

# Estimating the Number of Pregnant Women Infected With Zika Virus and Expected Infants With Microcephaly Following the Zika Virus Outbreak in Puerto Rico, 2016

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## ABSTRACT

**Importance** Zika virus (ZIKV) infection during pregnancy is a cause of congenital microcephaly and severe fetal brain defects, and it has been associated with other adverse pregnancy and birth outcomes.

**Objective** To estimate the number of pregnant women infected with ZIKV in Puerto Rico and the number of associated congenital microcephaly cases.

**Design, Setting, and Participants** We conducted a modeling study from April to July 2016. Using parameters derived from published reports, outcomes were modeled probabilistically using Monte Carlo simulation. We used uncertainty distributions to reflect the limited information available for parameter values. Given the high level of uncertainty in model parameters, interquartile ranges (IQRs) are presented as primary results. Outcomes were modeled for pregnant women in Puerto Rico, which currently has more confirmed ZIKV cases than any other US location.

**Exposure** Zika virus infection in pregnant women.

**Main Outcomes and Measures** Number of pregnant women infected with ZIKV and number of congenital microcephaly cases.

**Results** We estimated an IQR of 5900 to 10 300 pregnant women (median, 7800) might be infected during the initial ZIKV outbreak in Puerto Rico. Of these, an IQR of 100 to 270 infants (median, 180) may be born with microcephaly due to congenital ZIKV infection from mid-2016 to mid-2017. In the absence of a ZIKV outbreak, an IQR of 9 to 16 cases (median, 12) of congenital microcephaly are expected in Puerto Rico per year.

**Conclusions and Relevance** The estimate of 5900 to 10 300 pregnant women that might be infected with ZIKV provides an estimate for the number of infants that could potentially have ZIKV-associated adverse outcomes. Including baseline cases of microcephaly, we estimated that an IQR of 110 to 290 total cases of congenital microcephaly, mostly attributable to ZIKV infection, could occur from mid-2016 to mid-2017 in the absence of effective interventions. The primary limitation in this analysis is uncertainty in model parameters. Multivariate sensitivity analyses indicated that the cumulative incidence of ZIKV infection and risk of microcephaly given maternal infection in the first trimester were the primary drivers of both magnitude and uncertainty in the estimated number of microcephaly cases. Increased information on these parameters would lead to more precise estimates. Nonetheless, the results underscore the need for urgent actions being undertaken in Puerto Rico to prevent congenital ZIKV infection and prepare for affected infants.

# INTRODUCTION

Zika virus (ZIKV) infection during pregnancy is a cause of congenital microcephaly and severe fetal brain defects, and it has been associated with pregnancy loss, ocular birth defects, and severe arthrogryposis in the extremities.<sup>1- 10</sup> Since it was first reported in Brazil in May 2015, ZIKV, a mosquito-borne flavivirus, has spread throughout the Americas.<sup>11</sup> The Puerto Rico Department of Health (PRDH) reported the first case of autochthonous transmission of ZIKV in December 2015.<sup>12</sup>

As of August 4, 2016, Puerto Rico reported 5897 confirmed cases of ZIKV infection, more than any other US location, and the number is expected to rise.<sup>12- 14</sup> Among the confirmed cases, 901 have been among pregnant women,<sup>14</sup> and the first case of microcephaly in a fetus with confirmed ZIKV infection was announced by the PRDH on May 13, 2016.<sup>15</sup> Given that the outbreak in Puerto Rico was growing in early 2016 and that microcephaly risk appears to be highest with ZIKV infection during the first trimester,<sup>4,7,16- 18</sup> few pregnancies with first-trimester exposure have delivered, to date.

We estimated the number of pregnant women infected with ZIKV in Puerto Rico and the number of associated congenital microcephaly cases expected up to 9 months after the outbreak. Because the range of infant outcomes associated with congenital ZIKV infection is not well understood, estimating the number of infants exposed to maternal ZIKV infection during fetal development also provides an estimate for the number of infants that could potentially have ZIKV-associated adverse outcomes. These estimates, the number of pregnant women with ZIKV infection and the number of microcephaly cases, can guide public health strategies in the care and counseling for women of reproductive age, as well as inform planning for services for affected children and families.

