Dengue Virus During Pregnancy and Pregnancy Outcomes

Alfia Karimova*

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Abstract

Dengue is one of the most wide-spread mosquito-borne viral diseases in the world. 390 million people are infected annually and 2.5 billion people live in areas where outbreaks occur every 3-5 years. Thus far studies on the consequences of dengue exposure during pregnancy have focused on more severe, symptomatic cases which account for only a quarter of total infections. Effects of a typical dengue infection, which is asymptomatic, are unknown. I combine data from the Passive Dengue Surveillance System and birth records for Puerto Rico for the years 1990-2010 to examine the relationship between dengue and pregnancy outcomes. My identification strategy uses rainfall as an instrument for dengue and allows me to estimate the upper and lower bounds for effects of dengue on outcomes of interest. I find strong evidence that prenatal dengue exposure decreases birth rates. Pregnancy loss occurs in at least 15% of pregnancies with dengue, which includes both symptomatic and asymptomatic cases; annually there are 1-6% fewer births due to dengue in Puerto Rico. These effects are driven by exposure in the second trimester. Dengue exposure *in utero* also reduces gestation, and there is weak evidence that it reduces infant size even among-full-term pregnancies, although I cannot rule out null effects. Finally, this study illustrates the importance of accounting for measurement error, as specifications which ignore measurement error produce coefficients that may understate the detrimental effects of dengue exposure during pregnancy by several orders of magnitude.

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1 Introduction

World Health Organization (WHO) refers to dengue as the "most important mosquito-borne viral disease in the world" (WHO, 2012). In the last 50 years its incidence grew by a factor of 30, and expanded to previously unaffected regions (WHO, 2009). Most recent estimates suggest that as many as 390 million people become infected annually (Bhatt et al., 2013), with 2.5 billion people living in endemic regions and outbreaks occurring every 3-5 years (WHO, 2009). At the moment, there is no effective vaccine for dengue[1] and no treatment, with clinical management playing only a supportive role (Wilder-Smith et al., 2010). Results in the existing literature may be affected by small sample sizes, selection into the study, and potentially contaminated control groups. Current research also largely ignores asymptomatic cases which account for three quarters of total infections (Bhatt et al., 2013), so that the consequences of a typical dengue infection during pregnancy are unknown. Understanding the full scope of the burden of the dengue virus, including its effects during the prenatal period, is important, in light of the large and growing body of literature suggesting that prenatal environment can have long-lasting consequences, coupled with the fact that dengue affects a considerable share of the world's population.

In this study, I combine data from the Passive Dengue Surveillance System and more than 1 million birth records for Puerto Rico for the years 1990-2010 to analyze the relationship between dengue and pregnancy outcomes, addressing several potential issues in the literature. Using the number of monthly confirmed dengue cases in each municipality, combined with information on the residence of the mother, the date of birth and gestation length, I construct a measure of dengue exposure during pregnancy. The innovation of this paper is use of a novel identification strategy to estimate upper and lower bounds for the effect of *in utero* dengue exposure on the outcome of interest. Although confirmed cases of dengue measures

[1]Dengue vaccine CYD-TDV (Dengvaxia) is licensed in only 20 countries. Current evidence suggests that its effectiveness may vary with seroprevalence, and WHO recommends its use only in areas with high seroprevalence as the vaccine may actually increase the risk of dengue fever for individuals who are not infected (WHO, 2018).

true cases of dengue with error, and this measurement error is likely non-classical, under a set of plausible assumptions OLS estimate is a lower bound for the effect of prenatal dengue exposure on pregnancy outcomes. I also employ an instrumental variable strategy, with the second lag of cumulative monthly rainfall as an instrument for dengue incidence, which is motivated by the literature on the effects of climate on the mosquito that carries the virus. Under the same set of assumptions, IV estimate is an upper bound for the parameter of interest. As a check of the exclusion restriction, I show that rainfall is not correlated with birth outcomes in areas in the United States with climate similar to Puerto Rico where dengue is not present.

I find strong evidence that exposure to dengue during pregnancy reduces birth rates. My results imply that in Puerto Rico there are 1-6% fewer births due to dengue exposure in a given month, or 557-3342 fewer births per year. Back of the envelope calculations suggest that miscarriage occurs in at least 15% of pregnancies with dengue, which includes both symptomatic and asymptomatic cases, and is roughly consistent with the medical literature. These effects are driven by second trimester exposure. The estimates are robust to controlling for local area time-varying changes in the dependent variable, as well as local area specific seasonal effects. Pregnancies exposed to dengue are shorter, but they are not any less likely to carry to full-term. I find weak evidence that even among full-term births, prenatal dengue exposure reduces infant size, although I cannot confidently rule out null effects. In contrast to the earlier studies, I find no evidence that dengue exposure increases the risk of Cesarean delivery, suggesting that these effects may be limited to more severe cases. I also show that I am unable to replicate my main estimates of dengue effects on birth rates using placebo dengue or placebo rainfall exposure.

This study adds to the literature in several ways. I address several potential empirical issues that may affect existing studies. Research focuses almost solely on mothers who exhibit dengue symptoms and are subsequently tested for the virus, so that mothers who are possibly infected but have an asymptomatic case are excluded. Therefore, it is possible

that the documented outcomes apply only in the more severe dengue cases, and not a typical dengue infection. Furthermore, because the studies enrol women either at the time of delivery or when they obtain prenatal care, they ignore potential pregnancy losses which occur before a pregnancy is detectable by the mother.[2] I estimate the risk of an adverse event for *any* dengue infection during pregnancy. To date, the evidence for such cases is limited. I am able to provide an upper and lower bounds for the effects of dengue exposure on pregnancy health, which are consistent with the estimates from the existing medical literature. This bounding exercise is important, as the differences between upper and lower bounds are several orders of magnitude, and focusing solely on the lower bound estimates may lead to severely under-estimating the adverse effects of dengue on prenatal health.

2 Background

2.1 Mosquito vectors

The dengue virus is transmitted to humans through the bite of an infected female *Aedes* mosquitos. Specifically, *Aedes aegypti* is responsible for most transmissions,[3] although several dengue outbreaks have been linked to *Aedes albopictus*, *Aedes polynesiensis*, and *Aedes scutellaris*. *Aedes aegypti* is a tropical and subtropical species of mosquito. Given its inability to withstand colder temperatures, *Aedes aegypti* is also uncommon at high altitudes. This mosquito is largely active during daylight hours and resides in close proximity to humans. Female mosquitos tend to spend their life within 100 metres of the house where they emerge as adults (Murray et al., 2013; WHO, 2009). This means that humans are responsible for virus transmission across communities, as people carrying the virus travel to areas where mosquitos can transmit infections. Then female mosquitos will ingest infected blood during feeding, and after an 8-12 day incubation period, the virus may be transmitted to other

[2] Also, most of the dengue diagnoses were tested for with a dengue IgM assay, which identifies presence of a dengue infection in the preceding three months, so that mothers who tested negative could have still carried the virus earlier in the pregnancy (Pouliot et al., 2010).

[3] This mosquito is also responsible for transmission of yellow fever, chikungunya, and Zika virus.

humans through subsequent feedings, as the mosquito carries the virus for the rest of its life, with the typical lifespan of 1-2 weeks. The mosquito uses a wide range of larval habitats, including many household containers for water storage and plants, as well as a variety of rain-filled habitats, such as used tires, blocked gutters, and outdoor garbage. This means that dengue is more common in poor areas with inadequate water supply, and the subsequent need for water storage (Kyle & Harris, 2008; WHO, 2009). In addition, poor individuals are less likely to live in houses with air conditioning and insect screening, increasing the likelihood of exposure to infected mosquitos (Gubler, 2012).

