Zika Virus: Endemic Versus Epidemic Dynamics and Implications for Disease Spread in the Americas

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Abstract:

Since being introduced into Brazil in 2014, Zika virus (ZIKV) has spread explosively across Central and South America. Although the symptoms of ZIKV are generally mild, recent evidence suggests a relationship between prenatal exposure to ZIKV and microcephaly. This has led to widespread panic, including travel alerts and warnings to avoid pregnancy. Because ZIKV is an emerging disease, response efforts are complicated by limited understanding of disease dynamics. To this end, we develop a novel state- and class-structured compartment model for ZIKV. Our model shows that the risk of prenatal ZIKV exposure should decrease dramatically following the initial wave of disease, reaching almost undetectable levels in endemic systems. Our model also suggests that efforts to reduce ZIKV prenatal exposures through mosquito management and avoidance may have minimal benefit, and may even result in increased risk of microcephaly in later years of an outbreak.

After being discovered in Ugandan forests in 1947[1], Zika virus (ZIKV) remained a relatively minor arboviral disease for 60 years[2]. In 2007, however, an outbreak of ZIKV on Yap Island[3] in the Pacific Ocean signaled spread of the virus beyond its historic range[2-4]. From Yap Island, ZIKV was transported to French Polynesia in 2013[5] and then on to Brazil in 2014[6-8]. Once in Brazil, the virus took off, 'spreading explosively'[9] throughout both South and Central America. By early 2016, for example, local transmission of ZIKV had been reported in 20 countries and territories in the Americas[10]. Initially, ZIKV was not viewed as a significant public health threat. Indeed, with a negligible mortality rate and symptoms resembling a mild form of dengue (DENV)[2], the ZIKV outbreak appeared to be more of a nuisance than a public health emergency. In November 2015, however, alarms were raised about a potential connection between ZIKV transmission and increasing rates of newborn microcephaly[11].

Currently, the link between ZIKV and microcephaly is only postulated, not proven[12]. Nevertheless, the >20-fold increase in microcephaly in regions of Brazil where ZIKV is spreading[13] has been enough to initiate drastic precautionary action. The United States Centers for Disease Control (CDC), for example, posted a travel alert recommending that pregnant women avoid regions in the Caribbean and Latin America where ZIKV transmission is ongoing[14]. Meanwhile, public health officials in El Salvador and Colombia have suggested that women delay pregnancy up to two years until ZIKV outbreaks can be controlled[15].

Like other viruses in the genus *Flavivirus*, for example DENV, West Nile Virus (WNV) and Yellow Fever Virus (YFV), ZIKV is spread by mosquitoes. For ZIKV, the primary vectors appear to be members of the genus *Aedes*[16], including the notorious *Ae. aegypti*. This is of concern because *Aedes* species are widespread in warmer temperate and tropical regions[17,18]. In addition, although chemical larvicides and adulticides are somewhat effective at reducing certain *Aedes* populations, these mosquitoes can reproduce in very small containers of standing water.

This makes complete eradication difficult[19], casting doubt on claims that mosquitoes can be controlled sufficiently to stop ZIKV transmission.

One puzzling aspect of the recent ZIKV outbreak in South/Central America is why correlation is only now emerging between prenatal exposure to ZIKV and microcephaly. ZIKV is not a particularly new disease. In fact, phylogenetic analyses indicate that ZIKV has likely been circulating in Africa and parts of Asia for approximately 100 years[20]. Why, then, has microcephaly not been reported in African/Asian countries at the same alarming rates currently making headlines in Brazil? Assuming that there is a link between ZIKV and microcephaly, there are several potential explanations. First, there may be under-reporting of microcephaly in Africa/Asia, making tracking of microcephaly difficult and complicating comparison to the situation in South/Central America. Second, the ZIKV strain currently circulating in the Americas, which is derived from a more recently evolved Asian lineage[8,21], might be associated with more severe complications, including microcephaly. Third, intrinsic differences may exist between African/Asian and American populations, and this might modify either the extent of ZIKV spread or the risk of severe ZIKV complications. Population-wide differences could, for example, reflect genetic predisposition[22]. Alternatively, differences in microcephaly incidence may indicate differing immunological statuses of people in the two regions, and this might be a function of previous exposure to ZIKV or other related diseases.

Without knowing why disease epidemiology differs between South/Central America versus Africa/Asia, it is difficult to predict how the ZIKV outbreak will progress. Epidemiological modeling is a powerful tool that has previously proven useful for understanding the spread and dynamics of other vector-borne diseases, including other flaviviruses[23,24]. Here, we construct a compartment model (see Supplemental Information I, Figure S1) to describe ZIKV transmission, both in countries where the disease is endemic, and in countries where the disease has been newly introduced. In contrast to most other disease models, we use an age- and class-structured

framework that allows us to focus directly on the biggest ZIKV-related health concern—the dynamics of prenatal exposure.

Results

High Rates of Prenatal ZIKV Exposures Early in an Epidemic

Figure 1 shows the predicted number of women who experience a ZIKV infection during pregnancy as a function of years since ZIKV arrival in a country or region. Remarkably, we predict that for a large range of mosquito biting and recruitment rates and life expectancies, nearly half of all women who are or become pregnant during the first year of a ZIKV outbreak will experience a ZIKV infection during their pregnancy (see also Supplementary Information II, Figure S2). Even more alarming, efforts to minimize these exposure rates appear to have limited benefits. In Figure 2a, for example, a two-fold reduction in mosquito biting rates only results in 1% fewer pregnant women exposed to ZIKV, while a four-fold reduction gives 48% fewer prenatal exposures. Though the latter is an appreciable decrease, it is still far short of the 75% reduction in biting rates required to achieve it. In Figure 2b, we likewise find that a five-fold reduction in mosquito recruitment rates only gives a 7% reduction in prenatal exposures to ZIKV, while a ten-fold reduction in mosquito recruitment offers a 32% decrease in prenatal ZIKV cases. Bleakest of all is Figure 2c, which shows that decreased mosquito life expectancy offers an almost negligible reduction in prenatal ZIKV exposures, even over a ten-fold range in mosquito lifespans.

