age groups <15 years and >65 years. Assuming that infected men transmit the disease to women in their semen, but that the converse is not true, some extra incidence in women is to be expected. An alternate hypothesis would be that women visit doctors more often than men. To test this, the incidence of dengue fever was compared in men and women in 2015 and in 2013 (before Zika reached Rio de Janeiro): in both years, women were 30% more likely to be reported with dengue.
Conclusion: Women in the sexually active age group are far more likely to get Zika than men (+90% increase); sexual transmission is the most probable cause. Women in the 15–65 years age group are also 30% more likely to be reported with dengue than men, which is probably due to women being more careful with their health.
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1. Introduction

Viral diseases transmitted by *Aedes aegypti* mosquitoes, such as dengue, yellow fever, chikungunya, and Zika, have traditionally been restricted to the tropical regions of the world, given the intolerance of the vectors to colder climates.[1] In these regions transmission tends to be modulated by temperature, slowing down significantly when temperatures drop below 20 °C. The trend in global warming has long been argued to be a threat to public health, as this will extend the reach of tropical diseases.[1–3] Preparedness for these diseases is the order of the day for the health agencies of countries with a temperate climate.

The emergence Zika as a global pandemic threat is changing the traditional risk scenarios. The Zika virus has the ability to infect other species of mosquitoes,[4,5] thereby potentially extending its reach. *Aedes albopictus*, for instance, is well established in

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temperate climates. Moreover, the Zika virus can also be transmitted directly from human to human.[6] The sexual route seems to be the most common alternate form of transmission, but the virus is also present in other bodily fluids such as saliva and urine.[7–9]

The recent arrival of Zika in Brazil in 2014, and the speed with which it spread throughout the country and into neighboring countries in just a few months, seems to indicate alternate forms of transmission.

In this study, the age-adjusted incidence of Zika compared to dengue in the city of Rio de Janeiro was analyzed and the relative importance of the sexual route of transmission to the overall incidence of Zika was estimated. By considering this additional and asymmetric route of transmission, it was expected that a higher incidence of Zika would be seen in women in the sexually active age group.

2. Methods

The data used in this analysis were obtained from the Rio de Janeiro health secretariat, and consist of every notified case of Zika and dengue for the years 2013 (dengue only), 2015 (Zika and dengue), and 2016 (Zika and dengue, up to April). Each record includes the date of notification, International Classification of Diseases tenth revision (ICD-10) code, age in years, sex, and gestational status.

The officially estimated population of Rio de Janeiro for 2015, based on the 2010 census, was also used (6.4 million people: 3 million men, 3.4 million women; Figure 1). All age-adjusted incidences used in this study were calculated using this population as standard.

The cases were aggregated to the same age classes, as shown in the city's age pyramid (Figure 1). The classes are 5 years wide and incidence values are presented as the number of cases per 100 000 inhabitants.

The incidence of Zika in women was calculated with and without pregnant women, to avoid biases. The city health services have systematically tested pregnant women displaying a skin rash, due to the high risk of babies developing neurological complications caused by intrauterine Zika virus infection.

To check the statistical significance of the increase in incidence observed in women, a Poisson generalized linear model (GLM) was first fitted to the number of cases of Zika and dengue (2013) aggregated by age class. Since these initial models displayed significant over-dispersion, a negative binomial GLM was fitted to the same data. Let Y be the number of cases; the final model is then:

$$\begin{aligned} Y_i &\sim \mathrm{NegBin}(\mathrm{p_i}, \mathrm{r}) \\ p_i &= \mathrm{r}/(\mathrm{r}+\mu_i) \\ \log(\mu_i) &= \beta_0 + \beta_1\,\mathrm{Sex[i]} + \beta_2\mathrm{Active[i]} + \beta_3\mathrm{Pregnant[i]} \\ &\quad + \beta_4\mathrm{Sex[i]} \times \mathrm{Active[i]} \end{aligned} \tag{1}$$

The 'Active' dummy variable takes the value 1 for age classes above 15 years and less than 65 years of age, and 0 otherwise.