Different phases of mosquito lifecycle are sensitive to various climate variables.[4] Indeed, temperature and precipitation have been recognized as factors which influence dengue incidence in several endemic areas around the world (Barrera et al., 2011; Campbell et al., 2013; Chen et al., 2010; Descloux et al., 2012; Eastin et al., 2014; Hii et al., 2012; Johansson et al., 2009; Jury, 2008; Rosa-Freitas et al., 2006; Wu et al., 2007; Yang et al., 2009). Research suggests that the temperatures between 15-18°C and 32°C are optimal for mosquito survival (Azil et al., 2010; Chadee et al., 2007; Eastin et al., 2014; Ellis et al., 2011; Martens et al., 1997; Rowley & Graham, 1968), and peak transmission occurs when mean temperature is in the 27-30°C range (Eastin et al., 2014; Johansson et al., 2009; Yang et al., 2009). Studies specific to dengue in Puerto Rico find that rainfall is strongly associated with mosquito density, especially in the dry south-coastal part of the island. (Johansson et al., 2009; Jury, 2008).

[4]The duration of larval development ranges between 7-9 days at 30-35°C and 40 days at 15°C (Delatte et al., 2009; Tun-Lin et al., 2000), the feeding frequency increases at warmer temperatures (Brunkard et al., 2008; Parker, 1952), and mosquito survival requires temperatures between 5°C and 40°C (Eastin et al., 2014), with longest lifespan at just above 20°C (Brady et al., 2013). The incubation period of the virus is also affected by temperature(Rohani et al., 2009; Tun-Lin et al., 2000; Watts et al., 1987). Water is required for egg and larva development and mosquito breeding. However, the relationship between rainfall and dengue incidence is also complex: rainfall increases areas suitable for larval habitat and vector population, but may also destroy habitats by flooding (Gubler, 2012).

2.2 Dengue during pregnancy

Dengue infections during pregnancy may lead to several types of adverse outcomes. Symptomatic dengue infections, which produce a febrile episode, pose a possible risk to the fetus (Sharma & Gulati, 1992).[5] Specifically, weeks 3-5 of gestation are critical for development of the human nervous system (Sharma & Gulati, 1992). Dengue epidemics, as well as influenza and malaria outbreaks, have been linked to higher rates of malformation of the offspring (Lynberg et al., 1994; Moretti et al., 2005; Sharma & Gulati, 1992). Maternal infections can result in a spontaneous abortion, stillbirth, or preterm birth (Goldenberg & Thompson, 2003; Kline et al., 1985; Romero et al., 2006).[7]

A systematic review of the medical literature in 2010 identifies 30 published studies on the dengue infection during pregnancy (Pouliot et al., 2010). 28 of these studies are either case reports or case series (groups of case reports), and identify elevated rates of Cesarean deliveries, preterm birth, and pre-eclampsia among women diagnosed with dengue. Two comparative studies described in the literature review, provide conflicting evidence (Restrepo et al., 2003; Tan et al., 2008), and are based on small samples. More recent studies, which are largely case series or case reports, find higher rates of fetal death due to exposure at any point during pregnancy (Gurumurthy et al., 2014; Kariyawasam & Senanayake, 2010; Singla et al., 2015), and exposure late during the gestation period is associated with greater risk of preterm births and Cesarian delivery (Gurumurthy et al., 2014; Kariyawasam & Senanayake,

[5]Elevated body temperature of the mother, or maternal hyperthermia, has been shown to cause malformations of the embryo in animal studies (Edwards, 1986; Warkany, 1986). In humans, a clear causal link has not been established as maternal hyperthermia is typically caused by a fever due to a viral or bacterial illness, which may also be harmful to the fetus, making it difficult to isolate the mechanism which leads to fetal anomalies (Moretti et al., 2005). Nonetheless, maternal hyperthermia experienced in the first trimester of pregnancy is associated with an increase in the prevalence of malformations of the fetus, with neural tube defects[6] being the most common (Chambers et al., 1998; Shaw et al., 1998).

[7]There are several potential mechanisms through which maternal infection can result in such outcomes. Either the fever due to infection or the infection itself may result in the death of the fetus and subsequent expulsion (immediate or deferred). Alternatively, it has been demonstrated that heat application has a potential to stimulate labour (Khamis et al., 1983). Therefore, fever (or its causes) may increase uterine contractions and lead to expulsion of the fetus, which may or may not be viable depending on gestational age. It is not known whether *Aedes* mosquitos, which transmit the dengue virus, have a particularly strong attraction to pregnant women, as is the case with *Anopheline* mosquitos, responsible for transmission of malaria (Carroll et al., 2007; Restrepo et al., 2003).

2010; Singla et al., 2015), as well as maternal death (Kariyawasam & Senanayake, 2010). A recent meta-analysis of the literature concludes that a dengue infection during pregnancy leads to an increase in the likelihood of pregnancy loss, preterm birth and low birthweight (Paixão et al., 2016).

The study closest to this one is Hanf et al. (2014), which uses registered births in French Guiana in the urban area of Cayenne during the 2004-2007 period to match with dengue surveillance data on the number of confirmed cases during the same period. They control for a number of maternal characteristics and find that moderate and high epidemic dengue in the first trimester is associated with higher rates of preterm birth and post-partum haemorrhage. However, the study is limited to a short time period and to a small geographical area, does not consider fetal death as an outcome, or address the issue of measurement error. As I will show, ignoring the measurement error may lead to underestimating adverse effects of dengue by several orders of magnitude.

3 Methods

3.1 Data

The main data for this study comes from individual birth records from the universe of live births in Puerto Rico during the 1990-2010 period available from Puerto Rico Department of Health.[8] Birth records contain information on gestational age, along with the month and year of birth (records before 2005 include the exact day of birth), which I use to calculate the date of conception. In addition, records include information on a rich set of infant health outcomes, along with mother's municipality of residence, mother's demographic characteristics, and use prenatal care. From the original sample of 1,134,330 I eliminate birth records with missing data for any covariates or outcomes of interest, or records that report birthweight or

[8] I omit births from 2004 as the records for this year are missing several key variables, including length of gestation.

gestation above the 99.75 percentile or below 0.25 percentile.[9] The final sample consists of 1,113,649 observations. Summary statistics for maternal characteristics and birth outcomes are presented in Table 1.

Table 1: Summary statistics

Variable	Mean	Std. Dev.
Maternal characteristics		
Age 19 and under	0.191	0.393
Age 20-34	0.734	0.442
Age 35-49	0.075	0.263
Urban	0.518	0.5
Married	0.517	0.5
White	0.919	0.273
Completed high school	0.729	0.444
Tobacco use	0.011	0.105
Alcohol use	0.001	0.038
Select pregnancy characteristics		
Birthweight (grams)	3114.112	522.23
Low birthweight	0.106	0.307
Gestation (weeks)	38.231	2.182
Preterm birth	0.146	0.353
Cesarean delivery	0.382	0.486
Length (inches)	20.077	1.405
First birth	0.427	0.495
Dengue exposure (per 1,000)		
Trimester 1	0.157	0.269
Trimester 2	0.167	0.301
Trimester 3	0.184	0.332
Months 1-9	0.508	0.664
N	1,113,649	

[9] I also drop births that were conceived late in 2010 and ended prematurely, because I am unable to define third trimester-exposure assuming normal gestation for such births.

Data on dengue incidence for years 1989-2010 comes from the Passive Dengue Surveillance System (PDSS), maintained by the Dengue Branch of Centers for Disease Control and Prevention (CDC). I use monthly positively diagnosed cases of dengue per 1,000 population as a measure of dengue exposure (defined for each municipality-month). Data on population in each municipality comes from the U.S. Census Bureau for years 1980, 1990, 2000, and 2010, and I use linear interpolation to construct estimates of population in intercensal years. Figure 1 shows the annual number of confirmed and reported cases in Puerto for years 1989-2010. On average 1'818 dengue cases are confirmed each year in non-epidemic years; during dengue epidemics the average number of cases increases to 6'049, indicating considerable variation in dengue exposure over time.[10] As illustrated in Figure 2, there is also considerable cross-sectional variation in dengue incidence, and dengue is present in each municipality, with the incidence particularly high on the west side of the centre of the island.