Dramatic Decrease in Prenatal ZIKV Exposures Within 1-2 Years

Despite the disheartening statistics for the first year of a ZIKV epidemic, there is a silver lining. In the years following the initial dramatic explosion of ZIKV cases, we predict a sudden and rapid decrease in prenatal ZIKV exposures, ultimately reaching an almost undetectable level. Importantly this decrease is not a result of any control strategies or vector management efforts.

Instead, it is an intrinsic property of the system – a property that arises as a result of the interplay between transmission of infection, build-up of immunity in the human population, and the timing of human reproduction. In fact, in an ironic twist, efforts to control ZIKV transmission through mosquito management and avoidance of biting insects may actually backfire (at least in the long run), increasing, rather than decreasing the ultimate number of ZIKV prenatal exposures. In Figure 1, for example, damped oscillations of prenatal ZIKV exposures out to 100 years are highest for the lowest mosquito biting and recruitment rates and shortest mosquito life expectancies, but are practically undetectable for the highest mosquito biting and recruitment rates and longest mosquito life expectancies.

Figure 2 elaborates on Figure 1, showing cumulative prenatal ZIKV exposures for different mosquito biting and recruitment rates and mosquito life expectancies. Clearly, when the mosquito population can be suppressed to very low levels, this reduces ZIKV prenatal exposures for long periods of time (compare the light grey lines with the dark grey or black lines in Figure 2). However, if suppression is less effective, resulting in lower but still appreciable mosquito biting rates, recruitment, and life expectancies, then suppression can actually result in more cases of prenatal ZIKV. For example, there is a cross-over point at 16 years, where the cumulative number of prenatal ZIKV exposures at a mosquito biting rate of $b = 0.5$ day^{-1} surpasses that at a biting rate of $b = 1$ day^{-1} (compare the dark grey and black lines in Figure 2a). We see this same type of crossover for mosquito recruitment rates of $A = 1000$ day^{-1}area^{-1} versus $A = 5000$ day^{-1}area^{-1} at 32 years (Figure 2b), and for mosquito life expectancies of $\mu^{-1} = 10$ days versus $\mu^{-1} = 50$ days at 7 years (Figure 2c).

High Levels of Disease Transmission Prevent Prenatal Exposures

Figure 3 expands on Figures 1 and 2, showing yearly prenatal exposures to ZIKV that would be expected in regions where the virus has been endemic for many years (i.e., equilibrium exposure

rates). Compared to the >400 prenatal exposures per 1000 births that characterized certain first year epidemic scenarios (see Figure 1, Supplemental Information II, Figure S2a), predicted yearly exposures in regions where the disease is endemic are at least 50-fold lower (and usually even lower, see Supplemental Information II, Figure S2b), typically below 5 infections per 1000 births. Similar to epidemic predictions, analysis of endemic scenarios suggests that, over the majority of realistic parameter space, prenatal ZIKV exposures counter-intuitively decrease with mosquito biting and recruitment rates and with mosquito life expectancies. Again, this results from the interplay between disease transmission, build-up of population-level immunity, and the timing of reproduction. In particular, when mosquito biting rates, recruitment, and longevity are high, so too is disease spread. As a result, there is ample opportunity to acquire a ZIKV infection, meaning that very few individuals born in a region with endemic ZIKV will reach reproductive age without having been previously exposed to the virus (see dashed lines in Figure 3). However, for lower mosquito biting rates, recruitment, and life expectancies, opportunities for disease acquisition are reduced. If this reduction is not sufficient to make the likelihood of infection during pregnancy negligible, then the net result can be a higher risk of disease acquisition while pregnant, despite a lower overall risk of disease acquisition at any stage of life.

To explore the implications of our model findings over the full range of parameter space (see Table One), we use a Latin Hypercube Sampling (LHS) analysis (see Materials and Methods), yielding Figure 4. Interestingly, comparing partial rank correlation coefficients (PRCCs) for endemic versus epidemic ZIKV, we find that the majority of parameters that are negatively correlated with prenatal exposures in endemic regions are positively correlated with prenatal exposures in regions where ZIKV has been newly introduced (i.e., is still epidemic). Thus, consistent with Figures 1-3, mosquito biting rates, recruitment, and life expectancy are associated with a reduced risk of prenatal exposures when ZIKV circulation reaches an equilibrium level, but result in a greatly increased risk of prenatal exposures during the initial wave of disease. The

same is true of human-to-mosquito and mosquito-to-human transmission, as well as the length of the human viremic period – parameters which, like biting rates and mosquito recruitment, should intuitively amplify disease spread. Not surprisingly, parameters associated with a high risk of prenatal exposures under epidemic conditions are the same parameters associated with a large basic reproduction number, R_0 (i.e., they tend to make disease spread more favorable, see Materials and Methods). These are also the same parameters associated with high rates of ZIKV immunity in children. This latter finding reiterates the mechanism responsible for the counterintuitive reduction in prenatal exposures when there is high disease transmission in endemic systems. In particular, when ZIKV has been in a region for a number of years, parameters positively correlated with childhood immunity ensure that the majority of children acquire ZIKV prior to reaching reproductive age.

Discussion

Since the announcement that microcephaly may be related to ZIKV infection during pregnancy, public health officials have been scrambling to find solutions for halting the current ZIKV outbreak in South and Central America. Meanwhile, North America is preparing for the inevitable arrival of ZIKV, which is expected in the coming months, as temperatures begin to warm and mosquitoes become active. Unfortunately, without a full understanding of disease dynamics, it is difficult to predict how the future course of the ZIKV epidemic will unfold, and nearly impossible to determine the best strategies for managing it. In this paper, we take a step towards understanding the population level consequences of ZIKV transmission by constructing a dynamic compartment model for ZIKV. ZIKV is unique among vector borne viruses in that it poses its greatest threat during pregnancy. Consequently, we build a novel age- and class-structured model that allows us to specifically consider prenatal exposure to the virus.

