Zika in Rio de Janeiro: Assessment of basic reproductive number and its comparison with dengue

Leonardo S Bastos [1] Daniel AM Villela [1] Luiz Max de Carvalho [1,2]
Oswaldo G Cruz [1] Marcelo FC Gomes [1] Betina Durovni [3]
Maria Cristina Lemos [3] Valeria Saraceni [3] Flavio C Coelho [4]
Claudia T Codeço [1]

Abstract

Zika virus infection was declared a public health emergency of international concern in February 2016 in response to the outbreak in Brazil and its suspected link with congenital anomalies. In this study we use early notification data and disease natural history parameters to estimate the basic reproductive number $\Re_0$. Our estimates of the basic reproductive number for Zika in Rio de Janeiro ($\Re_0 = 3.9$, 95% CI: 3.1 – 5.3) were higher than those obtained for dengue using data from two early epidemics in the city (year 2002: 2.5 [2.1 – 3.1]; year 2012: 1.5 [1.4 – 1.8]). Given the role of *Aedes aegypti* as an arbovirus vector, we also assessed the $\Re_0$ of Zika given entomological and epidemiological factors already reported for dengue transmission. Surprisingly, we find that Zika's $\Re_0$ under a vectorial-only transmission model is lower than the basic reproductive number for dengue. These results suggest that either our current knowledge regarding the vectorial capacity of *Aedes aegypti* as a vector for Zika is incomplete or other modes of transmission are important players in sustaining this epidemic.

[1] Programa de Computação Científica, Fundação Oswaldo Cruz, Rio de Janeiro - RJ, Brazil.

Introduction

In February 2016, Zika virus infection was declared a public health emergency of international concern [14] in response to the outbreak in Brazil and its suspected link with congenital anomalies [4, 3, 22]. This came as a surprise, as since its first isolation in 1947 in the Zika forest in Uganda [9], the virus had remained mostly unnoticed, due to its status as a benign disease. Isolated outbreaks have been reported before in Africa and Asia/Oceania but all of them involved small populations [8]. It was in Brazil that the Zika virus (ZIKV) found a large pool of susceptible individuals, and the range of possible clinical outcomes became apparent, including birth defects, neurological and auto-immune disorders [3]. The epicentre of the American epidemic was in North-East Brazil, where ZIKV was introduced in mid 2014, according to outbreak reports, although a molecular study [10] suggested introduction took place an year earlier. Currently, all 26 Brazilian states have confirmed local transmission of ZIKV, with an estimate of 440,000 to 1,300,000 infections [16]. In the Americas, 34 countries and territories had already confirmed autochthonous ZIKV cases by April 2016.

Transmission of ZIKV between humans is mostly attributed to mosquitoes of the genus *Aedes* (*Stegomyia*), although direct evidence is still scarce. Only two out of eleven reported outbreaks found infected mosquitoes: *Aedes albopictus* in Gabon and *Aedes hensilii* in Yap Island [8]. In the current Zika epidemic in the Americas, *Aedes aegypti* is suspected to be the primary vector, based on its widespread distribution and role as dengue vector. However, a recent laboratory study comparing susceptibility to ZIKV of seven *Aedes aegypti* and *Aedes albopictus* strains suggests that, although susceptible, these lineages are comparatively weakly competent vectors for ZIKV [7].Other modes of transmission have been reported, such as vertical and sexual transmission in humans, and the potential role of other mosquitoes have been raised. Nonetheless, their relevance for the overall transmission dynamics of Zika remains to be determined [29]. A recent study has also found ZIKV in neotropical primates in Brazil [11], but the role of natural reservoirs is still not clear.

[2] Institute of Evolutionary Biology, University of Edinburgh, UK.

[3] Secretaria Municipal de Saúde do Rio de Janeiro, Rio de Janeiro - RJ, Brazil.

[4] Escola de Matemática Aplicada, Fundação Getulio Vargas (FGV), Rio de Janeiro - RJ, Brazil.