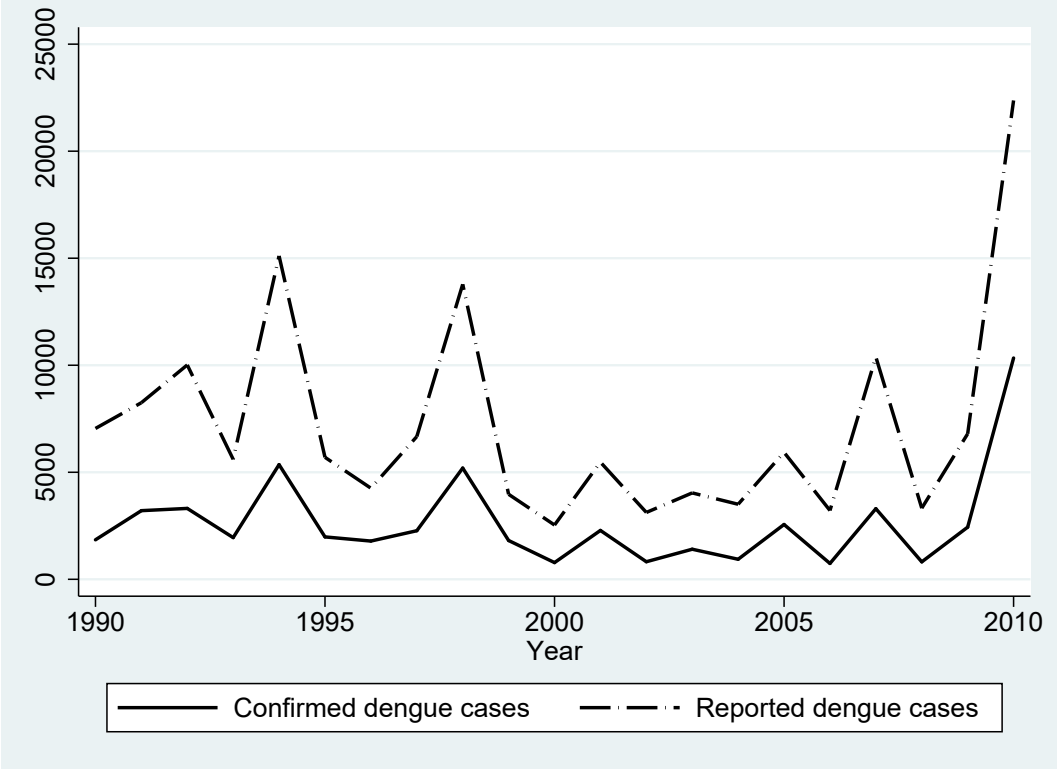
To construct a measure of dengue exposure during pregnancy, following Currie & Rossin-Slater (2013), I estimate *intended* exposure instead of relying on the reported length of gestation to avoid a bias from correlation between longer pregnancies and pregnancy outcomes. I assume that the day of birth falls on the 15th of every month[11] and calculate the date of conception using reported gestational age based on last menstrual period, less 14 days. Counting 9 months (270 days) forward to mark the intended pregnancy duration, I then create weights proportional to exposure to neighbouring calendar months for each gestation month. Dengue exposure is defined as cumulative exposure in months 1-9 of the pregnancy. Table 1 reports average dengue exposure in the bottom panel. For an average mother, 0.509 (per 1,000) dengue cases will be diagnosed in her municipality of residence during her pregnancy. Exposure increases with gestational age, but this may be an artifact of omission of miscarriages from the data.

Data on temperature and rainfall comes from the Global Historical Climatology Network.

[10] The years with a dengue outbreak are 1994, 1998, 2007, and 2010.

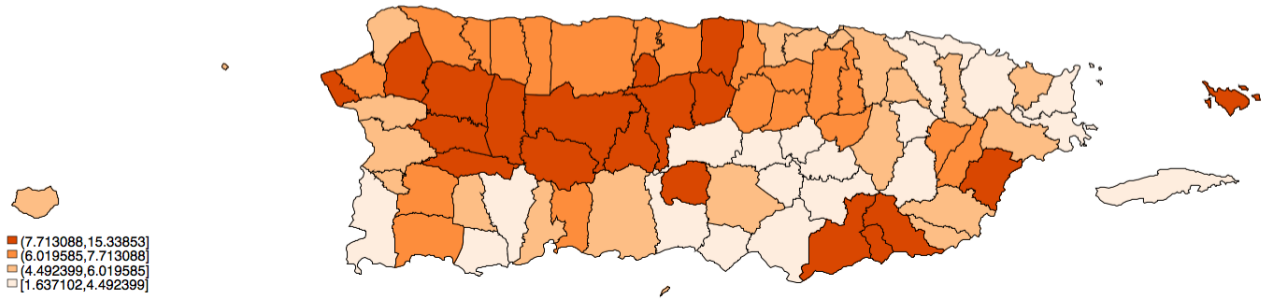
[11] In the data for 1990-2003 data that contains the exact date of birth shows, the distribution of births across days of the month is nearly uniform.

Figure 1: Annual dengue cases, 1990-2010



Source: Passive Dengue Surveillance System from the Centers for Disease Control and Prevention

Figure 2: Distribution of dengue burden

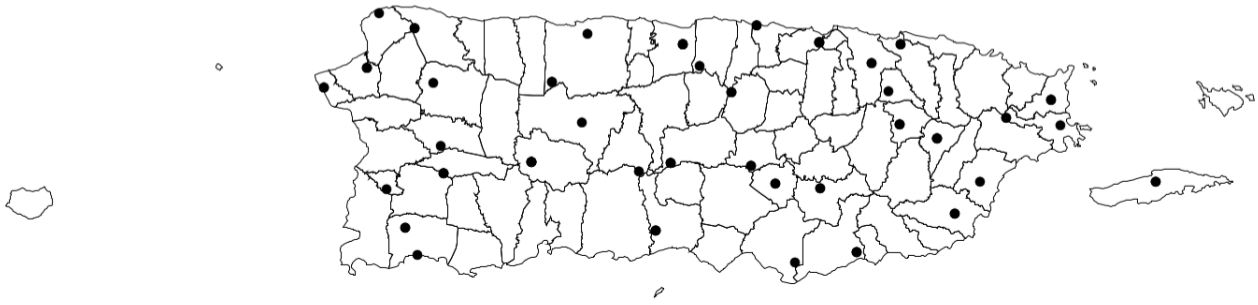


Note: This map shows average monthly confirmed dengue cases per 100,000. Source: Passive Dengue Surveillance System from the Centers for Disease Control and Prevention, 1990-2010.

Daily precipitation and max/min temperature for years 1989-2010 are available for 38 stations in Puerto Rico. Figure 3 shows the locations of these stations. I construct county weather variables from the daily weather station data by taking an inverse-distance weighted average

of the 5 closest weather-stations with non-missing observations.[12]

Figure 3: Map of weather stations



Note: This map shows location of weather stations in Puerto Rico. Source: Global Historical Climatology Network

Additional controls are unemployment rate in the month of conception (from the US Bureau of Labor Statistics), and population density, as dengue risk increases in population density due to higher rate of transmission. I arrive at the annual measure of population density by dividing annual population estimates by the land area in square miles from the 2000 Census of Population and Housing.