3. Results

During the recent Zika epidemic in Rio de Janeiro, which started in late 2015, a total of 29 301 cases, 20 315 women and 8986 men, were notified as suspected Zika cases based on clinical assessment. During the same period, 102 754 total cases of dengue were notified, with 46 305 being men and 56 449 being women. The incidence by age group for Zika in the period January 2015 to April 2016 is shown in Figure 2. After removing the pregnant women from the dataset, the incidences shown in Figure 3 were obtained. The age distribution of pregnant women removed from the sample is shown in the **Supplementary Material** (Figure S1).

For comparison, Figure 4 shows the age distributed incidence of dengue in the 2015–2016 period. Note that the extra incidence in women is far less pronounced. The dengue incidence in 2013 was

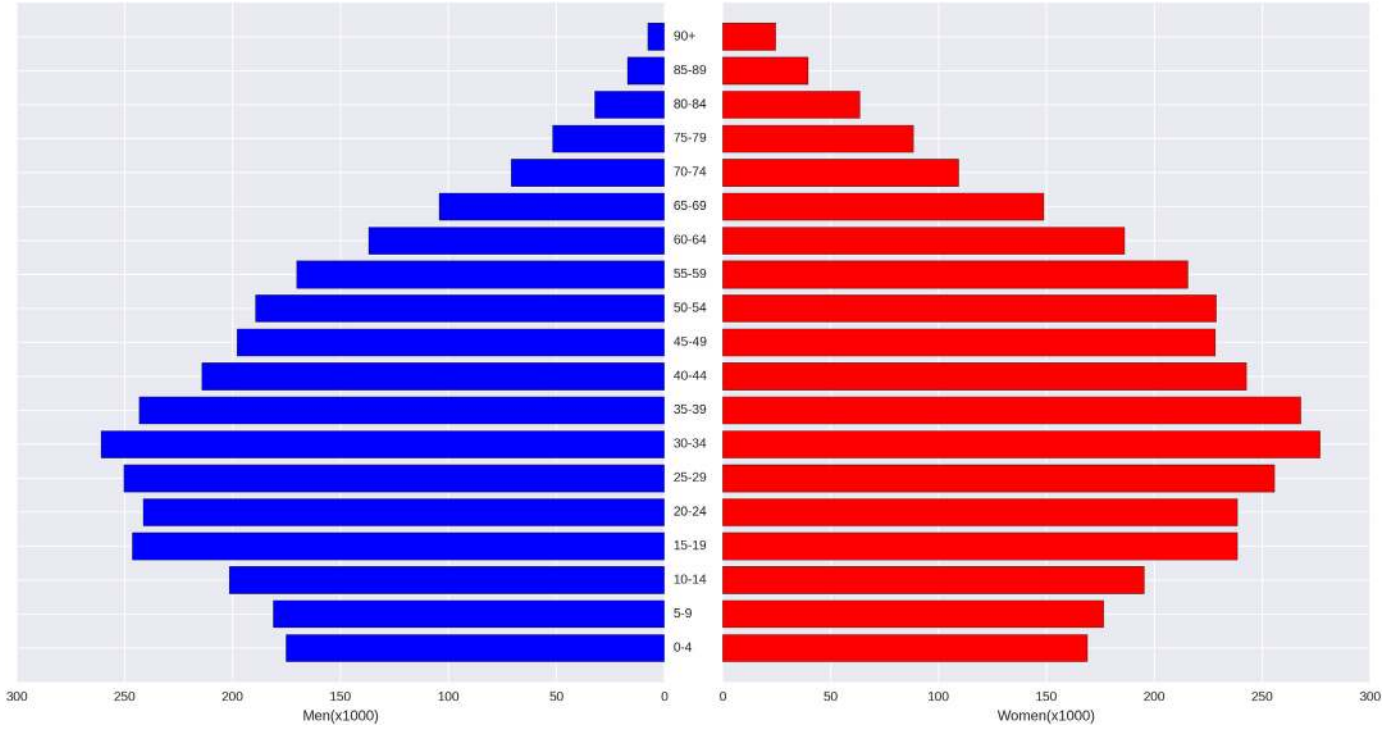

Figure 1. Age pyramid for the city of Rio de Janeiro. These numbers are official projections based on the census of 2010. The male population is represented in blue, and the female population in red.