## METHODS

We estimated ranges for the expected number of women with ZIKV infection during pregnancy in the initial ZIKV outbreak in Puerto Rico, the number of microcephaly cases due to ZIKV infection during pregnancy, and total congenital microcephaly cases accounting for baseline prevalence of congenital microcephaly in Puerto Rico. We first reviewed published reports for relevant parameters and accounted for numerous uncertainties by developing uncertainty distributions reflecting lack of knowledge for parameter values. We then used Monte Carlo simulation techniques to sample parameters from these distributions and, for each sampled set, estimated an expected outcome by sampling from a random process with those parameters. As a result, the uncertainty ranges presented here reflect both the effect of parameter uncertainty on expected values for the outcomes and random variation in the outcomes about these expected values. Institutional review board approval was not required, as this study (conducted from April to July 2016) used publicly available data to generate estimates of outcomes of interest.

In our model, we assumed there was no ZIKV exposure prior to the outbreak and accounted for declining risk due to exposure prior to pregnancy as the epidemic progresses. We also made the simplifying assumption that pregnancies resulting in a live birth are uniformly spread across months, although there is variation in actual birth rates by month.<sup>19</sup> This assumption allowed us to estimate outcomes relative to the overall infection rate in the initial outbreak, irrespective of the specific, unknown time course of the outbreak. With the mean rate of pregnancy per month and the estimated value for the overall ZIKV infection rate, we estimated the number of pregnant women infected with ZIKV within each trimester of pregnancy during the outbreak.

We used the estimated number of women infected in each trimester and trimester-specific estimates of microcephaly risk given maternal infection to estimate the number of excess microcephaly cases resulting from the initial ZIKV outbreak. The number of microcephaly cases in the absence of the ZIKV epidemic was estimated using the estimated total number of annual pregnancies and a background microcephaly risk of 2 to 6 cases per 10 000 births.<sup>20</sup> Additionally, using previously described methods, we projected when the first infants with microcephaly due to ZIKV were likely to be born.<sup>21</sup>

For parameters with limited information available a priori, we assumed the uncertainty to be distributed uniformly throughout the range of possible values. For parameters with a specified range and a most likely value, we used a triangular uncertainty distribution to concentrate higher likelihood in the vicinity of the assumed most likely value. The resulting estimates were summarized using the median, interquartile range (IQR), and 95% uncertainty intervals (UIs) of 100 000 Monte Carlo simulations. Given the high level of uncertainty in model input parameters, the IQRs, the most likely range of outcomes, are presented as the primary results.

All statistical analyses were conducted in SAS version 9.3 (SAS Institute). Details on the assumptions, derivation of the models, and the Monte Carlo uncertainty estimation process are provided in the eMethods in the Supplement.

# Incidence of ZIKV Infection

We estimated the incidence of ZIKV infection for the general population of Puerto Rico in 2016. Despite the adverse pregnancy outcomes associated with ZIKV infection during pregnancy, available data do not indicate that pregnant women differ in their susceptibility to ZIKV infection compared with the general population.<sup>7,16,22,23</sup> We considered data from other mosquito-borne illnesses in Puerto Rico and data from ZIKV outbreaks in other locations. Although chikungunya is an alphavirus and ZIKV is a flavivirus, both viruses are transmitted by the same vector (*Aedes aegypti*) in Puerto Rico. *Aedes aegypti* have limited flight ranges of typically 100 m and the setting of the vector may be more important than the genus of the virus in terms of transmission rates.<sup>24,25</sup> Additionally, both the current ZIKV outbreak and the recent chikungunya outbreak in Puerto Rico introduced these viruses to a sero-naïve population. A study of blood donors in Puerto Rico found an overall incidence of chikungunya infection of 23.5% in approximately the first year after introduction.<sup>26</sup> Another recent study of chikungunya in Puerto Rico found seroprevalences of 19% and 28% in 2 communities with intensive vector control efforts and 41% and 55% in 2 communities without those efforts, approximately 2 years after the initial cases were diagnosed.<sup>27</sup> While dengue viruses are also transmitted by the same vector, the long-term circulation of multiple dengue serotypes in Puerto Rico limits the relevance of the data for a newly introduced arbovirus. However, in 2 older dengue outbreaks in Puerto Rico in 1969 and 1982, in which novel serotypes were introduced, infection rates were 46% and 31%, respectively.<sup>28,29</sup>

Recent ZIKV outbreaks in other settings have resulted in a sero-incidence of 66% to 73%.<sup>17,30</sup> Older sero-surveys, which were not associated with outbreaks, found the prevalence of ZIKV antibodies to range widely from 6% to 75%.<sup>31-37</sup> However, there is significant cross-reactivity for flavivirus antibody tests; therefore, ZIKV sero-surveys should be interpreted with caution in settings with other endemic flaviviruses.<sup>38</sup> Given these data, we allowed for substantial uncertainty in the incidence of ZIKV infection in 2016 in Puerto Rico. First, we assumed it would not be lower than 10% nor higher than 70%. Based on the blood donor data for chikungunya, the incidence of ZIKV infection in 2016 is likely to be on the lower end of this range, possibly around 25%. We used a triangular distribution to capture the uncertainty between the minimum (10%), maximum (70%), and most probable (25%) outcome (Table 1). The IQR or most likely value for the cumulative risk of ZIKV infection was therefore estimated to be of 25% to 44%.