3.2 Empirical methodology

To study the consequences of the dengue virus on pregnancy outcomes, I examine how birth outcomes respond to *in utero* dengue exposure. I wish to estimate the following base OLS specification:

$$y_{bmy} = \beta D_{bmy} + X^b_{bmy}{}'\Gamma^b + \bar{X}^m_{bmy}{}'\Gamma^m + \alpha_b + \phi_m + \rho_y + \epsilon_{bmy}, \tag{1}$$

where y_{bmy} is mean outcome of interest for cohort bmy born in month m of year y in municipality (barrio) b, D_{bmy} is a measure of dengue exposure during pregnancy, X^b_{bmy} is a vector of municipality-level controls measured in the month of conception, such as unemployment rate and population density, $\bar{X}^m_{bmy}$ is a vector of mean maternal characteristics for

[12]Suppose there are two stations 5km and 10km away. Therefore, the weight assigned to the observation from the first station is $\frac{1/(5^2)}{1/(5^2)+1/(10^2)}$ and the weight assigned to the second station is $\frac{1/(10^2)}{1/(5^2)+1/(10^2)}$.

cohort bmy, α_b, ϕ_m and ρ_y control for municipality, month and year fixed effects, respectively, and ϵ_{bmy} is an error term.[13] However, I do not observe D_{bmy}, or true dengue exposure in the population, but instead have data on confirmed cases of dengue $D^*_{bmy} = f(D_{bmy}, u_{bmt})$ which are a function of both true dengue incidence and measurement error. For simplicity, I assume that:

$$D^*_{bmy} = D_{bmy} + u_{bmy}, \tag{2}$$

where $u_{bmy} < 0$, as confirmed cases of dengue under-report true infection rate in the population. Using D^*_{bmy} instead of D_{bmy} to estimate equation 1 means the OLS estimate $\hat{\beta}^{OLS}$ will be biased:

$$plim\ \hat{\beta}^{OLS} = \frac{\beta(\sigma^2_D + \sigma_{Du}) + \sigma_{D\epsilon} + \sigma_{u\epsilon}}{\sigma^2_D + \sigma^2_u + 2\sigma_{Du}}, \tag{3}$$

where $\sigma_{Du} = plim\frac{1}{n}(D'u)$, and other terms are similarly defined. The direction of the bias of the OLS estimator is not immediately clear.

However, under the assumptions listed below, $\hat{\beta}^{OLS}$ is biased towards 0, so that the results will understate adverse effects of dengue on pregnancy outcomes. If y_{bmy} measures a desirable or positive outcome, I expect that $\sigma_{D\epsilon} < 0$ because dengue is correlated with poverty, and poverty is negatively correlated with positive pregnancy outcomes. I also expect that $\sigma_{u\epsilon} > 0$ because I suspect that under-reporting is less prevalent (u is less negative) in the population with good pregnancy outcomes, if low-SES population is less likely to get tested for dengue. I impose the assumption that the two terms cancel each out. Next, I must impose another restriction that $\sigma^2_u + \sigma_{Du} > 0$. Although the sign of σ_{Du} is not known, $\sigma_{Du} < 0$ is consistent with the case where during a dengue outbreak the number of reported cases exceeds laboratory capacity for testing - which happened during the 1994 epidemic

[13] I estimate identical regression when studying outcomes y_{ibmy} measured at the individual level, such as birthweight, the only difference being that $\bar{X}^m_{bmy}$ is replaced with X^m_{ibmy}, or maternal characteristics are measured at the individual level.

(Rigau-Perez et al., 2001).[14]Therefore, this assumption entails that the covariance between the measurement error and the true number of dengue cases σ_{Du} cannot be negative and larger in magnitude than the variance of the measurement error σ_u^2 (Black et al., 2000). To summarize, β estimate from equation 1 is a lower bound on true value of β if the following assumptions hold: $\sigma_{Du} + \sigma_u^2 > 0$ and $\sigma_{D\epsilon} + \sigma_{u\epsilon} = 0$.

I use rainfall R as an instrumental variable to instrument for dengue exposure, estimating the following first-stage specification:

$$D^*_{bmy} = \theta R_{bmy} + X^b_{bmy}{}'\Pi^b + \bar{X}^m_{bmy}{}'\Pi^m + \omega_b + \gamma_m + \tau_y + w_{bmy}. \tag{4}$$

Substituting $\hat{D}^*{}_{bmy}$ predicted from equation 4 to estimate equation 1 means that:

$$plim(\hat{\beta}^{IV}) = \beta \frac{\sigma_{RD} + \sigma R\epsilon}{\sigma_{RD} + \sigma Ru}. \tag{5}$$

$\sigma_{R\epsilon} = 0$ if R satisfies the exclusion restriction. If rainfall is uncorrelated with under-reporting, then IV allows me to get consistent estimates of the parameter of interest. However, this assumption is unlikely to hold, given that rainfall is positively correlated with dengue and dengue is correlated with measurement error. If $\sigma_{Du} < 0$ and $\sigma_{Ru} < 0$, then β^{IV} provides an upper bound for the true value of β.[15]

I use IV and OLS results to provide upper and lower bounds for the impact of dengue exposure on pregnancy outcomes, while relying on some relatively minor assumptions. There are two important conceptual issue with this identification strategy. Because I cannot identify dengue at the individual level, municipality measure of dengue will also pick up effects of greater physical burden of caring for ill family members during an outbreak or due to loss of income because of illness, even in the absence of a maternal dengue infection. In addition,

[14]If $\sigma_{Du} > 0$, or measurement error decreases as prevalence of dengue increases - which may be the case if individuals are more aware about dengue during an outbreak and are therefore more likely to get tested, then $\sigma_u^2 + \sigma_{Du} > 0$ holds without additional assumptions. This particular mechanism seems unlikely because dengue has been endemic in Puerto Rico for three decades and in general public awareness is relatively high (Leite et al., 2014; Pérez-Guerra et al., 2005).

[15]If$\sigma_{Du} > 0$, then likely $\sigma_{Ru} > 0$, so that $\hat{\beta}^{IV}$ has the correct sign but is biased downwards, as is $\hat{\beta}^{OLS}$.

adverse effects of dengue on outcomes at birth may be dominated by the positive effect of selection on survival.[16]

4 Results

4.1 Rainfall as an IV

In order for rainfall to be a valid instrument for dengue, it must satisfy two conditions: (1) rainfall should be correlated with dengue (relevance), (2) rainfall should affect the dependent variable only through dengue (exclusion restriction). I evaluate several potential instruments based on the literature about the relationship between dengue transmission and climate variables. Specifically, I use cumulative monthly rainfall and share of days with dengue-ideal temperature, which is defined as: (1) minimum and maximum temperature within 15-32°C, or (2) mean temperature is between 27 and 30°C. Time lag between mosquito birth and symptoms in humans is 3-8 weeks (Eastin et al., 2014) and larval development can last 7-40 days (Tun-Lin et al., 2000; Wu et al., 2007), suggesting that effects of climate variables can operate with a lag of up to 96 days. Previous studies found that the effects of climate variables operate with a lag of anywhere between 1 week to 4 months (Barrera et al., 2011; Brunkard et al., 2008; Chen et al., 2010; Rosa-Freitas et al., 2006; Wu et al., 2007). Therefore, I focus on the first four lags of climate variables as potential instruments for dengue incidence. First stage results, where I estimate Equation 4 with various instrumental variables in place of R_{bmy}, are shown in Table 2. Generally, they indicate that both rainfall and share of days with dengue-ideal temperatures are correlated with confirmed dengue cases. F-statistic on the first-stage model is the highest at 29 for the specification using second lag of cumulative monthly rainfall (column 3, third panel down). This F-statistic exceeds the critical value for

[16] One may be concerned that rainfall may also be correlated with incidence of other mosquito-born illnesses, such as Zika virus or chickengunya, which produce pregnancy effects similar to dengue. However, Zika and chickungunya were not present in Puerto Rico during the period of analysis (the first case of chickungunya in Puerto Rico was diagnosed in 2014 (Sharp et al., 2014) and Zika did not appear until 2016 (Hennessey et al., 2016)).

the weak instrument test from Staiger & Stock (1994); Stock & Yogo (2002), suggesting that second lag of cumulative monthly rainfall is a strong predictor of confirmed dengue cases. Despite that temperature is an important determinant of dengue incidence in climate-based models, the specifications using share days with dengue ideal temperature as a predictor for positive dengue cases have relatively low F-statistics. However, this result is not unexpected given that climate in Puerto Rico is relatively mild and on average about 25 days a month have temperature 18-32°C, suggesting not much variation in the independent variable.