At the early stages of an epidemic, estimation of the basic reproductive number, $\Re_0$, is of interest as it provides a measurement of the transmission potential of the virus. Such measurement is important to support preparedness plans and assess risk of epidemic emergence into areas without the epidemic. Moreover, estimation of $\Re_0$ can also contribute to the understanding of the epidemiology of this disease and how it changes geographically and temporally. Some estimates of $\Re_0$ for Zika have been reported recently in the literature for Yap Island, Federal State of Micronesia, and French Polynesia [26, 17], but in both localities the sizes of human populations are small.

Here, we report estimates of $\Re_0$ in Rio de Janeiro, Brazil, a large urban centre. Among the most dengue affected cities in Brazil, Rio de Janeiro is a metropolis with 6.5 million inhabitants which was the port-of-entry in the country of three of four current circulating dengue viruses. Climatic and environmental conditions favour year-round transmission of dengue, with a well characterized seasonal profile. Rio de Janeiro city is also of international interest due to recent major sporting events, including 2014 FIFA World Cup and the upcoming 2016 Summer Olympic Games.

We estimate the basic reproductive number of Zika from notification cases in the city of Rio de Janeiro using the method proposed by Pinho *et al.* (2010) [30]. For comparison with dengue epidemics in the same area, we apply the same method to two dengue outbreaks occurring just after introduction of dengue serotypes 3 and 4 in the city [28, 27]. We calculated $\Re_0$ for 2002 and 2012 dengue epidemics from the number of notification cases reported just after the introduction of serotypes DENV-3 and DENV-4, respectively.

The second goal of this study was to check the hypothesis of *Aedes aegypti* transmission of ZIKV, considering its vectorial capacity as measured by Chouin-Carneiro *et al.* [7]. Massad *et al.* [20] assessed the risk of introduction of yellow fever in a dengue endemic area by assuming the same mode of transmission and the entomological parameters that describe arbovirus transmission. We employ the indirect approach taken by Massad *et al.* [20] combined with the model formulated by Pinho *et al.* [30] to estimate $\Re_0$ for dengue using the transmission efficiency measured by Chouin–Carneiro *et al.* [7].

Methods

Data

Infectious disease surveillance in Brazil is handled by the Brazilian Notifiable Diseases Information System (SINAN), where each suspected, and eventually confirmed, case of Zika infection is notified as ICD-10 diagnosis code A92.8 (other specified mosquito-borne viral fevers). Dengue surveillance in Brazil dates back to the 1990s, and suspected cases are notified in the SINAN as ICD-10 diagnosis code A90 (Dengue fever) or A91 (Dengue haemorrhagic fever). Dengue serotype DENV-3 was first observed in the state of Rio de Janeiro, in the neighbouring Nova Iguaçu city, in January 2001 [28], while the serotype DENV-4 was first observed in Rio de Janeiro state in Niterói city in March 2011 [27].

In order to calculate dengue's reproductive number, we assume the epidemics of 2002 and 2012 in the city of Rio de Janeiro were mainly caused by serotypes DENV-3 and DENV-4, respectively. These are taken to represent the introduction of new serotypes, for which the population had no previous immunity. This is important in order to make results comparable with Zika.

Case notification counts of dengue and Zika from the notification system are each aggregated to form their respective time series by epidemiological weeks, describing the outbreaks in the city of Rio de Janeiro. Both Zika and dengue notification data are stratified by ten health districts (HD), which are essentially health surveillance sub–areas in the city of Rio de Janeiro.

Estimation of the force of infection

In order to estimate the weekly force of infection of Zika, we adjusted a linear model of the logarithm of notification counts adjusted by time, given by the number of weeks of the early outbreak period. We take the 43th epidemic week of 2015 (from the 18th to the 24th of October 2015) as the starting week, after which notification of suspected cases of Zika

became mandatory in the city of Rio de Janeiro. In order to select the end of the early outbreak period we apply the time windows that fit this exponential model, i.e., over which the error is smaller according to the sum of residuals, given by standard deviation.