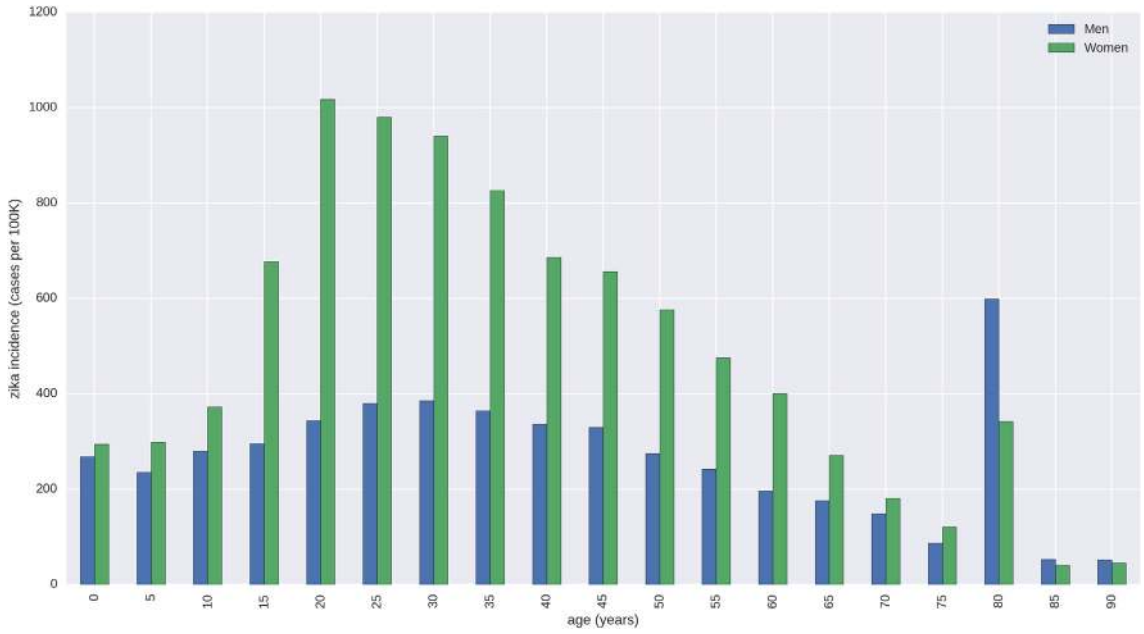

Figure 2. Incidence of Zika in men and women by age group. The incidence is in units of cases per hundred thousand.

also investigated (Figure 5), to make sure that the pattern was not specific to the 2015 dengue epidemic.

The combined incidence in the sexually active age group, from 15 years to 65 years of age, is shown in Table 1, along with the ratio of the incidence in women to the incidence in men in the same age group.

The regression results indicated a significantly higher Zika incidence for sexually active women (1.7767, 95% confidence interval (CI) 0.500 to 3.053, $p = 0.006$). Sex alone was not a significant predictor of Zika incidence (−0.2120, 95% CI −1.207 to 0.783, $p = 0.676$). For dengue, being in the sexually active age group and being a woman was not a significant risk factor (0.7196, 95% CI −0.321 to 1.761, $p = 0.138$). Again, sex alone did not prove to be a significant risk factor for dengue.