Microcephaly in Brazil

Interestingly, our model predictions immediately reconcile the strikingly high incidence of microcephaly in Brazil, despite this never being documented as a complication of ZIKV in Africa or Asia, where the disease has been endemic for many years. In particular, we find that rates of prenatal exposures during the first one to two years of a ZIKV outbreak should be remarkably high (typically over 40%, see Figure 1 and Supplemental Information II Figure S2a). However, after this initial surge, there should be a precipitous decline in prenatal exposures and, by the time the disease has become endemic, very few women should acquire ZIKV during pregnancy. The cause is two-fold. First, after the initial wave of infection, the overall disease burden in the community decreases as immunity builds up in a previously naïve population. Second, prenatal exposures are further suppressed by the age structure associated with human reproduction. In particular, because most females do not reproduce until they are at least 15 years old, and usually older[25], there is sufficient time during childhood to acquire ZIKV and develop immunity. This immunity then protects the fetus, even if the mother is bitten by an infectious vector. In other words, high rates of ZIKV infection during childhood act as a 'natural vaccine' that effectively prevents ZIKV infection during the critical pregnancy stage.

Notice that the protective effects of natural ZIKV infection hinge upon having high levels of ZIKV circulating in the community. This, in turn, depends upon mosquito densities and biting rates, as well as the intrinsic ability of ZIKV to spread from humans to mosquitoes and vice versa. Although dengue (from which we derive our model parameters) is thought to exhibit the type of 'flash and fade' dynamics required for the protective mechanisms we propose[26], the precise rates of transmission of ZIKV are unknown. Nevertheless, there are several lines of evidence to suggest that ZIKV also exhibits the transmissibility necessary to achieve high population-level immunity. First, the explosive dynamics of ZIKV in both French Polynesia[5] and Brazil[11] indicate that, once introduced into a population, ZIKV spreads rapidly. Second, there

have been two estimates of ZIKV prevalence based on serological studies and surveys. The first, in Nigeria in 1979, suggested that 52% of the population had neutralizing antibodies against ZIKV[27]. The second, on Yap Island following the 2007 outbreak, indicated that approximately 73% of the population had been exposed to ZIKV during the epidemic[4]. These percentages are similar to estimates from our model (see Figure 3), and should be sufficient to observe protective benefits against infection during pregnancy.

Management Implications

The issue of 'natural vaccination' raises an interesting but difficult question. Is the best approach to managing ZIKV infection really to target mosquitoes and mosquito exposure? Although such targeting might help to prevent near-term infection of pregnant woman (see Figures 1 and 2), it also slows the rate at which ZIKV immunity is acquired in the population as a whole. This delay not only results in ZIKV spread over a longer period of time, but also means that women who would have been exposed to ZIKV prior to pregnancy under high transmission scenarios, might not come in contact with the disease until they are carrying a child under lower transmission scenarios. This is exactly what we see in model predictions. For systems with lower mosquito recruitment (as might be achieved through larvicides or efforts to empty container breeding habitats), higher mosquito death rates (as might be achieved through adulticides), and lower mosquito biting rates (as might be achieved through mosquito avoidance and repellants), prenatal ZIKV exposures continue for a longer period of time and ultimately reach a higher endemic level as compared to systems with larger populations of aggressively biting mosquitoes (see Figures 1-3).

Although our findings indicate that there may be some advantage to allowing ZIKV transmission, we do not want to suggest in any way that we support immediate cessation of mosquito control programs in South and Central America. Before such a decision can be made, more information

is necessary. This includes laboratory measurements of rates of ZIKV transmission to and from mosquitoes, measurements of mosquito densities in affected regions, extensive surveys of ZIKV seroprevalence rates (including among pregnant women), determination of the pregnancy stages associated with risk (see Supplemental Information III Figure S3), and longer term analysis of waning immunity (which could compromise some of the protective benefits that we predict from disease acquisition). Another, separate consideration is the effectiveness of mosquito control programs. If mosquito control can successfully reduce ZIKV transmission levels to near or below what is necessary for disease persistence ($R_0 < 1$, see Materials and Methods), then mosquito eradication is unquestionably the best strategy (see Figure 2).

Interestingly, as compared to the uncertain consequences of active control of mosquito populations, the benefits of delayed pregnancy are much clearer. Indeed, we predict that, in regions with intense mosquito activity, high rates of prenatal ZIKV exposure should only last for one or two years. Therefore, even if it proves impossible to reduce mosquito populations sufficiently to stop or dramatically slow the spread of ZIKV, there may still be a benefit to postponing pregnancy. Consequently, while the recommendations to delay pregnancy by the El Salvadorian and Colombian governments were likely motivated by an overly optimistic expectation that ZIKV transmission can be halted, this advice may nonetheless be highly effective for reducing rates of microcephaly. Delayed pregnancy has the advantage of avoiding ZIKV complications in the near-term, while still allowing rampant ZIKV spread that then 'vaccinates' females, protecting them for when they do eventually become pregnant. An even better, though more costly, solution would be to administer serological tests to women who want to become pregnant. Women with ZIKV antibodies could proceed with pregnancy plans 1-2 months following a positive test, while women who have not been infected could be advised to wait for an additional period of time and then retest.

Conclusions

In the coming months, we anticipate intense study of ZIKV. Hopefully, this will provide researchers with increased information on the virus' natural history and epidemiology. As this information becomes available, it will enable progressively more detailed models of ZIKV transmission that will allow for clearer predictions of how the ZIKV outbreak is likely to impact the Americas. More accurate estimates of disease transmission rates, incorporation of latency periods in vector and host populations, the potential for waning immunity and even seasonality effects are some of the details that continued study should elucidate. This paper presents a framework for including all of these anticipated effects. That said, based on our sensitivity analysis over a wide range of parameter space, we expect that our qualitative conclusions will be robust, even as more details are added. New information will help to tighten model predictions, including better estimation of whether ZIKV can be suppressed by mosquito control techniques and, if not, how the trade-offs between short-term mosquito control and long-term population immunity should be balanced to minimize prenatal ZIKV exposure. Ultimately, this will be valuable information for management of what is surely one of the most pressing disease outbreaks in recent history.