We also estimated the force of Zika infection for each one of the ten health districts (HD) of Rio de Janeiro, using a mixed linear model, where the number of reported cases in each HD is proportional to $exp\{\Lambda_{HD} \cdot t\}$, with $\Lambda_{HD} = \Lambda_0 + \lambda_{HD}$. Parameter Λ_0 is a baseline force of infection, and λ_{HD} is a zero-mean random effect by district. We use the same early outbreak period defined in the overall case in order to estimate the force of infection by health district.

Direct estimation of the basic reproductive number ($\Re_0$)

We use the $\Re_0$ formulation proposed by Pinho *et al.* [30] to model the dynamics of dengue fever in Salvador, Brazil, and apply it to assess Zika's basic reproductive number in the city of Rio de Janeiro. The model considers a vector-borne transmission, modelling for mosquito as a vector compartments of susceptible, exposed and infected mosquitoes, and for humans, susceptible, exposed, infected and recovered ones. Hence, the disease transmission involves a cycle of two infectious generations, mosquitoes and humans. The concept of basic reproductive number gives us the average number of secondary cases per generation after an initial infected individual.

This approach relies on the assumption that the number of cases in the early outbreak grows exponentially, hence proportional to $\exp\{\Lambda \cdot t\}$, where t is the time in weeks since the outbreak start and Λ is the force of infection. The basic reproductive number is estimated by the following equation:

$$\Re_0 = \sqrt{\left(1 + \frac{\Lambda}{\mu_m}\right)\left(1 + \frac{\Lambda}{\gamma}\right)\left(1 + \frac{\Lambda}{\tau_e^{-1} + \mu_m}\right)\left(1 + \frac{\Lambda}{\tau_i^{-1}}\right)}, \quad (1)$$

where γ is the human recovery rate, μ_m is the mosquito mortality rate, τ_i is the median intrinsic incubation period in humans, and τ_e is the median extrinsic incubation period in mosquitoes. In equation 1 we neglect adult mosquito control, c_m, as well as human mortality

rate, μ_h, which are present in the original formula in [30]. The former is taken to be zero since no structured intervention was taking place during the time window analysed. Regarding the latter, human mortality rate in Brazil is orders of magnitude lower than the intrinsic incubation period and human recovery rate, which are on the order of a few days. The life expectancy at birth in Brazil was of 75 years in 2014. Therefore, we can safely neglect the human mortality rate μ_h for our purposes of estimating $\Re_0$.

We compiled a range of values for the necessary parameters taken from previous studies in Table 1. We also calculate $\Re_0$ according to different methods, where the equations and results are available in the supplementary material.

Indirect basic reproductive number of Zika

Massad *et al.* [20] derived a mathematical method for estimating the reproductive number of yellow fever indirectly using an estimation of dengue's basic reproductive number obtained from the exponential growth method. The underlying assumption was that both diseases share the same vector, and consequently, some parameters of their $\Re_0$ expressions could be considered equal.

We used the same approach to derive an expression for Zika reproductive number in a dengue endemic area, assuming that mosquitoes bite at the same rate and survive with the same daily probability, regardless of being infected by each virus. From the $\Re_0$ derivation found by Pinho *et al.* [30] for their model, we have the following expressions for the reproductive number of Zika and dengue, $\Re_{0,z}$ and $\Re_{0,d}$, respectively:

$$\Re_{0,z} = \sqrt{\frac{b^2\beta_{m,z}\beta_{h,z}}{\gamma_z\mu_m(1+\tau_{e,z}\mu_m)}\frac{\bar{M}}{H}}, \tag{2}$$

$$\Re_{0,d} = \sqrt{\frac{b^2\beta_{m,d}\beta_{h,d}}{\gamma_d\mu_m\left(1+\tau_{e,d}\mu_m\right)}\frac{\bar{M}}{H}}, \tag{3}$$