4. Discussion

If Zika virus is being transmitted both through vectors and sexually in Brazil and other American countries in this recent epidemic, it is important to estimate the relative importance of each route. According to the available evidence, the principal way to transmit Zika virus sexually is through exposure to infected seminal fluid. Female to male sexual transmission of Zika virus has been reported,[10] but no information is available about how likely such a transmission is. Assuming heterosexual intercourse to be far more prevalent than homosexual sex between men, a surplus of Zika cases in women due to sexual transmission can be expected. Moreover active viruses have been isolated from semen more than 3 weeks after the onset of symptoms,[9] which greatly increases the

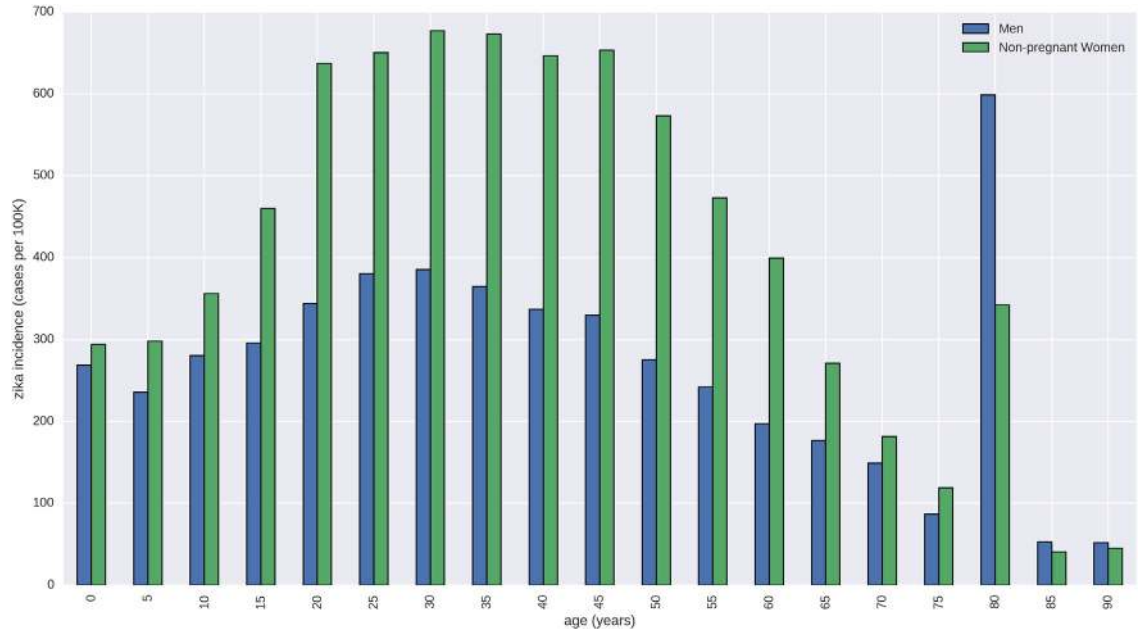

Figure 3. Incidence of Zika in men and women by age group, excluding pregnant women. Pregnant women are excluded because extra efforts were made by the health services to identify all possible Zika cases in this group due to their babies being at high risk of developing neurological complications.