## Pregnant Population

The expected number of women who become pregnant each month was estimated using a binomial process with a rate of one-twelfth of the 2015 live birth rate in Puerto Rico (written communication with PRDH; May 2016) and the 2015 US Census estimate for the population of Puerto Rico (Table 1).<sup>39</sup>

## Risk for Microcephaly

Congenital microcephaly was defined as clinically diagnosed microcephaly and did not include microcephaly based solely on head circumference. In 2013-2015, the annual rate of congenital microcephaly ranged from 2.6 to 5.5 per 10 000 live births in Puerto Rico (written communication with PRDH Birth Defects Surveillance Program; May 2016). Therefore, we used a uniform uncertainty distribution of 2 to 6 microcephaly cases per 10 000 live births. The risk for microcephaly given maternal ZIKV infection during pregnancy was based primarily on estimates derived from Bahia, Brazil.<sup>18</sup> These data indicated a strong association between maternal ZIKV infection in the first trimester and subsequent risk for microcephaly. We used a 1% to 13% risk for microcephaly given first trimester maternal ZIKV infection with a uniform distribution to reflect uncertainty.<sup>18</sup> Available data are limited but indicate that the risk for microcephaly associated with infection in the second and third trimesters of pregnancy is lower or might be no greater than the baseline microcephaly risk. Therefore, we set the most likely risk for microcephaly in these trimesters to 0.03% (range, 0%-0.7%) and 0% (range, 0%-0.2%), respectively, using triangular distributions to capture the uncertainty.

## RESULTS

Using the estimated distribution for each parameter given in Table 1, we estimated that an IQR of 5900 to 10 300 pregnant women (median, 7800; 95% UI, 3500-15 000) might be infected during the initial ZIKV outbreak in Puerto Rico (Table

2). Of these maternal infections, an IQR of 100 to 270 (median, 180; 95% UI, 30-500) might result in microcephaly due to congenital ZIKV infection. Multivariate sensitivity analyses indicated that 2 model input parameters, cumulative incidence of ZIKV infection and risk for microcephaly given maternal infection in the first trimester, were the primary drivers of both magnitude and uncertainty in the estimated number of microcephaly cases.

As the risk for microcephaly seems to be highest with first-trimester ZIKV infection, most of the microcephaly cases are expected to be delayed relative to the ZIKV outbreak. The first reported ZIKV cases occurred in late 2015, so microcephaly cases among live-born infants would be expected to occur as early June 2016, with some earlier cases possibly associated with second-trimester infection, and would continue into 2017. In the absence of a ZIKV outbreak, an IQR of 9 to 16 microcephaly cases (median, 12; 95% UI, 4-23) would be expected in Puerto Rico in a given year. Accounting for both the baseline prevalence of microcephaly and the estimated 100 to 270 microcephaly cases attributable to ZIKV infection during the initial ZIKV outbreak, we estimated a total of 110 to 290 microcephaly cases (median, 190; 95% UI, 50-510) between mid-2016 and mid-2017 (Table 2).

## DISCUSSION

As of August 4, 2016, the number of laboratory-confirmed ZIKV cases in Puerto Rico continued to rise. Assuming that the cumulative incidence of ZIKV infection in 2016 will be in the range of 10% to 70% and most likely close to 25%, we estimated that 5900 to 10 300 women may be infected with ZIKV during pregnancy in Puerto Rico in 2016. This estimate also provides an estimate of the number of infants at risk for ZIKV-associated adverse outcomes. Additionally, we estimated that if maternal infection in the first trimester of pregnancy is associated with a 1% to 13% risk for microcephaly, up to a 0.7% risk in the second trimester and up to a 0.2% risk in the third trimester, an additional 100 to 270 infants may be born with congenital microcephaly in Puerto Rico as a result of the ZIKV outbreak. To our knowledge, this is the first attempt to predict the number of ZIKV infections in pregnant women and the excess microcephaly cases that might be expected in Puerto Rico.