METHODS:

We build a dynamic compartment model for ZIKV (see Supplemental Information, Figure S1) and use this to analyze disease dynamics, both in regions where ZIKV did not previously exist, and in regions where the virus is endemic. Because the primary concern with this virus is its potential to cause microcephaly in newborns, we focus on a structured population model that accounts for age-structure, gender, and pregnancy status in the human population. For human disease transmission, we use an S-I-R (Susceptible-Infected-Recovered) framework that assumes life-long immunity in people who have had a ZIKV infection. We use an S-I-R model based on

observations of neutralizing ZIKV antibodies in patients that have recovered from ZIKV[27]. Life-long immunity is also a common attribute for other closely related flaviviruses, for example DENV[26] and YFV[28]. Specifically, our model is as follows:

Humans (S-I-R):

Pre-reproductive females and males:

$$\frac{dS_j}{dt} = \overbrace{\delta(S_p + I_p + R_p)}^{birth} - \overbrace{\eta_j S_j}^{maturation} - \overbrace{\frac{\beta_h b}{N_h} S_j I_v}^{infection} \quad (1.a)$$

$$\frac{dI_j}{dt} = \overbrace{-\eta_j I_j}^{maturation} + \overbrace{\frac{\beta_h b}{N_h} S_j I_v}^{infection} - \overbrace{rI_j}^{recovery} \quad (1.b)$$

$$\frac{dR_j}{dt} = \overbrace{-\eta_j R_j}^{maturation} + \overbrace{rI_j}^{recovery} \quad (1.c)$$

Reproductive females (*not pregnant*):

$$\frac{dS_x}{dt} = \overbrace{\frac{\eta_j}{2} S_j}^{maturation} - \overbrace{\eta_{xy} S_x}^{maturation} - \overbrace{pS_x}^{pregnancy} + \overbrace{\delta S_p}^{delivery} - \overbrace{\frac{\beta_h b}{N_h} S_x I_v}^{infection} \quad (2.a)$$

$$\frac{dI_x}{dt} = \overbrace{\frac{\eta_j}{2} I_j}^{maturation} - \overbrace{\eta_{xy} I_x}^{maturation} - \overbrace{pI_x}^{pregnancy} + \overbrace{\delta I_p}^{delivery} + \overbrace{\frac{\beta_h b}{N_h} S_x I_v}^{infection} - \overbrace{rI_x}^{recovery} \quad (2.b)$$

$$\frac{dR_x}{dt} = \overbrace{\frac{\eta_j}{2} R_j}^{maturation} - \overbrace{\eta_{xy} R_x}^{maturation} - \overbrace{pR_x}^{pregnancy} + \overbrace{\delta R_p}^{delivery} + \overbrace{rI_x}^{recovery} \quad (2.c)$$

Reproductive females (*pregnant*)*:*

$$\frac{dS_p}{dt} = \overbrace{pS_x}^{pregnancy} - \overbrace{\delta S_p}^{delivery} - \overbrace{\frac{\beta_h b}{N_h} S_p I_v}^{infection} \quad (3.a)$$

$$\frac{dI_p}{dt} = \overbrace{pI_x}^{pregnancy} - \overbrace{\delta I_p}^{delivery} + \overbrace{\frac{\beta_h b}{N_h} S_p I_v}^{infection} - \overbrace{rI_p}^{recovery} \quad (3.b)$$

$$\frac{dR_p}{dt} = \overbrace{pR_x}^{pregnancy} - \overbrace{\delta R_p}^{delivery} + \overbrace{rI_p}^{recovery} \quad (3.c)$$

Reproductive males:

$$\frac{dS_y}{dt} = \overbrace{\frac{\eta_j}{2}S_j}^{maturation} - \overbrace{\eta_{xy}S_y}^{maturation} - \overbrace{\frac{\beta_h b}{N_h}S_y I_v}^{infection} \quad (4.a)$$

$$\frac{dI_y}{dt} = \overbrace{\frac{\eta_j}{2}I_j}^{maturation} - \overbrace{\eta_{xy}I_y}^{maturation} + \overbrace{\frac{\beta_h b}{N_h}S_y I_v}^{infection} - \overbrace{rI_y}^{recovery} \quad (4.b)$$

$$\frac{dR_y}{dt} = \overbrace{\frac{\eta_j}{2}R_j}^{maturation} - \overbrace{\eta_{xy}R_y}^{maturation} + \overbrace{rI_y}^{recovery} \quad (4.c)$$

Post-reproductive females and males:

$$\frac{dS_m}{dt} = \overbrace{\eta_{xy}(S_x + S_y)}^{maturation} - \overbrace{\eta_m S_m}^{death} - \overbrace{\frac{\beta_h b}{N_h}S_m I_v}^{infection} \quad (5.a)$$

$$\frac{dI_m}{dt} = \overbrace{\eta_{xy}(I_x + I_y)}^{maturation} - \overbrace{\eta_m I_m}^{death} + \overbrace{\frac{\beta_h b}{N_h}S_m I_v}^{infection} - \overbrace{rI_m}^{recovery} \quad (5.b)$$

$$\frac{dR_m}{dt} = \overbrace{\eta_{xy}(R_x + R_y)}^{maturation} - \overbrace{\eta_m R_m}^{death} + \overbrace{rI_m}^{recovery} \quad (5.c)$$

where S, I and R are populations that are susceptible to, infected with, and recovered from (and thus immune to) ZIKV respectively and subscripts on the state variables are: j for children, x for reproductive-aged females that are not pregnant, p for reproductive-aged females that are pregnant, y for males within the age range of reproductive females, and m for adults beyond reproductive age (as based on female reproduction). Notice that, in equations (1-5), mortality only occurs in the post-reproductive class. Although this is not, strictly speaking, true, it is a good approximation for countries where the primary source or mortality is senescence. We also do not assume additional death in infected classes because, unlike many other flaviviruses, mortality associated with ZIKV is negligible (at least, outside of the prenatal stage).