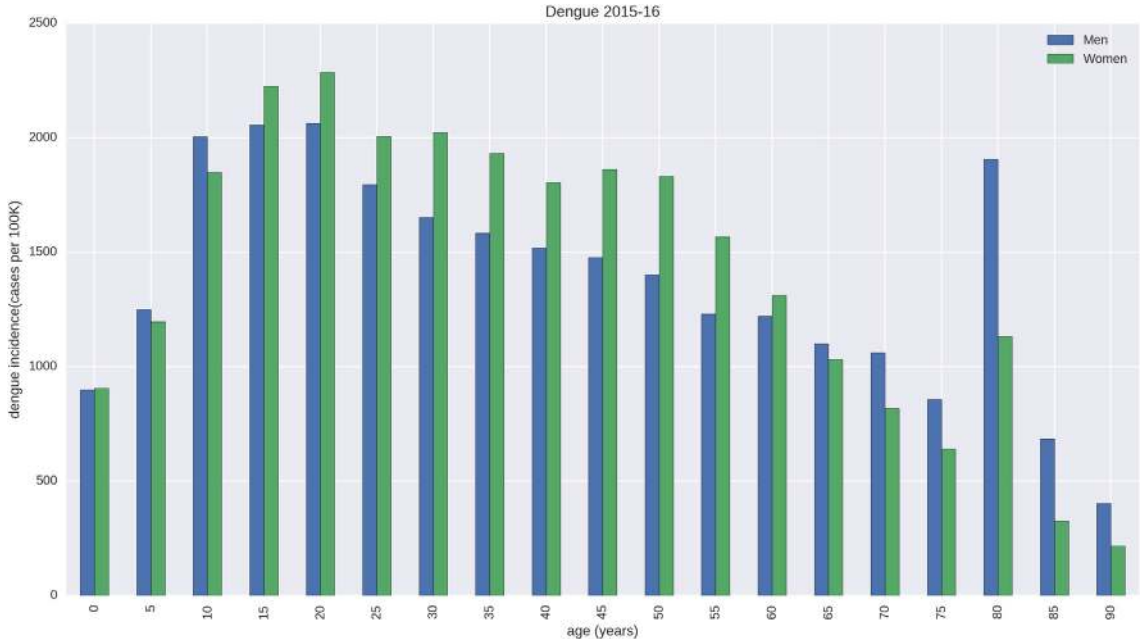

Figure 4. Age-adjusted incidence of dengue in men and women for the 2015–2016 period.

transmission period for susceptible females. On the other hand, without significant sexual transmission and in the absence of an observational bias favoring women, an equal incidence across age groups would be expected.

What was observed, however, was a markedly higher incidence in women, as shown in Figure 2. As mentioned in the Methods section, there is at least one observational bias towards reporting women cases, due to concerns about microcephaly and the risks to babies. In order to minimize this, pregnant women were removed from the sample (Figure 3). What is seen is that the extra incidence remains, but is relatively smaller. However, this extra incidence is more pronounced in the reproductive age group; these women are more likely to visit a physician regularly and thus Zika will be detected if they are infected.

To confirm the hypothesis that women are more likely to be diagnosed with exanthematic fever syndromes during their reproductive years, dengue incidence was assessed by age group (Figures 4 and 5). During the 2015–2016 period, it is possible that some Zika cases may have been misdiagnosed as dengue, thus 'contaminating' the dengue incidence with sexual transmission. Thus the incidence of dengue in 2013 was also assessed, when Zika was unlikely to be circulating in Rio de Janeiro. It can also not be discounted that there is evidence that pregnant women are more likely to develop severe dengue.[11] Other factors that could explain the higher incidence in women are (1) women are more likely to stay at home and be more exposed to the vector, and (2) women of a fertile age are more predisposed to see a doctor as soon as they develop symptoms for fear of complications in an as yet

