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A theoretical estimate of the risk of microcephaly during pregnancy with Zika virus infection

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ABSTRACT

Objectives: There has been a growing concern over Zika virus (ZIKV) infection, particularly since a probable link between ZIKV infection during pregnancy and microcephaly in the baby was identified. The present study aimed to estimate a theoretical risk of microcephaly during pregnancy with ZIKV infection in Northeastern Brazil in 2015.

Methods: Temporal distributions of microcephaly, reported dengue-like illness and dengue seropositive in Brazil were extracted from secondary data sources. Using an integral equation model and a backcalculation technique, we estimated the risk of microcephaly during pregnancy with Zika virus infection.

Results: If the fraction of Zika virus infections among a total of seronegative dengue-like illness cases is 30%, the risk of microcephaly following infection during the first trimester was estimated at 46.7% (95% CI: 9.1, 84.2), comparable to the risk of congenital rubella syndrome. However, the risk of microcephaly was shown to vary widely from 14.0% to 100%. The mean gestational age at delivery with microcephaly was estimated at 37.5 weeks (95% CI: 36.9, 39.3).

Conclusions: The time interval between peaks of reported dengue-like illness and microcephaly was consistent with cause–outcome relationship. Our modeling framework predicts that the incidence of microcephaly is expected to steadily decline in early 2016, Brazil.

1. Introduction

There has been a growing concern over Zika virus (ZIKV) infection (Musso et al., 2015; Ventura et al., 2016), particularly since a probable link between ZIKV infection during pregnancy and microcephaly was identified (Schuler-Faccini et al., 2016). Clinical symptoms of ZIKV are self-limiting in general and the infection is sometimes even sub-clinical, but severe complications including microcephaly and Guillain–Barré syndrome justify global effort to actively monitor and control the spread of this disease. The transmission potential of Zika virus infection in the South Pacific has been shown to be comparable to dengue and chikungunya viruses (Nishiura et al., 2016a).

Brazil has experienced a large ZIKV epidemic with the notification of a substantial number of microcephaly cases, which have increased almost 20-fold compared to the recent years. In particular, Northeastern Brazil has notified more than 85% of all microcephaly cases that have been reported in Brazil, 2015 as of the end of 2015. Considering that the risk of microcephaly is a substantial public health concern, it is fruitful to quantify the risk of contracting microcephaly given ZIKV infection during early gestational period of pregnancy. Elucidating the epidemiological mechanism of microcephaly could also shed light on future course of the ongoing epidemic.

The present study estimated the risk of microcephaly during pregnancy with ZIKV infection, analyzing epidemiological datasets of reported dengue-like illness and microcephaly in Northeastern Brazil in 2015.

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2. Materials and methods

2.1. Epidemiological data

We analyzed the epidemiological datasets of microcephaly and dengue-like illness, retrieved from publicly available secondary data sources. Both of them are reported as the cumulative number, and we focused on the dataset from Northeastern Brazil (Ministério da Saúde, 2016a). Microcephaly is defined as a head circumference of more than 2 SDs below the mean for age and gender, and can be caused by a variety of reasons including infection with Zika virus (suspected), syphilis, toxoplasmosis, rubella, cytomegalovirus and other infectious agents. Dengue-like illness is collected as a part of syndromic surveillance (Ministério da Saúde, 2016b), and is clinically defined as a patient who has acute febrile illness accompanied by at least two of the following symptoms: headache, retro-orbital pain, myalgia, arthralgia, prostration and rash (Ministério da Saúde, 2009). The latest time at which the data were collated for the study was 20th February, 2016. Accessible data of microcephaly have been available from week 47 of 2015 for 6 weeks (Ministério da Saúde, 2016a). Due to increased awareness, the reporting coverage is likely to have been considerably elevated from 2016 and the validity of microcephaly diagnoses has been questioned elsewhere (Victora et al., 2016). For this reason, we focused on microcephaly data within 2015 only.

In addition, the following three pieces of information were retrieved. First, the number of serological samples and the outcome of serological testing for dengue virus over time were also collected, focusing on Northeastern Brazil (Ministério da Saúde, 2016b). Second, a point estimate of the proportion of pregnant women among a total population was calculated using Brazilian census (United Nations Population Division, 2016). Third, gestational age distribution of delivery in Brazil was extracted to calculate the variance of the time from pregnancy to delivery (Pereira et al., 2013). Due to scarcity of the dataset, gestational ages of 22–29 weeks and 43 weeks and longer were omitted from the distribution during the implementation of statistical estimation.