where the total mosquito population size is denoted by $\bar{M}$, the human population size by H, the mosquito biting rate b, the proportion β_m of mosquito bites in infected humans considered to be infective to the vector, and the proportion β_h of infected mosquito bites effectively infective to humans – parameters are indexed by dengue (d) and Zika (z), accord-

ingly. Some of these parameters are difficult to estimate, but by taking the ratio between equations 2 and 3, we obtain $\Re_{0,z}$ indirectly from $\Re_{0,d}$:

$$\Re_{0,z} = \Re_{0,d}\sqrt{\left(\frac{1+\tau_{e,d}\mu_m}{1+\tau_{e,z}\mu_m}\right)\frac{\gamma_d}{\gamma_z}\frac{\beta_{h,z}}{\beta_{h,d}}\frac{\beta_{m,z}}{\beta_{m,d}}}, \tag{4}$$

which is convenient because some parameters are cancelled out. If one assumes that bites from mosquitoes infected with any of thes two viruses are equally likely to infect susceptible humans, that is $\beta_{h,z} = \beta_{h,d}$, it is possible to estimate the basic reproductive rate of Zika based on that of dengue obtained from previous epidemics, assuming infection routes are the same. On the other hand, by estimating $\Re_z$ and $\Re_d$ independently (direct approach), one can use equation 4 to estimate the ratio $\beta_{h,z}/\beta_{h,d}$ if the remaining parameters are known, still assuming that transmission dynamics are identical.

Parameter uncertainty

The use of the equations (1) and (4) requires some knowledge about the disease natural history parameters. Table 1 presents a compilation of the literature on necessary parameters to calculate $\Re_0$ according to different methods. A systematic review of the literature on Zika [18] published estimates of incubation and infection periods of ZIKV based on (only) 25 Zika cases, mostly among Europeans and north Americans returning from Zika endemic countries and found values consistent with dengue [30, 1, 6]). Another study [12] comparing outbreaks of Zika in the Pacific islands of Micronesia, the Yap Main Islands and Fais, has found similar incubation and infection periods for Zika.

We assume that the uncertainty of each natural history parameter can be represented by a Gaussian distribution whose mean and standard deviation are calculated based on the values presented in Table 1 where each interval is assumed to be a symmetric 99% probability interval. The uncertainty for force of infection is also represented by a Gaussian distribution, where the mean is given by the maximum likelihood estimate (MLE), $\hat{\Lambda}$, and the standard deviation is given by the observed standard deviation of $\hat{\Lambda}$. Hence, using a Monte Carlo algorithm we derived the induced distribution of $\Re_0$ based on equations (1) and (4).

Table 1: Zika and Dengue fever natural history parameters.

Parameter	Zika	Dengue
Infectious period in human, γ^{-1} (days)	(2.9–8.8) [12]	(1.9–7.9) [12]
Intrinsic incubation period in humans, τ_i (days)	(4.4–7.6) [18, 12]	(3–10) [25, 6]
Extrinsic incubation period in mosquitoes, τ_e (days)	(4.4–17) [12]	(4.3–15) [6, 12]
Mosquito mortality rate, μ_m (days^{-1})	(0.02–0.09) [30]	(0.02–0.09) [30]
Transmission efficiency parameter, c	(0.045–0.155) [7]	(0.426–0.590) [13]

Results

Direct method

From January 2015 to mid-April 2016, 25,213 suspected cases of Zika were notified for the city of Rio de Janeiro. Of these, 17,585 were women and 7,628 men, corresponding to an attack ratio of approximately 395 per hundred thousand inhabitants, over the entire period. Figure 1 shows the weekly incidence time series in the city. The city-wide estimated rate Λ for Zika was 0.823 with standard deviation of 0.053. This estimate was obtained assuming a 7 weeks window of constant exponential growth which provided the best fit. The direct method yielded an estimate for the basic reproductive number for ZIKV in Rio de Janeiro of 3.92 (95% Confidence Interval: 3.09–5.31) (Table 3). We present the results of the uncertainty analysis along with the estimated forces of infection and reproductive numbers using different time windows for the exponential growth period in the supplementary material.