I also present suggestive evidence that rainfall does not violate the exclusion restriction. One may be concerned that rainfall influences income, which in turn affects birth outcomes. While this is likely true in the context of a developing country, where rainfall may influence agricultural productivity, income, and birth outcomes, in Puerto Rico agriculture is not a main source of income, contributing less than 1% to the national GDP. However, rainfall may still be correlated with other climate variables that affect outcomes of interest independently of dengue, thus violating the exclusion restriction. I show that there are no effects of rainfall on outcomes of interest using data from areas where dengue is not prevalent, using publicly available NCHS Vital Statistics Natality Birth Data for years 1990-2004 for the U.S.[17] In order to examine the effects of rainfall in climate comparable to Puerto Rico, I restrict the analysis to counties where average minimum and average maximum temperatures do not fall outside of 0-40°C range. Publicly available natality files report county identifiers only for counties with population of at least 100,000 (there are approximately 500 counties identified in the data); imposing the climate restriction leaves 80 counties in the continental U.S. sample. Table 3 reports reduced-form estimates for both Puerto Rico and U.S. samples, where I regress select outcomes of interest on prenatal exposure to rainfall. In Puerto Rico rainfall has a strong and negative effect on birth rate:[18] each additional mm of rainfall during the gestation period is associated with a 0.0008 reduction in birth rate with s.e. of 0.0001

[17]The data are downloaded from http://www.nber.org/data/vital-statistics-natality-data.html on March 7, 2018. Starting from 2005, no geographical information is provided in publicly available records, which does not allow me to link climate data to birth outcomes.

[18]Birth rate is defined as births per 1,000 population.

Table 2: First-stage estimates, dependent variable: monthly confirmed cases of dengue (per 1,000)

	(1) No lag	(2) Lag 1	(3) Lag 2	(4) Lag 3	(5) Lag 4
Share days with temp. 15-32°C	-0.0317	-0.0374*	-0.0835***	-0.0258	0.00479
	(0.0202)	(0.0217)	(0.0247)	(0.0211)	(0.0252)
R-squared	0.163	0.164	0.165	0.163	0.163
F-stat	2.466	2.971	11.45	1.504	0.0361
Share days with temp. 27-30°C	0.0239	0.0258	0.0515***	0.0294	-0.0391**
	(0.0168)	(0.0167)	(0.0195)	(0.0204)	(0.0178)
R-squared	0.163	0.164	0.165	0.164	0.164
F-stat	2.012	2.386	6.996	2.083	4.856
Rainfall (mm)	-0.000175	-4.30e-05	0.000642***	-0.000418**	0.000506***
	(0.000134)	(0.000207)	(0.000119)	(0.000161)	(0.000177)
R-squared	0.163	0.163	0.164	0.163	0.163
F-stat	1.707	0.0432	29.03	6.756	8.180
Rainfall (mm)	0.00161***	-0.00102	0.00151***	-0.000751*	-0.000179
	(0.000461)	(0.000709)	(0.000423)	(0.000424)	(0.000495)
Rainfall (mm) squared	-4.09e-05***	2.26e-05	-2.01e-05**	7.76e-06	1.58e-05
	(1.08e-05)	(1.95e-05)	(9.91e-06)	(7.80e-06)	(1.29e-05)
R-squared	0.164	0.163	0.164	0.163	0.164
F-stat	7.273	1.886	19.08	3.373	4.142
Share days with temp. 15-32°C	-0.0310	-0.0375*	-0.0878***	-0.0238	0.00220
	(0.0202)	(0.0216)	(0.0246)	(0.0210)	(0.0253)
Rainfall (mm)	-0.000137	9.05e-06	0.000765***	-0.000386**	0.000503***
	(0.000135)	(0.000203)	(0.000118)	(0.000157)	(0.000179)
R-squared	0.163	0.164	0.166	0.164	0.163
F-stat	1.914	1.505	26.40	3.505	4.090
Observations			19344		

This table shows estimates of the relationship between various monthly climate variables and dengue incidence. Robust standard errors in parentheses, clustered by municipality. * $p < 0.10$, ** $p < 0.05$, *** $p < 0.01$

(column 1). In contrast, the results suggest no such relationship in the U.S. sample (column 2). Similarly, estimating effects of rainfall on birthweight produces estimates of the opposite sign in the two samples, as shown in the last two columns, and although neither estimate is statistically significant, it is negative in the Puerto Rico sample and positive in the U.S. sample. Overall, reduced form results do not suggest that rainfall has an effect on pregnancy outcomes independent of dengue, indicating that it is unlikely to fail the exclusion restriction.

Table 3: Reduced-form estimates of rainfall exposure on pregnancy outcomes - U.S. and Puerto Rico

	(1)	(2)	(3)	(4)
VARIABLES	Birth rate (per 1,000)		Birthweight (gr)	
	P.R.	U.S.	P.R.	U.S.
Rainfall (mm)	-0.000803***	0.000102	-0.0522	0.0207
	(0.000100)	(0.000226)	(0.0494)	(0.0397)
Mean	1.250	1.082	3128	3283
Observations	18,692	11,155	1,112,991	4,310,315
R-squared	0.639	0.683	0.070	0.150 0

Note: This table reports coefficients from the regressions of dependent variables on prenatal exposure to (second lag) of cumulative prenatal exposure to rainfall, where total prenatal exposure to rainfall is calculated assuming 9-month gestation from the date of conception. Puerto Rico sample includes all births in years 1990-2010, excluding 2004, subject to sample selection criteria described in Section 3.1. U.S. sample consists of births from municipalities larger than 100,000 with minimum and maximum average temperatures within 0-40°C for years 1990-2004. All regressions include controls for municipality/county, year, and month of birth fixed effects, unemployment and population density in the month of conception, and maternal characteristics, and are weighted by the underlying county/municipality population. Robust standard errors are in parentheses, clustered by municipality. * $p < 0.10$, ** $p < 0.05$, *** $p < 0.01$

4.2 Birth rates

Having established that second lag of cumulative monthly rainfall is a valid instrument for dengue, I next examine effects of dengue on birth rates, using both OLS and IV approaches. The top panel of Table 4 reports various estimates of the effect of dengue exposure during pregnancy on monthly birth rate from equation 1, where birth rate is defined as the number of live births per 1,000 population and prenatal dengue exposure is defined as the cumulative number of confirmed dengue cases per 1,000 population diagnosed in 9 months after the estimated date of conception. The first column presents estimate of $\hat{\beta}^{OLS}$. An additional case of dengue per 1,000 is associated with a 0.019 fewer births per 1,000 (s.e. 0.003). The estimate of $\hat{\beta}^{IV}$ shown in column 2 is almost 7 times as large (-0.13 with s.e. of 0.021). [19]

The negative relationship between dengue exposure and birth rate may reflect several mechanisms other than fetal death. Dengue exposure prior to conception may lead to lower frequency of sexual intercourse, or greater difficulty conceiving during illness. Also, if mothers intentionally avoid conception in months with high risk of dengue exposure (either because it is harmful to fetal health or they have a more difficult time during pregnancy when ill), then the negative effect of dengue exposure early in the gestation period may simply reflect avoidance behaviour by mothers. Given that the exact date of conception is not observed, there is a possibility that dengue exposure in the first month of pregnancy may capture pre-conception exposure. Therefore, ignoring dengue exposure in month 1 of pregnancy prevents counting "lost" births that are due to decline in intercourse, lower fecundity, or intentional avoidance by mothers. This approach, which is my preferred specification, yields almost identical OLS and IV estimates as when month 1 exposure is included in total prenatal exposure (results reported in columns 3 and 4).

[19] Observations are weighted by municipality population size. Results without weights are virtually identical. For example, using specifications in columns 1 and 2, unweighted regressions yield point estimates of -0.0158 for OLS and -0.168 for IV.