For the vector population, we assume an S-I model. Specifically:

Mosquitoes (S-I):

$$\frac{dS_v}{dt} = A - \overbrace{\mu S_v}^{death} - \overbrace{\frac{\beta_v b}{N_h} S_v\left(I_j + I_x + I_p + I_y + I_m\right)}^{infection} \quad (6.a)$$

$$\frac{dI_v}{dt} = -\overbrace{\mu I_v}^{death} + \overbrace{\frac{\beta_v b}{N_h} S_v\left(I_j + I_x + I_p + I_y + I_m\right)}^{infection} \quad (6.b)$$

where S_v are the susceptible vectors and I_v are the infected vectors. We choose this model for the vector because it is structurally identical to a number of classic DENV models[23]. Furthermore, it is simple enough to allow us to focus on the effects of age-structure and pregnancy in the human population and to avoid issues of model over-parameterization that would diminish the model's predictive value. In particular, notice that, although we have 17 state variables, there are only 12 parameters (11 if you assume a constant human population size), most of which are well defined based on human life-history. For mosquito and disease parameters, we use values previously determined from analysis of DENV models. We believe that this is valid based on the relatedness of DENV and ZIKV, the fact that these two diseases share a common set of mosquito vectors (*Aedes* spp.), and the relative lack of specific information on ZIKV transmission. Although ZIKV-specific parameters (β_h, β_v, and r) can be updated as new information becomes available in coming months, based on the already broad ranges assumed for these parameters, we do not anticipate any significant changes to our qualitative conclusions. Table One defines model parameters along with corresponding ranges.

Basic Reproduction Number: We find the basic reproduction number, R_0, for the system in equations (1-6) as follows[29]:

$$R_0 = \frac{1}{\sqrt{2}}\sqrt{\frac{\beta_h \beta_v b^2 S_v^*}{\mu k_1 k_4 k_5 (k_2 k_3 - \delta p) N_h^2}\left(\kappa_j S_j^* + \kappa_x S_x^* + \kappa_p S_p^* + \kappa_y S_y^* + \kappa_m S_m^*\right)} \quad (7.a)$$

where:

$$\kappa_j = k_4 k_5 (k_3 + p)\eta_j + k_4 k_3 \eta_j \eta_{xy} + \left(2k_4 k_5 + k_5 \eta_j + \eta_j \eta_{xy}\right)(k_2 k_3 - \delta p) \quad (7.b)$$

$$\kappa_x = 2k_1k_4\left(k_3k_5 + k_3\eta_{xy} + k_5p\right) \quad (7.c)$$

$$\kappa_p = 2k_1k_4\left(\delta k_5 + \delta\eta_{xy} + k_2k_5\right) \quad (7.d)$$

$$\kappa_y = 2k_1(k_2k_3 - \delta p)\left(k_5 + \eta_{xy}\right) \quad (7.e)$$

$$\kappa_m = 2k_1k_4(k_2k_3 - \delta p) \quad (7.f)$$

$$S_j^* = \frac{N_h\delta\eta_{xy}\eta_m}{\delta(\eta_j\eta_m+\eta_j\eta_{xy}+\eta_{xy}\eta_m)+\eta_j\eta_{xy}\eta_m} \quad (7.g)$$

$$S_x^* = \frac{N_h\delta\eta_j\eta_m}{2\delta(\eta_j\eta_m+\eta_j\eta_{xy}+\eta_{xy}\eta_m)+\eta_j\eta_{xy}\eta_m} \quad (7.h)$$

$$S_p^* = \frac{N_h\eta_j\eta_{xy}\eta_m}{\delta(\eta_j\eta_m+\eta_j\eta_{xy}+\eta_{xy}\eta_m)+\eta_j\eta_{xy}\eta_m} \quad (7.i)$$

$$S_y^* = \frac{N_h\delta\eta_j\eta_m}{2\delta(\eta_j\eta_m+\eta_j\eta_{xy}+\eta_{xy}\eta_m)+\eta_j\eta_{xy}\eta_m} \quad (7.j)$$

$$S_m^* = \frac{N_h\delta\eta_j\eta_{xy}}{\delta(\eta_j\eta_m+\eta_j\eta_{xy}+\eta_{xy}\eta_m)+\eta_j\eta_{xy}\eta_m} \quad (7.k)$$

and $k_1 = \eta_j + r$, $k_2 = \eta_{xy} + p + r$, $k_3 = \delta + r$, $k_4 = \eta_{xy} + r$, and $k_5 = \eta_m + r$. Notice that equations (7.g-k) assume a fixed population size, thus $p = 2\eta_{xy}$. When $R_0 > 1$ the disease-free equilibrium is unstable, meaning that ZIKV spread is predicted. In contrast, when $R_0 < 1$, the disease-free equilibrium is stable, and ZIKV should not persist in the system.