For comparison, we also calculate $\Re_0$ using other published formulas.

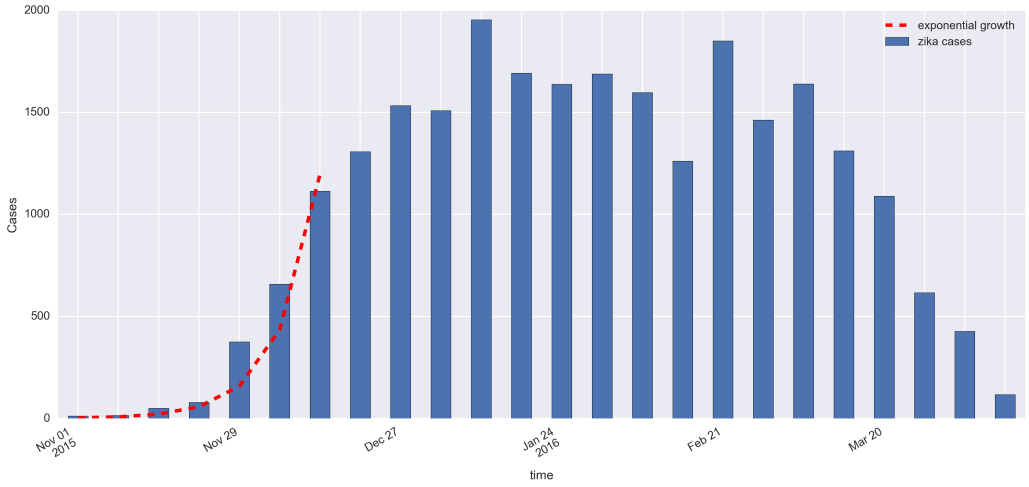

Figure 1: Epidemic curve of Zika in Rio de Janeiro, 2015-16 (blue bars). Red dashed line shows the exponential growth of Zika cases, with an estimated constant rate $\hat{\Lambda} = 0.823$, during the first seven weeks.

Table 2 presents the estimates for the basic reproductive number for Zika by health district in Rio de Janeiro. The $\Re_0$s are also displayed in a map of Rio de Janeiro (Figure 2). The health districts 3.2, 3.3 and 5.2 are those with higher reproductive numbers, all $\Re_0$ being greater than four on average. Also, these areas are historically the areas with more notified cases of Dengue.

Indirect method

Applying the natural history parameters from Table 1 into equation (4) leads to the conclusion that the $\Re_0$ for Zika should be 53% (95% CI: 33%–78%) of dengue fever's $\Re_0$, if both diseases share the same *Aedes aegypti* main transmission route: $\Re_{0,z} = 0.53\Re_{0,d}$.

Estimates of $\Re_0$ for dengue in 2002 and 2012 in Rio de Janeiro are 2.51 (95% CI: 2.07–3.14) and 1.54 (95% CI: 1.39–1.79), respectively (Table 3). This indirect method using both dengue epidemics produces an average estimate of $\Re_0$ for ZIKV that is much smaller than the one obtained from the exponential growth method. Moreover, the average estimate of

Table 2: Estimates for the basic reproductive number for Zika by health district in Rio de Janeiro.

Health district	$\hat{\Re}_0$	2.5%	97.5%
1.0	3.33	2.86	4.14
2.1	3.23	2.83	3.86
2.2	2.86	2.36	3.42
3.1	3.78	3.05	5.51
3.2	4.08	3.09	4.97
3.3	4.66	3.73	5.80
4.0	3.61	2.69	4.33
5.1	3.82	2.57	6.73
5.2	4.10	3.19	4.97
5.3	3.86	2.95	5.66

Zika's $\Re_0$ is smaller than 1 in the case of using 2012 dengue data, indicating no capacity for sustaining an epidemic. By contrast, in the case of Zika's $\Re_0$ obtained from 2002 dengue's numbers, the average estimate is higher than 1, but the 95% CI does not rule out that $\Re_0 < 1$. More importantly, estimates from direct observation from notifications point to a basic reproductive number for Zika higher than dengue's number, whereas the indirect method leads to a smaller basic reproductive number. The implications of such contradictory result are left for the discussion.