Table 4: Effects of prenatal dengue exposure on birth rate

	(1) OLS	(2) IV	(3) OLS	(4) IV	(5) OLS	(6) IV	(7) OLS	(8) IV	(9) OLS	(10) IV
					Dependent variable: births per month per 1,000					
Dengue Exposure	-0.0190***	-0.130***	-0.0203***	-0.142***	-0.0203***	-0.155***	-0.0252***	-0.179***	-0.0202***	-0.146***
	(0.00325)	(0.0209)	(0.00355)	(0.0205)	(0.00344)	(0.0212)	(0.00425)	(0.0240)	(0.00362)	(0.0210)
Mean of dep. var.	1.251	1.251	1.251	1.251	1.251	1.251	1.251	1.251	1.251	1.251
Observations	18,692	18,692	18,692	18,692	18,692	18,692	18,692	18,692	18,692	18,692
R-squared	0.641	0.595	0.641	0.592	0.652	0.596	0.687	0.641	0.658	0.607
Exclude month 1 exposure			X	X	X	X	X	X	X	
Municipality										
linear trends					X	X				
-year effects							X	X		
-month effects									X	X

Note: Dengue exposure is measured as the total number of laboratory-confirmed cases of dengue per 1,000 diagnosed during the gestation period in mother's municipality of residence. All regressions include controls for municipality/county, year, and month of birth fixed effects, unemployment and population density in the month of conception, and maternal characteristics, and are weighted by the underlying county/municipality population. Robust standard errors are in parentheses, clustered by municipality. * $p < 0.10$, ** $p < 0.05$, *** $p < 0.01$

Because treatment does not vary at the individual level, a potential concern with these estimates is that they may pick up municipality-specific time-varying heterogeneity in birth rates, rather than effects of dengue specifically. I estimate alternative specifications with additional controls to account for municipality-specific variation in the dependent variable over time: I add municipality linear trends (columns 5 and 6) and municipality-year effects (columns 7 and 8), which allow for more flexibility. Both OLS and IV estimates slightly increase in magnitude (to 0.0250 and 0.195, respectively), but overall remain robust to alternative specifications.

In the remaining two columns I report estimates from models where I control for municipality-month effects. All regressions include month fixed effects, which account for seasonal differences in pregnancy outcomes. The seasonal differences reflect both the causal effect of seasonal environmental factors and selection effects, if mothers whose gestation does not overlap with dengue season differ from mothers whose pregnancy overlaps with dengue season. However, seasonal effects may differ across municipalities if mothers whose pregnancy overlaps with dengue season in high exposure municipalities are different from mothers who conceive at the same time but in low exposure municipalities. Seasonal environmental effects may also differ across municipalities. Adding municipality-month effects controls for municipality-specific seasonal variation in pregnancy outcomes; however the difference in the estimated coefficients in negligible from the specifications where I do not control for municipality-month effects.

Generally, estimating equation 1 by OLS and IV suggests that exposure to dengue has a negative and statistically significant effect on birth rates, with point estimates robust to controlling for municipality-specific time-varying change in the birth rate, as well as differential seasonal effects across municipalities.

Back of the envelope calculations suggest that in an average Puerto Rico municipality in a given month there are 1-6 percent fewer births due to dengue exposure compared to a

municipality with no dengue.[20] They also suggest that pregnancy loss due to dengue infection occurs in at least 15% of infections among pregnant women, and this includes asymptomatic infections as well, which have largely been ignored in the literature.[21] Assuming that risk of miscarriage is about 15% in a healthy pregnancy, these results imply an odds ratio of 2+ for women with a dengue infection (with or without symptoms) compared to an odds ratio of 3.5 (confidence interval 1.15 - 10.77) calculated in a recent meta-study (Paixão et al., 2016).

4.3 Birth outcomes

Next, I evaluate effects of prenatal dengue exposure on several measures of prenatal health, using the sample of all individual birth records. Table 5 shows that increase in prenatal dengue exposure by 1 more case per 1,000 shortens gestation by 0.016 to 0.196 weeks, or 0.1-1.4 days, with both OLS and IV estimates statistically significant. However, the results suggest no effect on the fraction of births that are full-term, or the share of births that are male is affected by dengue exposure.[22]

I also examine trimester-specific effects of prenatal dengue exposure on pregnancy outcomes in Table 6. The results in columns 1 and 2, where birth rate is the dependent variable, clearly indicate that the negative effects of dengue exposure are concentrated in the second trimester, while effects of the first and third trimester exposure are both small and not statistically significant. For individual-level outcomes, the OLS and IV coefficients are generally not consistent with each other and sometimes have opposite signs, making it difficult to draw

[20] Average exposure to dengue during pregnancy is 0.5 per 1,000 (Table 1), which means that average effect is 0.01 to 0.07 fewer births per 1,000, using point estimates from columns 3 and 4 in Table 4. Relative to the mean of 1.251 births per 1,000, these effects imply a 0.8-5.6 percent reduction in birth rate.

[21] I arrive at these numbers the following way. If I assume that the infection rates among pregnant women are the same as in the general population, then the estimated coefficients imply that there are 0.001251 infected pregnant women (given the mean of 1.251) but 0.02 to 0.14 fewer births. However, dengue is underreported, and in Puerto Rico specifically, it was been estimated that there are 21-115 infections infections for each laboratory-diagnosed case of dengue Bhatt et al. (2013); Shankar et al. (2018). Using the upper bound for the multiplication factor suggests each additional diagnosed dengue case actually represents 0.14 infected pregnant women, implying that the risk of pregnancy loss occurs in at least 15% of all infected pregnancies (using the estimate from Bhatt et al. (2013) who calculate an multiplication factor of 52 increases minimum risk up to 30%).

[22] Male fetus is more vulnerable *in utero* (Kraemer, 2000), so that the share of births that are male can serve as a proxy for pregnancy health at the population level.

Table 5: Effects of prenatal dengue exposure on pregnancy outcomes

	(1)	(2)	(3)	(4)	(5)	(6)
	Gestation (weeks)		Full-term		Male	
VARIABLES	OLS	IV	OLS	IV	OLS	IV
Exposure	-0.0159**	-0.196***	-0.255	-1.826	0.0414	0.201
	(0.00626)	(0.0685)	(0.153)	(1.162)	(0.105)	(0.609)
Mean of dep. var.	38.22	38.22	49.35	49.35	51.37	51.37
Observations	1,113,649	1,113,649	1,113,649	1,113,649	1,113,649	1,113,649
R-squared	0.070	0.068	0.075	0.075	0.000	0.000
Excluding month 1	X	X	X	X	X	X

Note: Dengue exposure is measured as the total number of laboratory-confirmed cases of dengue per 1,000 diagnosed during the gestation period in mother's municipality of residence. Binary outcomes are multiplied by 100. All regressions include controls for municipality/county, year, and month of birth fixed effects, unemployment and population density in the month of conception, and maternal characteristics, and are weighted by the underlying county/municipality population. Robust standard errors are in parentheses, clustered by municipality. * $p < 0.10$, ** $p < 0.05$, *** $p < 0.01$

conclusions.