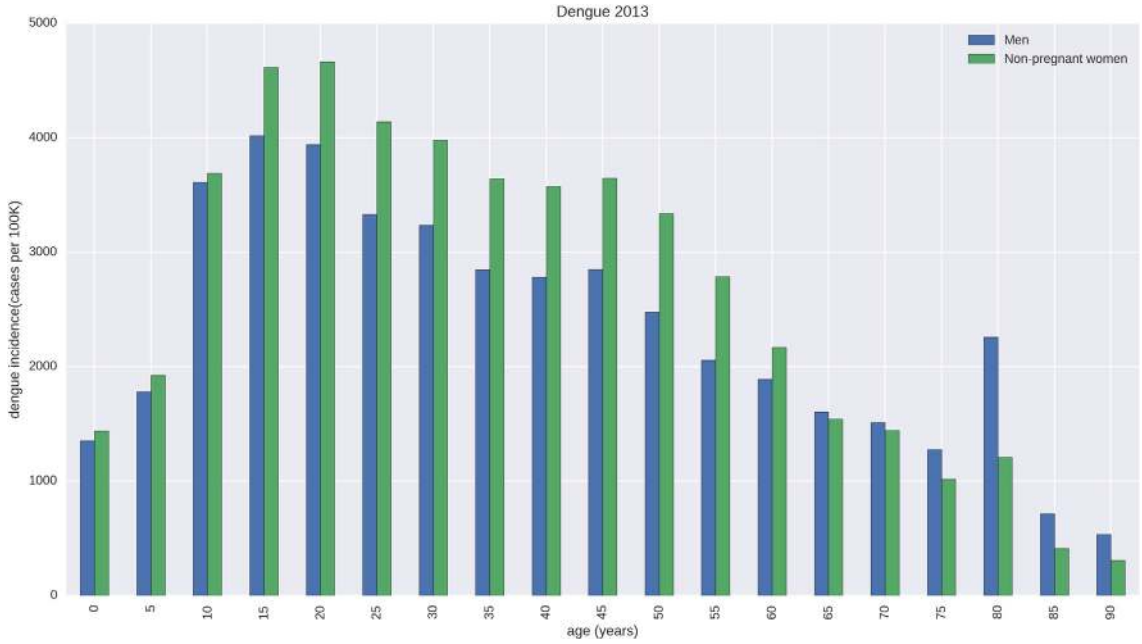

Figure 5. Age-adjusted incidence of dengue in men and women for the year 2013. Notice the pattern is similar to that observed in 2015–2016.

Table 1
Aggregated incidence in men and women in the sexually active age group of 15–65 years. The last column shows the ratio of the incidence in women to the incidence in men.

Disease	Incidence in women	Incidence in men	Ratio, women/men
Zika	5382.58	2854.85	1.88
Dengue 2015–16	16 628.04	13 941.05	1.19
Dengue 2013	32 201.37	25 410.52	1.27

undetected pregnancy. The authors believe that the 2013 dengue data serve as a good control for the differential exposure of women to the vector. As for the behavioral changes associated with the fear of having a baby with microcephaly, the 2015–2016 data on dengue also represent a good control for this, due to the similarity of the symptoms of dengue and Zika.

As can be seen in Table 1, the extra detection in women due to the behavior of seeing a doctor regularly could account for at most a 30% higher incidence than in men, if all the extra incidence of dengue in women is attributed to this factor. However, for Zika, even discounting pregnant women, an incidence that is almost 90% higher than for men is observed. This extra incidence can be attributed to the extra cases caused by sexual transmission.

Through sexual transmission, Zika is no longer constrained to tropical and subtropical regions and will be able to reach northern Europe, the northern USA and Canada, and northern Australia, as well as Japan and Korea. Although it would be harder for the disease to invade these higher latitudes, the incidences are likely to be higher as men who catch Zika abroad can transmit locally for weeks or even months.

The immediate consequence of this higher incidence of Zika in women in the reproductive age group is a much higher expected number of neurologically compromised babies than if the disease was only transmitted through vectors. Going further, women living in Zika-infested areas will think twice about falling pregnant, at least those with access to birth control. This could well lead to a drop in the birth rate, particularly in the middle classes.

As the Aedes mosquito is known to be present in the southern states of the USA around the Gulf of Mexico,[3] in southern Europe,[2] and in northern Australia, an outbreak could start because of a returning traveler, especially if sexual transmission propagates it as well. Health authorities in developed countries are already warning travelers visiting Zika-infected areas to consider delaying pregnancies.[12,13] What would happen to the birth rate in these countries if Zika became endemic? A drop in births in Europe could have serious economic consequences.[14]

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.ijid.2016.08.023.

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