Discussion

The basic reproductive number of Zika in Rio de Janeiro was estimated at 3.93 (95% CI: 3.09–5.31). This value is higher than the estimates for French Polynesia, which varied from 1.5 to 3.1 [26, 17], but consistent with those calculated for the Yap Island, ranging from 4.5 to 5.813 [26]. These numbers are also within the range of other viral diseases transmitted by *Aedes aegypti*, as dengue and Chikungunya, as reported in the literature [21]. In Rio de

Table 3: Estimates and 95%CI for the basic reproductive number for Zika and dengue in Rio de Janeiro. Direct estimates are obtained from equation (1) and indirect from equation (4).

	$\hat{\Re}_0$	2.5%	97.5%	Method
Zika	3.923	3.086	5.312	direct
Dengue 2002	2.509	2.079	3.147	direct
Dengue 2012	1.539	1.392	1.787	direct
Zika using dengue 2002	1.312	0.806	2.009	indirect
Zika using dengue 2012	0.808	0.507	1.200	indirect

Janeiro, DENV-3 and DENV-4 were introduced recently, providing us with the opportunity of directly comparing $\Re_0$'s within the same city. Zika's $\Re_0$ in 2015 was 1.5 greater than that of dengue epidemic of 2002, just after introduction of DENV-3, and 2.5 times greater than of dengue epidemic in 2012, just after introduction of DENV-4.

These differences in transmission can be attributed to several factors. For example, since DENV-3 and DENV-4 invaded a population were the remaining dengue viruses were already circulating, some immunological protection could already be in place; or it is also possible that vector competence differed between strains, either due to ecological, physiological, or genetic mechanisms [24]. Climate is also an important factor influencing mosquito vectorial capacity, hence year-specific (seasonal) factors cannot be ruled out [19]. At this point, these are hypotheses to be tested. In any case, such high $\Re_0$ for Zika suggest a highly disruptive potential for Zika epidemics, higher than that already observed for dengue epidemics.

The first wave of the Zika epidemic in Rio de Janeiro showed exponential growth during 7 weeks, and plateau at around 1500 cases per week during the whole summer of 2015-2016 (Figure 1). The decay observed in the last weeks of March and April can be attributed to notification delays, but the plateau up to February deserves further investigation. During this same period, dengue notification increased from 200 cases per week in November to 500 in February 2016 and to 1000 in April 2016 (`http://info.dengue.mat.br`). This growth in dengue cases, associated with high temperatures observed in this El Nino year, indicate

that conditions for mosquito borne transmission existed. One possible explanation for comparatively slow spatial spread of Zika is spatial heterogeneity (Figure 2), since the city of Rio de Janeiro presents very heterogeneous areas. Forested mountains cross the city and create micro-climates in the valleys were most of the population lives; population density and living conditions also vary widely across the city. When calculating $\Re_0$ at the health district level, we find that $\Re_0$ is consistently above one, but varies from 2.86 to 4.6, also indicating some level of heterogeneity. Understanding spatial variation is important, as those who live far apart are less likely to infect one another than those who live in closer proximity to each other. Spatial heterogeneity is known to slow down epidemics and this could be an explanation for the pattern observed [5].