Table 6: Effects of prenatal dengue exposure on pregnancy outcomes, by trimester

	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)
	Birth rate		Full-term		Male		Gestation	
VARIABLES	OLS	IV	OLS	IV	OLS	IV	OLS	IV
Trimester 1 exposure	-0.0111	-0.242	0.0389**	-1.210*	0.966**	-24.75**	-0.217	-7.096
	(0.00836)	(0.281)	(0.0154)	(0.699)	(0.432)	(12.62)	(0.312)	(11.16)
Trimester 2 exposure	-0.0375***	-0.243**	-0.0391***	0.440	-0.962***	12.08*	-0.0107	2.097
	(0.00778)	(0.120)	(0.0138)	(0.309)	(0.324)	(6.679)	(0.262)	(5.229)
Trimester 3 exposure	-0.00538	0.123	-0.0166*	-0.976***	-0.0636	-17.59***	0.216	5.018**
	(0.00599)	(0.0875)	(0.00971)	(0.150)	(0.252)	(2.738)	(0.203)	(1.961)
Mean of dep. var.	1.251	1.251	38.22	38.22	49.35	49.35	51.37	51.37
Observations	18,692	18,692	1,113,649	1,113,649	1,113,649	1,113,649	1,113,649	1,113,649
R-squared	0.653	0.587	0.070	0.050	0.075	0.062	0.000	
Excluding month 1	X	X	X	X	X	X	X	X

Note: Dengue exposure in each trimester is measured as the total number of laboratory-confirmed cases of dengue per 1,000 diagnosed during the the trimester in mother's municipality of residence. Binary outcomes are multiplied by 100. All regressions include controls for municipality/county, year, and month of birth fixed effects, unemployment and population density in the month of conception, and maternal characteristics, and are weighted by the underlying county/municipality population. Robust standard errors are in parentheses, clustered by municipality. * $p < 0.10$, ** $p < 0.05$, *** $p < 0.01$

I briefly review the evidence on the consequences of prenatal dengue exposure on birth outcomes in Table 7. Restricting the sample to only full-term births allows me to focus on effects of dengue exposure net of effects which operate through a decrease in gestation below full-term. I also include a control for birth rate in the regression as a way to account for selection effects since the adverse effects of dengue on infant health may be dominated by positive selection on survival. The results reported in the top panel indicate that even among full-term pregnancies, exposure to dengue during the gestation period leads to a decline in birthweight, increase the share of births that are very low birthweight, and a decrease in infant length, although these coefficients are not precisely estimated. The estimates in the bottom panel suggest no statistically significant effect of dengue exposure during pregnancy on gestation length, the likelihood of a C-section, or incidence of neurological disorders (among full-term pregnancies). Estimating of trimester-specific effects (Table 8) indicate that the negative effects on birth outcomes are driven by exposure in mid- and late gestation, though again most of the coefficients are not statistically different form zero.

Table 7: Effects of prenatal dengue exposure on infant health

	(1) OLS	(2) IV	(3) OLS	(4) IV	(5) OLS	(6) IV	(7) OLS	(8) IV
	Birthweight		Low birthweight		Very low birthweight		Length	
Exposure	-2.322*	-23.32	0.0342	-0.128	0.0114	0.189*	-0.0137*	-0.169
	(1.205)	(21.14)	(0.0463)	(0.688)	(0.00689)	(0.100)	(0.00751)	(0.104)
Mean of dep. var.	3282	3282	3.525	3.525	0.0741	0.0741	20.48	20.48
Observations	549,598	549,598	549,598	549,598	549,598	549,598	549,598	549,598
R-squared	0.031	0.031	0.021	0.021	0.003	0.001	0.088	0.083
Excluding month 1	X	X	X	X	X	X	X	X
	Gestation (weeks)		C-section		Anencephaly		Spina Bifida	
Exposure	0.00419	-0.0639	-0.0629	-1.615	-0.00185	-0.0121	-0.00484*	-0.0299
	(0.00432)	(0.0559)	(0.144)	(4.216)	(0.00160)	(0.0249)	(0.00291)	(0.0430)
Mean of dep. var.	39.79	39.79	33.82	33.82	0.00655	0.00655	0.0129	0.0129
Observations	549,598	549,598	549,598	549,598	549,598	549,598	549,598	549,598
R-squared	0.031	0.029	0.066	0.066	0.000	0.000	0.000	0.000
Excluding month 1	X	X	X	X	X	X	X	X

Note: Dengue exposure is measured as the total number of laboratory-confirmed cases of dengue per 1,000 diagnosed during the gestation period in mother's municipality of residence. Binary outcomes are multiplied by 100. All regressions include controls for municipality/county, year, and month of birth fixed effects, unemployment and population density in the month of conception, and maternal characteristics, and are weighted by the underlying county/municipality population. Robust standard errors are in parentheses, clustered by municipality. * $p < 0.10$, ** $p < 0.05$, *** $p < 0.01$

Table 8: Effects of prenatal dengue exposure on infant health, by trimester

	(1) OLS	(2) IV	(3) OLS	(4) IV	(5) OLS	(6) IV	(7) OLS	(8) IV
	Birthweight		Low birthweight		Very low birthweight		Length	
Trimester 1 exposure	-1.405	-48.90	-0.137	-3.112	0.0655*	0.247	-0.0219	-0.358
	(4.230)	(132.0)	(0.137)	(5.564)	(0.0366)	(0.893)	(0.0185)	(0.393)
Trimester 2 exposure	-1.838	-16.75	0.146	1.598	-0.0210	0.169	-0.00435	-0.0596
	(2.300)	(70.79)	(0.107)	(3.231)	(0.0152)	(0.468)	(0.00847)	(0.252)
Trimester 3 exposure	-3.272	29.41	-0.00526	0.167	0.0210	0.106	-0.0199**	-0.155
	(2.080)	(56.09)	(0.0888)	(2.046)	(0.0206)	(0.363)	(0.00943)	(0.224)
Mean of dep. var.	3282	3282	3.525	3.525	0.0741	0.0741	20.48	20.48
Observations	549,598	549,598	549,598	549,598	549,598	549,598	549,598	549,598
R-squared	0.031	0.030	0.021	0.020	0.003	0.002	0.088	0.083
	Gestation (weeks)		C-section		Anencephaly		Spina Bifida	
Trimester 1 exposure	0.00238	-1.718*	1.074**	-0.436	-0.00324	0.195	0.00309	0.379
	(0.00983)	(0.893)	(0.457)	(16.08)	(0.00608)	(0.257)	(0.00912)	(0.456)
Trimester 2 exposure	-0.000534	0.844*	-0.202	-2.433	-0.00421	-0.135	-0.00428	-0.276
	(0.00559)	(0.441)	(0.267)	(10.59)	(0.00319)	(0.150)	(0.00438)	(0.237)
Trimester 3 exposure	0.0101	0.399	-0.447*	-0.905	0.00134	-0.0108	-0.00918*	-0.0112
	(0.00759)	(0.304)	(0.240)	(8.582)	(0.00296)	(0.0853)	(0.00531)	(0.138)
Mean of dep. var.	33.82	33.82	39.80	39.80	0.00654	0.00654	0.0129	0.0129
Observations	549,598	549,598	549,598	549,598	549,598	549,598	549,598	549,598
R-squared	0.031		0.066	0.066	0.000		0.000	
Excluding month 1	X	X	X	X	X	X	X	X

Note: Dengue exposure in each trimester is measured as the total number of laboratory-confirmed cases of dengue per 1,000 diagnosed during the the trimester in mother's municipality of residence. Binary outcomes are multiplied by 100. All regressions include controls for municipality/county, year, and month of birth fixed effects, unemployment and population density in the month of conception, and maternal characteristics, and are weighted by the underlying county/municipality population. Robust standard errors are in parentheses, clustered by municipality. * $p < 0.10$, ** $p < 0.05$, *** $p < 0.01$

4.4 Robustness checks

I assess the sensitivity of the estimated coefficients, using birth rate as the dependent variable in Table 9. First, I add back in the births I dropped when creating the estimating sample, but the coefficients change little indicating that sample selection is not driving the results I observe in the data. In the next two columns I include a control for the number of prenatal care visits. If during a dengue outbreak, the healthcare system is over-burned with dengue patients and pregnant mothers receive different medical care than they would have otherwise, which may produce the effects I observe in the data. Though it should be noted this channel seems unlikely since a typical dengue case does not require hospitalization. Indeed, controlling for prenatal care use has negligible impact on the estimated coefficients. In the last two columns, I exclude births from years with a dengue outbreak (1994, 1998, 2007, 2010). If during an epidemic pesticides are used and if they adversely impact prenatal health, or if dengue epidemics (and rainfall) are correlated with hurricanes, then excluding these years from the estimating sample should produce a null estimated effect. The estimated OLS effect changes little, but the estimate of β^{IV} is 3 times as large as comparing to the coefficient in column 4 of Table 4. In the bottom panel, I investigate whether dropping any particular epidemic year yields the change in the IV estimates. The magnitude of the estimated coefficients is quite stable, and all point estimates are statistically significant (the only exception is the IV estimate in the last column, where coefficient is 1.5 times as large compared to others). I conclude that no particular outbreak year drives the results.