Infection During Pregnancy: Focusing on the risk of microcephaly, the fraction of women who experienced an active ZIKV infection at any point during a pregnancy in year n is:

$$\Gamma_n = \frac{I_p(t_n)+\int_{t_n}^{t_n+365}\left[pI_x(t)+\frac{\beta_h b}{N_h}S_p(t)I_v(t)\right]dt}{S_p(t_n)+I_p(t_n)+R_p(t_n)+\int_{t_n}^{t_n+365}[pS_x(t)+pI_x(t)+pR_x(t)]dt} \quad (8)$$

where t is measured in days and t_n is the first day of year n. Notice that this means women whose pregnancies (infections) span two years (e.g., begin in October and end in June) are counted towards pregnancy (infection) totals for both years. Throughout the paper, we use equation (8) as a marker of disease intensity and the cost of ZIKV transmission. Specifically we explore how the risk of ZIKV infection during pregnancy changes depending on the length of time that ZIKV has been present in a country, as well as vector biology and/or management

actions. We then compare the risk of acquiring ZIKV during pregnancy in a country where the virus is endemic with the same risk in a country where ZIKV has been newly introduced. To study the dynamics of ZIKV early in an outbreak, we begin with human and vector populations at the disease-free equilibrium, and then introduce a single infected mosquito, following the time course of ZIKV transmission and prenatal exposures. To study dynamics of endemic ZIKV, we use a similar approach, but solve equations (1 – 6) numerically over a period of 500 years. This is sufficient time for the system to reach equilibrium across all parameter ranges considered.

Sensitivity Analysis:

We use a Latin Hypercube Sampling (LHS) scheme to explore model behavior over the full parameter space of our system. Specifically, we generate LHS matrices based on the parameter ranges in Table One, and then use a Partial Rank Correlation Coefficient (PRCC) analysis to investigate the dependence of key system predictions (R_0, endemic prenatal ZIKV exposures, peak prenatal ZIKV exposures, and endemic levels of immunity in the pre-reproductive class) on individual model parameters. For our LHS analysis of R_0, we assume the full parameter ranges defined in Table One. However, because the non-monotonicity of ZIKV exposures near $R_0 = 1$ (see Figure 3 and Supplemental Information V, Figure S5) would violate PRCC assumptions, for our LHS analysis of ZIKV exposures and immunity (where we use immunity to explain exposure patterns) we restrict the range for mosquito biting rates to $b \in (0.4, 1)$, for mosquito recruitment to $A \in (1000, 5000)$ and for mosquito-to-human transmission to $\beta_h \in (0.15, 0.75)$. This means that our PRCC analysis implicitly assumes that none of these parameters is so low that ZIKV spread is or is close to being unfavorable (i.e., $R_0 < 1$). For all analyses, we use 10,000 samples and a uniform distribution across parameter ranges (notice this means that we use uniform distributions across $\eta_j, \eta_{xy}, \eta_m, \delta, \mu$ and r ranges, even though these parameters are reported as inverse values in Table One for ease of interpretation). We only consider 11 parameters, rather than the full 12 in Table One, because we always fix the number of children per couple at two to

ensure a constant human population size. This is done to simplify model analysis. In reality, most global populations, and particularly those in regions with ZIKV outbreaks, are growing. We explore the effect that a changing population size has on model predictions in Supplementary Information IV.

Tables:

Table One Parameter Definitions and Ranges*

Parameter	Definition	Range	Ref.
η_j^{-1}	human age at first reproduction	15-25 years	25
η_{xy}^{-1}	human reproductive period	20-25 years	30
η_m^{-1}	human lifespan following reproduction	20-30 years	31
p/η_{xy}	children per female	2	-
δ^{-1}	gestation	37-40 weeks	-
N_h	human population size**	5000-15000 area^{-1}	32
A	mosquito recruitment	400-5000 day^{-1}area^{-1}	23,32
μ^{-1}	mosquito life expectancy	4-50 days	23,32
b	mosquito biting rate	0.3-1 day^{-1}	23,32
β_h	probability of mosquito to human transmission	0.1-0.75	23,32
β_v	probability of human to mosquito transmission	0.5-1	23,32
r^{-1}	human infectious period	3-14 days	23,32

* human population size and mosquito recruitment are defined for an arbitrary unit area; the important parameter is the ratio of number of mosquitoes ($N_v \longrightarrow A/\mu$) to humans ($N_h$). In reality, this is highly variable, depending on season, rainfall, habitat and geographical location. The average parameter values in Table One give a ratio of $N_v : N_h = 7.29$, which is reasonable based on pupal density estimates from a study in Rio de Janeiro[33] combined with the fact that the adult lifespan of *Ae. aegypti* is 2-4 weeks versus the approximately 2 day pupal stage.

**We set $p/\eta_{xy} = 2$ to ensure that the human population size remains fixed at a constant N_h. This essentially means that each couple has, on average, two children. We choose a fixed population because this makes it easier to understand system behavior, which would otherwise be complicated by an underlying change in population size. We realize, however, that most countries with ZIKV outbreaks have growing populations. We explore model behavior for a growing population in Supplemental Information IV.

Figures:

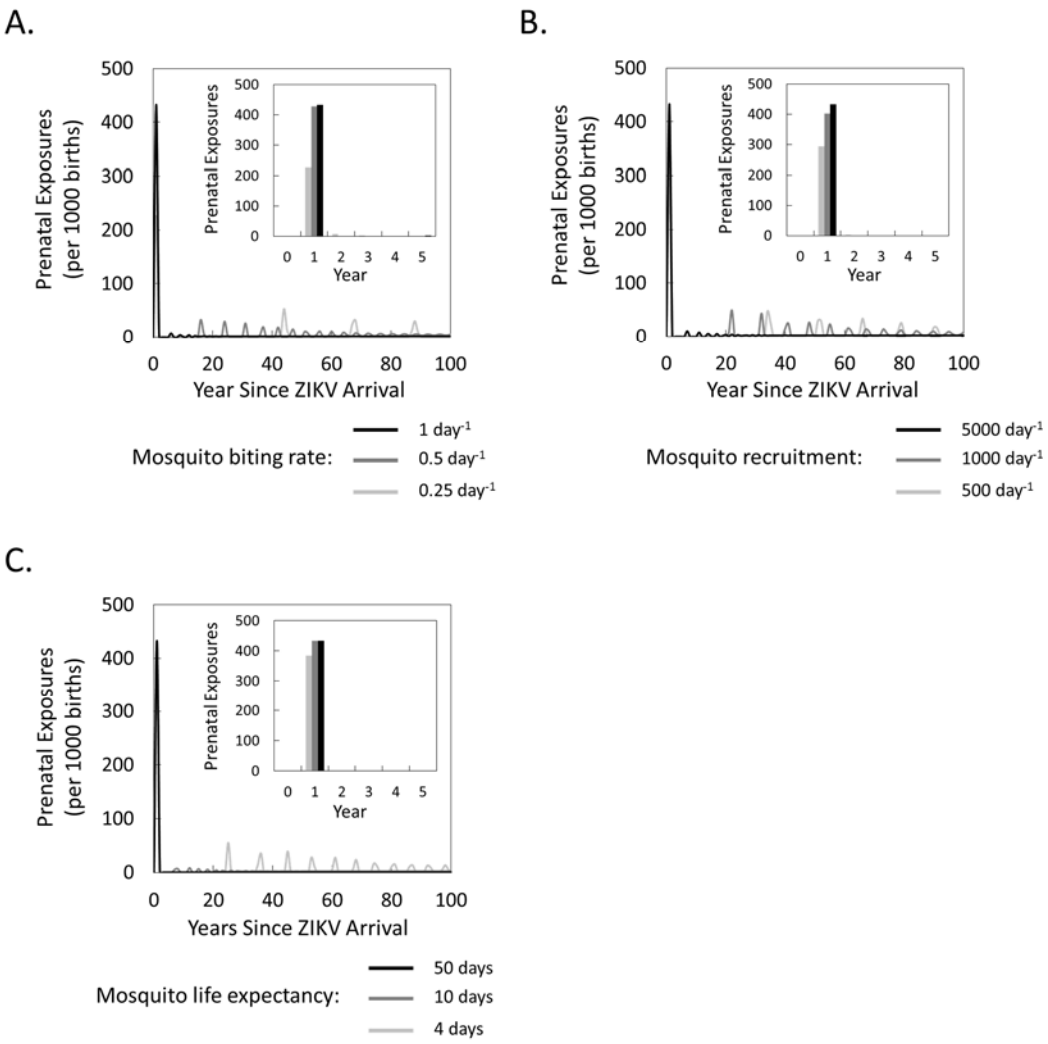

Figure 1 Number of women who experience a ZIKV infection during pregnancy as a function of years since ZIKV arrival in the country or region and (a) mosquito biting rate, (b) mosquito recruitment rate and (c) mosquito life expectancy. Insets show bar graphs for the first five years. In each panel, we assume average values for all parameters except the one being varied (see Table One).

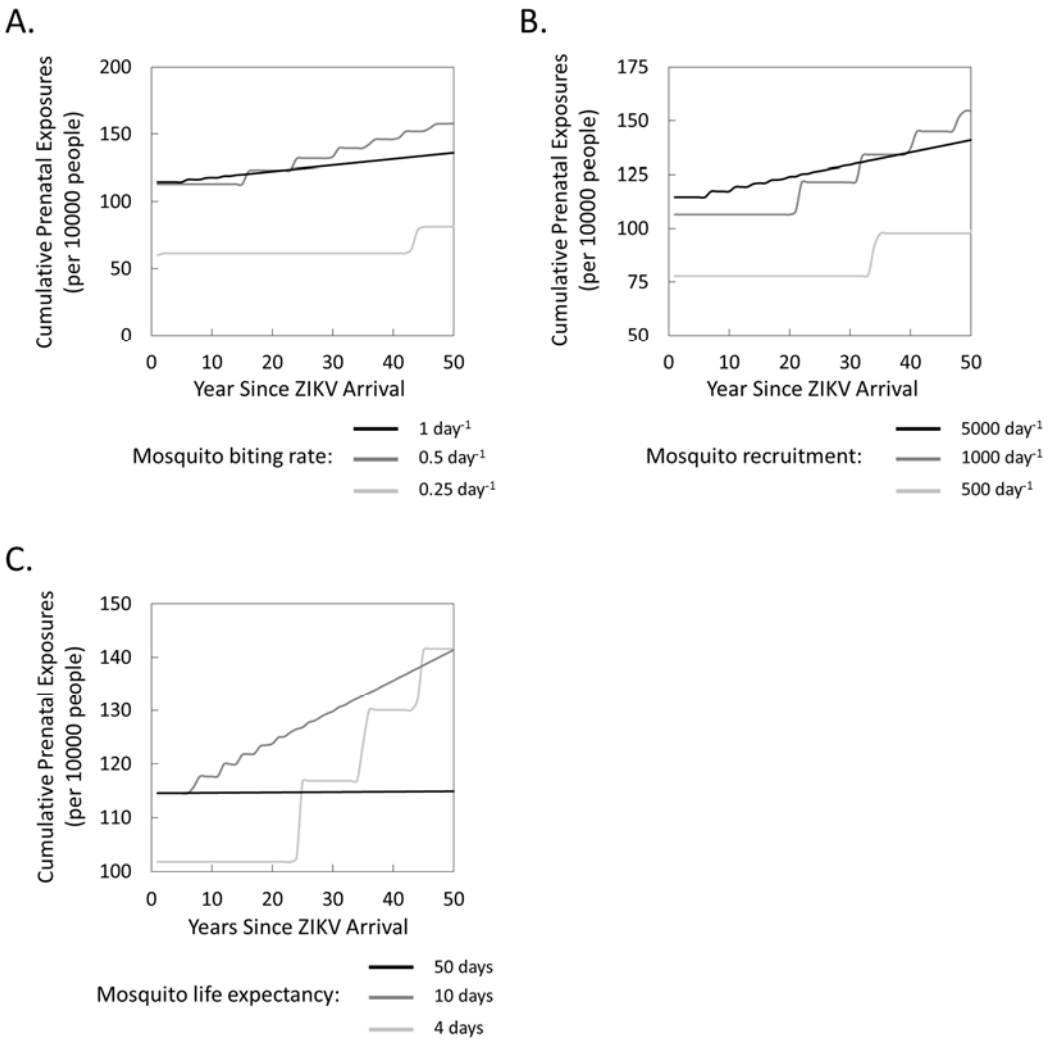

Figure 2 Cumulative number of prenatal ZIKV exposures as a function of years since ZIKV arrival in the country or region and (a) mosquito biting rate, (b) mosquito recruitment rate and (c) mosquito life expectancy. In each panel, we assume average values for all parameters except the one being varied (see Table One).