If current knowledge regarding the entomological parameters of ZIKV transmission is correct, $\Re_0$ for Zika should be about 53% (95% CI: 33%–78%) lower than the reproductive number dengue fever. Applying this factor to the observed measurements of dengue in Rio de Janeiro, the resulting theoretical estimation of Zika's reproductive number could be below 1. In other words, no Zika epidemic would be expected from a dengue vector whose life history parameters are those currently described in the literature. This low transmission potential of ZIKV in comparison to dengue virus is mainly due to the almost five times lower transmission efficiency for ZIKV in both *Ae aegypti* and *Ae albopictus* in comparison to dengue virus [7]. If we are to attribute the difference in $\Re_0$ to the vector transmission alone, we will have to review the life history parameters used in equation (4). In particular, other infection studies are important to corroborate the transmission efficiency parameter found for *Aedes aegypti*. The same concern is shared by Guzzetta et al. (2016) [15] when assessing the risk of Zika invasion in temperate areas.

An alternative explanation requires at least one of the assumptions of the indirect model to not be valid, in particular, that other routes of transmission, such as sexual[23] or other vectors[2], are an important component of the higher transmissibility of Zika. Also, another seemingly unlikely possibility is an asymmetric transmissibility in which the virus is not efficient in infecting mosquitoes but highly efficient in infecting humans.

In order to estimate Zika's force of infection, we define the beginning of the outbreak in the city of Rio de Janeiro as the epidemic week just after notification became compulsory. Zika and dengue cases come from syndromic surveillance systems, and most of them are diagnosed using clinical criteria only. In Rio de Janeiro, case notification of ZIKV infection only became compulsory by the end of October 2015. Although we clearly identify an early exponential outbreak after October 2015, the notification system could have potentially missed even earlier cases. Hence, caution is advised when interpreting these results. Furthermore, even though mandatory notification of Zika only started in October, there is evidence of earlier ZIKV circulation, without proper notification. More data is required to better understand the transmission dynamics of Zika. This will be improved as more specific diagnostic tests become available and more data are collected on the life history of this disease.

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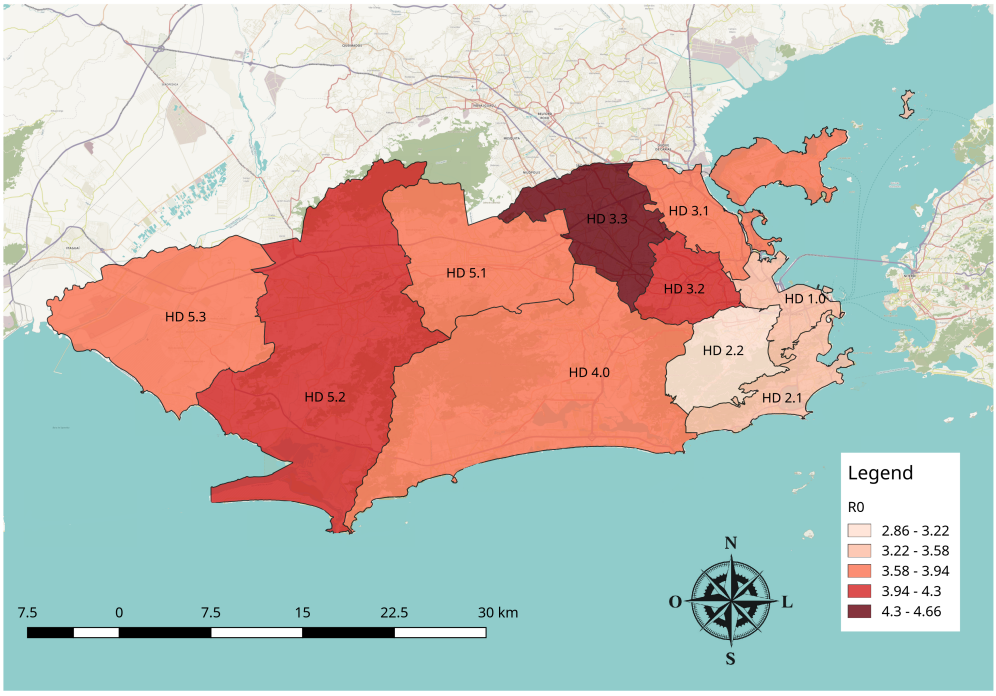

Figure 2: Estimates for the basic reproductive number for Zika by health districts in Rio de Janeiro.