2.2. Statistical analysis

Using the following integral equation model, we estimate, π, the conditional risk of microcephaly given ZIKV infection during the first trimester of pregnancy. Using the weekly incidence of dengue-like illness, c_{t-s+a}, which occurred between a_1 and a_2 weeks of gestation (i.e., between times $t-s+a_1$ and $t-s+a_2$), the expected number of microcephaly, $\mathrm{E}(m_t)$, at time t, is written as

$$E(m_t) = \frac{\pi z b}{q r} \sum_{s=1}^{\infty} \sum_{a=a_1}^{a_2} (1 - p_{t-s+a})\, c_{t-s+a} g_a f_s(\mu, \sigma^2), \tag{1}$$

where p_t is the time-dependent proportion of seropositive for dengue virus infection among all serological samples, and q is the proportion of ZIKV cases who sought medical treatment. z represents the fraction of ZIKV infections among seronegative dengue-like illness cases. b is a point estimate of the proportion of pregnant women among a total population. r is the proportion of actual microcephaly cases among all notified cases of microcephaly. g_a is the frequency of successful infection in fetus given an exposure at gestational age a, and f_s is the probability density function of the time from pregnancy to delivery. g_a was assumed be uniformly distributed during the first trimester of pregnancy, because this is the period when there appears to be a high risk of microcephaly (de Paula Freitas et al., 2016). Different sources define different lengths of the time for the first trimester ranging from 12 to 16 weeks, however the default parameterization was taken to be $a_1 = 1$ and $a_2 = 12$. In a sensitivity analysis, it was assumed that a_2 ranges from 12 to 16. f_s was assumed to follow a gamma distribution as the visual assessment of fit to term delivery data was satisfactory. Since the variance of gestational age at delivery appeared not to be deviated from term delivery in Brazil (De Araujo et al., 2016), and thus, the variance of f_s was fixed at 3.78 weeks^2 (Pereira et al., 2013). However, considering that microcephaly could lead to delivery at an early gestational age, the mean (μ) was jointly estimated with other parameters.

Tables 1 and 2 list estimated and known parameters and variables, respectively. This formulation is close to the idea used for congenital rubella syndrome (Gao et al., 2013; Cutts and Vynnycky, 1999), calculating the risk of fetus infection using epidemiological data and risk parameters governing infection in pregnant women.

A maximum likelihood method was employed to estimate unknown parameters, π, p_t, q, r and μ (among which p_t was dealt with as varying with time). Assuming that the weekly count of microcephaly cases follows a Poisson distribution, the corresponding likelihood function to estimate parameters based on the dataset from week 47 to 52 is

$$L_1(\pi, p_t, q, r, \mu; c_t, x_t) = \prod_{t=47}^{52} \frac{E(m_t; c_t)^{x_t} \exp\left(-E\left(m_t; c_t\right)\right)}{x_t!}, \tag{2}$$

where x_t is the observed incidence of microcephaly in week t.

The conditional risk of medical attendance given ZIKV infection, q was assumed to follow a binomial distribution. Supposing that l cases attended clinics among a total of k estimated number of infections, the likelihood function to estimate q is

$$L_2(q; k, l) = \binom{k}{l} q^l (1-q)^{k-l}, \tag{3}$$

Since there was no dataset that permitted us to explicitly estimate q in Brazil, we used Yap Island seroepidemiological data in 2007 and compensated the estimate from Eq. (3) into the information as a part of the right hand side of Eq. (1).

In addition to the syndromic data, serological testing has been performed for a small fraction of dengue-like illness cases over time. We assume that empirically examined seroepidemiological samples are representative of all reported dengue-like illness cases. The probability of seropositive becoming a confirmed dengue case given dengue-like illness status (i.e., given clinical/syndromic diagnosis) was also similarly calculated from binomial distribution. Assuming that there were i_t positive samples among a total of h_t serological samples, we have

$$L_3(p_t; h_t, i_t) = \prod_t \binom{h_t}{i_t} {p_t}^{i_t} (1-p_t)^{h_t - i_t}, \tag{4}$$

Similarly, referring to an epidemiological study that assessed diagnostic accuracy of reported microcephaly (and emphasized that more than half of reported microcephaly cases did not satisfy the clinical criteria of microcephaly) (Victora et al., 2016), a binomial sampling process of actual microcephaly cases b given a total of c reported microcephaly cases was modeled as

$$L_4(r; b, c) = \binom{c}{b} r^b (1-r)^{c-b} \tag{5}$$

Thus, the total likelihood is calculated as $L = L_1 L_2 L_3 L_4$. The maximum likelihood estimates of π, p_t, q, r and μ were identified by minimizing the negative log-likelihood. The 95% confidence interval (CI) was computed by using the profile likelihood. The parameter z was not estimated from empirical data due to its correlation with π. Instead, we varied z from 0 to 1.0, examining the sensitivity of π to the value of z.