Our modeling approach has several limitations. The primary limitation is uncertainty in key model parameters. Using Monte Carlo simulation, we repeatedly estimated the outcomes based on values for input parameters sampled from assumed uncertainty distributions. As a result, our estimates have wide uncertainty intervals reflecting the parameter uncertainty. The outer limits of these estimated uncertainty distributions should be interpreted with caution because the likelihood of the true outcome reaching these values is small. We also assessed sensitivity to key parameters and found that cumulative incidence of ZIKV infection and risk for microcephaly due to ZIKV infection in the first trimester were the principal drivers of the outcomes. As a result, increased information on these parameters would lead to more precise estimates. Ongoing surveillance and studies, especially among pregnant women infected with ZIKV in Puerto Rico, will provide information to improve estimates of the incidence of infection, the risk for microcephaly by trimester of ZIKV infection, and the risk for other adverse outcomes associated with congenital ZIKV infection.<sup>40</sup>

Ongoing surveillance and studies may also allow the estimation of the risk for maternal-fetal transmission, which has been documented in all trimesters of pregnancy and can lead to congenital microcephaly and other adverse outcomes.<sup>4,7,16,41</sup> Currently, there are few data available to quantify either the risk for congenital ZIKV infection or the risk for adverse outcomes beyond microcephaly due to congenital ZIKV infection. Furthermore, interventions were not accounted for in the model. The introduction of effective countermeasures, such as access to a wide range of effective contraceptives<sup>13</sup> or reduced contact with mosquitoes through personal protection or vector control, should result in a reduced number of infections and microcephaly cases.

Given the adverse pregnancy and birth outcomes associated with ZIKV infection during pregnancy, it is more important than ever for women who do not currently desire pregnancy to use effective contraception. A 2008 hospital-based survey among postpartum women with live-born infants in Puerto Rico indicated that 65.5% of pregnancies were not planned.<sup>13</sup> Additionally, few women in Puerto Rico are using the most effective contraceptive methods (eg, long-acting reversible contraception such as implants) likely owing to limited availability and access.<sup>13</sup> Without a vaccine to prevent ZIKV infection, increasing access to effective contraception for women who do not desire pregnancy is a key ZIKV countermeasure. In the context of a ZIKV outbreak, health care professionals (eg, physicians, nurse practitioners, and physician assistants) should discuss pregnancy intentions and reproductive options with women of reproductive age.<sup>42</sup> For women who desire pregnancy and live in areas where ZIKV infection may be a risk, preconception counseling should include a discussion of signs and symptoms of ZIKV infection, mosquito prevention strategies, and the risks of ZIKV infection during pregnancy.<sup>13,42</sup>

In addition to the need to rapidly implement prevention strategies, public health officials need to prepare for the births of infants to mothers with ZIKV infection during pregnancy and expected increase in microcephaly cases. The societal and economic costs of birth defects are high, and total lifetime cost of care for an infant born with structural birth defects can exceed \$1 million.<sup>43,44</sup> Furthermore, because we do not know the full spectrum of outcomes associated with ZIKV infection during pregnancy, public health systems need to monitor infants and children born to ZIKV-infected pregnant women for other potential adverse neurodevelopmental or cognitive effects.

In response to the ZIKV outbreak, PRDH leadership, in collaboration with the Centers for Disease Control and Prevention, is taking critical steps to protect pregnant women and their fetuses. Strategies implemented by PRDH leadership include integrated vector control programs, dissemination of ZIKV prevention kits (containing health information, mosquito repellent, a bed net, larvicidal tablets, and condoms), home-based vector control targeting pregnant women, and approaches to improve access and availability to effective contraceptives for women who do not desire pregnancy. In addition to these prevention efforts, the PRDH and the Centers for Disease Control and Prevention are conducting surveillance and close monitoring of all women infected with ZIKV during pregnancy to ensure linkage to services for children with special health care needs. These strategies aim to mitigate the numbers of adverse fetal and infant outcomes associated with ZIKV infection that threaten Puerto Rican families.

## CONCLUSIONS

Zika virus infection in pregnancy causes microcephaly and has been associated with other adverse pregnancy outcomes.<sup>10</sup> Prevention of both unintended pregnancies and ZIKV infections in pregnant women is a public health priority for areas with ZIKV outbreaks. Given that the outbreak in Puerto Rico started in late 2015, urgent action is needed to implement prevention measures to mitigate the devastating reproductive health outcomes of ZIKV infection during pregnancy.<sup>12</sup> Simultaneously, action is needed to prepare for the expected increase in microcephaly cases, which will strain existing resources for families of affected infants. It is imperative that public health officials be prepared for and plan to provide the services these families will need.

## ARTICLE INFORMATION

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