Finally, I use a placebo dataset with dengue or rainfall to test whether placebo effects can re-produce the main point estimates. I create a dataset at month-municipality level with placebo distribution for dengue exposure which has the same mean and deviation as the true distribution, and estimate equation 1 using this dataset. Repeating this process 1,000 times, I plot the distribution of the estimated placebo effects in the top panel of Figure 4. The distribution of the placebo estimate is centred around zero, while the point estimate from this study to the far left of the distribution. I repeat this exercise with placebo rainfall

exposure, and use them to estimate equation 4, with real dengue cases as the dependent variable. The distribution of the coefficients from these models is shown in the bottom panel. Placebo first-stage estimates also centre around 0, while the true coefficient estimate lies at the right tail.

5 Conclusion

Dengue is one of the most prevalent mosquito-borne viral diseases in the world. To date, the evidence on the consequences of dengue exposure during pregnancy for a typical dengue infection is limited. Using data on all live births in Puerto Rico for years 1990-2010, linked with data on dengue prevalence at the local level, I examine effects of prenatal exposure to dengue on birth rate and several outcomes at birth. I find that exposure to dengue during pregnancy is associated with a reduction in birth rate: pregnancy loss occurs in at least 15 % of all infected pregnancies. Unlike most existing studies, I provide estimates for effects of a typical infection, which includes both symptomatic and asymptomatic infections. My results suggest that there are 1-6% fewer births due to dengue exposure. Importantly, my results do not indicate that a typical infection is linked to a greater risk of Cesarean delivery, indicating that this finding is limited to more severe symptomatic cases.

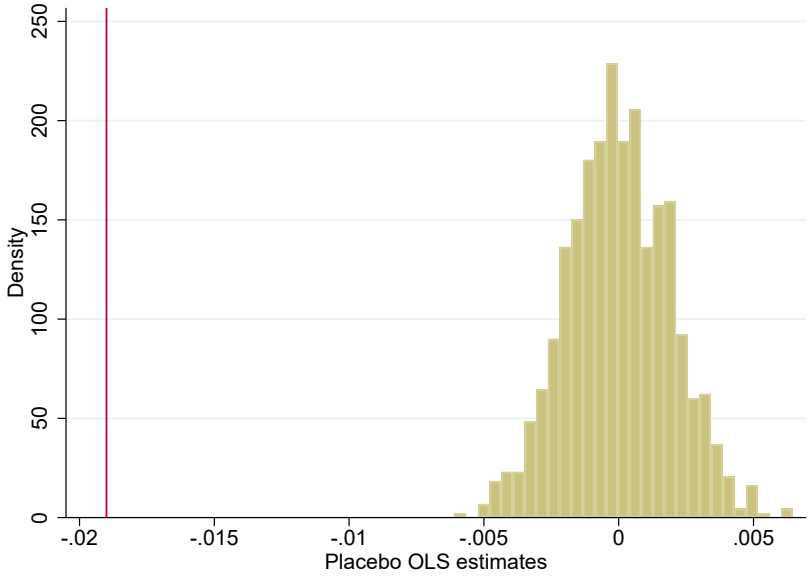
Table 9: Robustness checks

VARIABLES	(1) OLS	(2) IV	(3) OLS	(4) IV	(5) OLS	(6) IV	(7) OLS	(8) IV
Exposure	-0.0193***	-0.141***	-0.0344***	-0.284***	-0.0204***	-0.141***	-0.0146***	-0.438
	(0.00342)	(0.0208)	(0.00723)	(0.0551)	(0.00363)	(0.0206)	(0.00472)	(0.316)
Mean of dep. var.	1.247	1.247	1.255	1.255	1.251	1.251	1.251	1.251
Observations	18,693	18,693	16,823	16,823	18,692	18,692	14,956	14,956
R-squared	0.644	0.597	0.644	0.600	0.641	0.594	0.626	0.205
All births in the raw data	X	X						
Exclude >90p. dengue			X	X				
Control for prenatal care					X	X		
Drop epidemic years							X	X
Exclude month 1	X	X	X	X	X	X	X	X
Exposure	-0.0202***	-0.128***	-0.0216***	-0.130***	-0.0201***	-0.142***	-0.0160***	-0.329***
	(0.00403)	(0.0176)	(0.00375)	(0.0214)	(0.00376)	(0.0211)	(0.00384)	(0.123)
Mean of dep. var.	1.251	1.251	1.251	1.251	1.251	1.251	1.251	1.251
Observations	17,757	17,757	17,758	17,758	17,758	17,758	17,759	17,759
R-squared	0.641	0.604	0.649	0.612	0.636	0.586	0.623	0.362
Drop births in 1994	X	X						
Drop births in 1998			X	X				
Drop births in 2007					X	X		
Drop births in 2010								
Exclude month 1	X	X	X	X	X	X	X	X

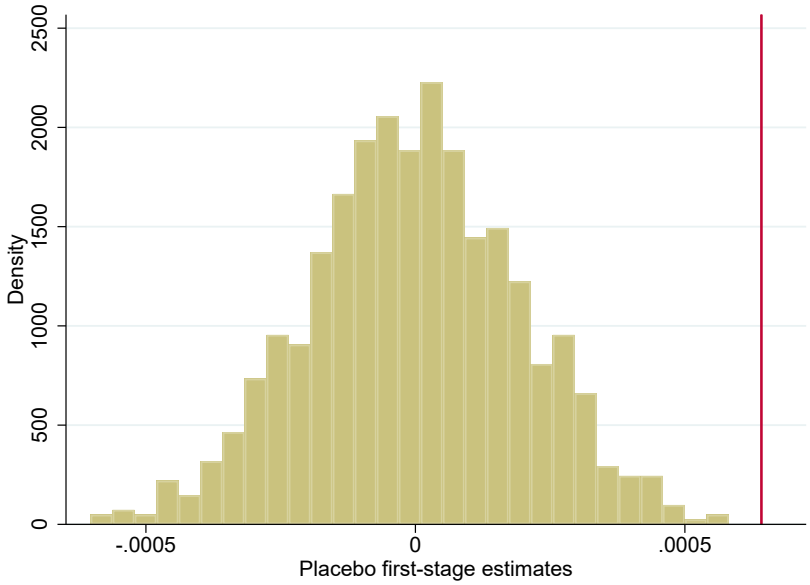
Note: Dengue exposure is measured as the total number of laboratory-confirmed cases of dengue per 1,000 diagnosed during the gestation period in mother's municipality of residence. Binary outcomes are multiplied by 100. All regressions include controls for municipality/county, year, and month of birth fixed effects, unemployment and population density in the month of conception, and maternal characteristics, and are weighted by the underlying county/municipality population. Robust standard errors are in parentheses, clustered by municipality. * $p < 0.10$, ** $p < 0.05$, *** $p < 0.01$

Figure 4: Placebo effects

Estimates of β^{OLS} from equation 1 using placebo dengue exposure



Estimates of θ from equation 4 using placebo dengue exposure



Note: The top panel shows the distribution of 1,000 estimated coefficients from equation 1, where placebo dengue distribution matches the mean and standard deviation of confirmed dengue cases. The vertical red line indicates the estimated effect from column 1 from Table 4. The bottom panel shows the distribution of 1,000 estimated coefficients from equation 4, where placebo rainfall distribution matches the mean and standard deviation of second lag of monthly rainfall. The vertical red line indicates the estimated effect from column 3, third panel down, from Table 2.

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