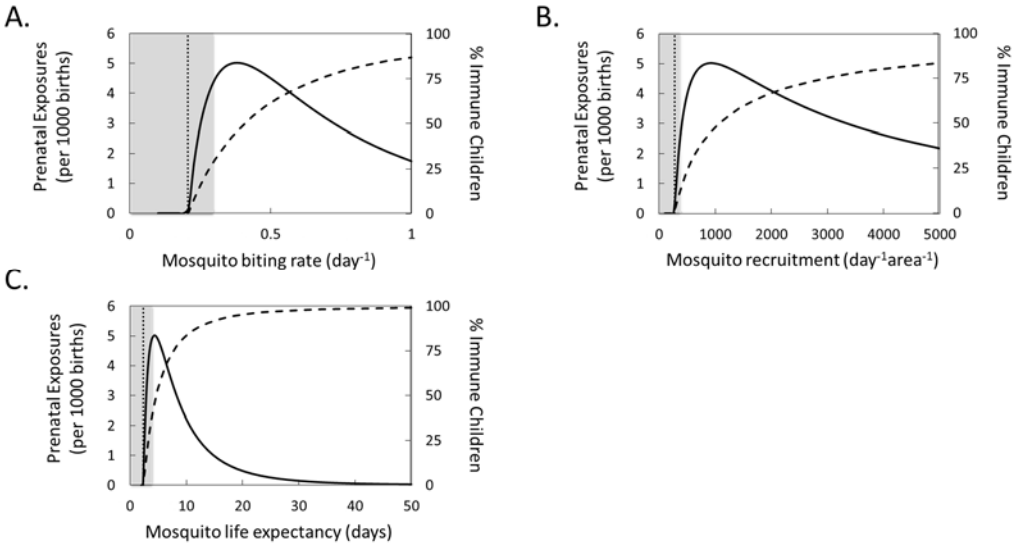

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Figure 3 Number of women who experience an active ZIKV infection at any point during pregnancy (solid line) and percentage of children (below reproductive age) that have acquired ZIKV immunity (dashed line) as a function of (a) mosquito biting rates, (b) mosquito recruitment rates and (c) mosquito life expectancy in a region with endemic disease (i.e., a system at equilibrium). The shaded regions on the three panels are biting rates, recruitment rates, and life expectancies outside of the ranges reported for dengue vectors and thus outside of the ranges for presumed ZIKV vectors as well. The dotted vertical line is $R_0 = 1$ for the system. In each panel, we assume average values for all parameters except the one being varied (see Table One).

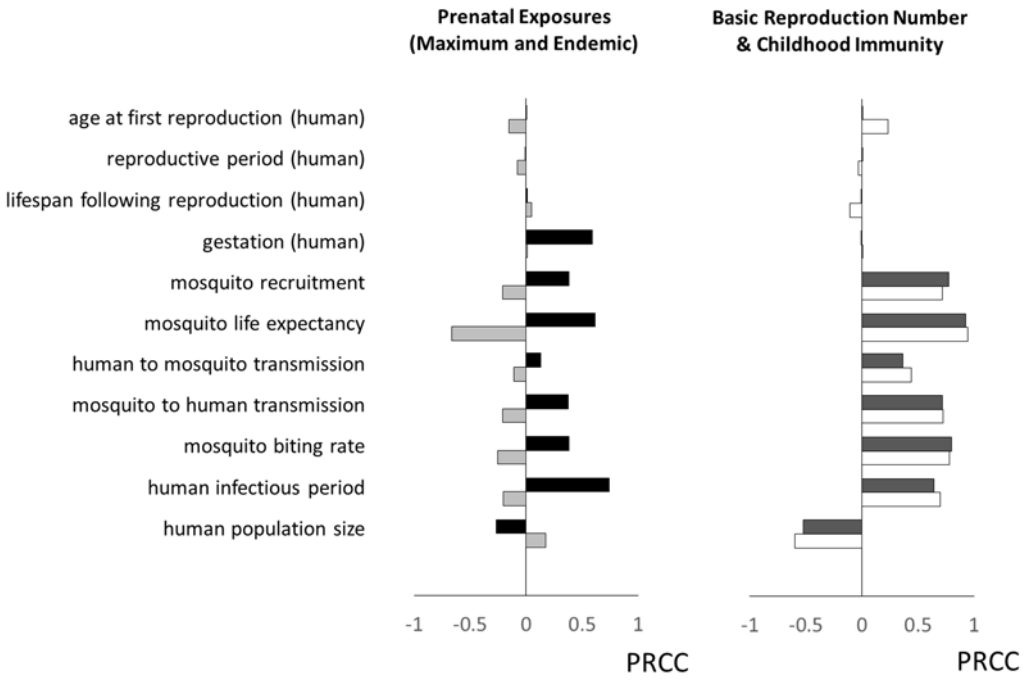

Figure 4 Partial Rank Correlation Coefficients (PRCCs) for the fraction of women who experience a ZIKV infection during pregnancy at the peak of an outbreak (black), and after ZIKV transmission has reached endemic levels (light grey), as well as PRCCs for the ZIKV basic reproduction number (white) and the fraction of children who acquire ZIKV immunity prior to reproductive age in regions where ZIKV is endemic (dark grey). For prenatal exposures and childhood immunity, we use the parameter ranges in Table One, but restrict the following: $b \in (0.4, 1)$, $A \in (1000, 5000)$ and $\beta_h \in (0.15, 0.75)$ to avoid issues with non-monotonicity. For the basic reproduction number, we use the full ranges for all parameters.

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