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It has come to light that Zika virus (ZIKV) infection during pregnancy can result in trans-placental transmission to the fetus along with fetal death, congenital microcephaly and/or Central Nervous System (CNS) malformations. There are projected to be > 9, 200, 000 births annually in countries with ongoing ZIKV transmission. In response to the ZIKV threat, the World Health Organization (WHO) is strategically targeting prevention of infection in pregnant women and funding contraception in epidemic regions. I propose that the damaging effects of ZIKV can be reduced by timing pregnancy seasonally to minimize maternal exposure. Like other acute viral infections—including the related flavivirus, dengue virus (DENV)—the transmission of ZIKV is anticipated to be seasonal. By seasonally planning pregnancy, this aspect of pathogen ecology can be leveraged to align sensitive periods of gestation with the low-transmission season.

# Preventing Zika Virus Infection during Pregnancy by Timing Conception Seasonally

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## Abstract

It has come to light that Zika virus (ZIKV) infection during pregnancy can result in trans-placental transmission to the fetus along with fetal death, congenital microcephaly and/or Central Nervous System (CNS) malformations. There are projected to be > 9,200,000 births annually in countries with ongoing ZIKV transmission. In response to the ZIKV threat, the World Health Organization (WHO) is strategically targeting prevention of infection in pregnant women and funding contraception in epidemic regions. I propose that the damaging effects of ZIKV can be reduced by timing pregnancy seasonally to minimize maternal exposure. Like other acute viral infections—including the related *flavivirus*, dengue virus (DENV)—the transmission of ZIKV is anticipated to be seasonal. By seasonally planning pregnancy, this aspect of pathogen ecology can be leveraged to align sensitive periods of gestation with the low-transmission season.

## Author Summary

Scientific consensus has now been reached that intrauterine Zika virus (ZIKV) infection can result in infection of the fetus and subsequent fetal death, congenital microcephaly and/or Central Nervous System (CNS) malformations. Preliminary data suggest miscarriage and congenital Zika syndrome are most likely when maternal infection occurs early in pregnancy, but fetal abnormalities have been found in women infected with ZIKV during all three trimesters, indicating all trimesters are vulnerable. Like related *flavivirus* infections, ZIKV transmission is likely to be seasonal. I propose that the risk of ZIKV infection to pregnant women can be reduced by planning pregnancy seasonally to align sensitive periods of gestation with the low-transmission season for ZIKV.

## Zika Virus & Microcephaly

ZIKV is mosquito-transmitted virus, vectored by *Aedes aegypti*, spreading rapidly across the globe [1]. Pregnant women infected with ZIKV risk severe fetal outcomes, including brain abnormalities—believed to be due to disruption of brain development caused by intrauterine infection—and death [2,3]. ZIKV was the suspected cause of the 2015/2016 outbreak of microcephaly in Brazil [4], and scientific consensus has now been reached

that prenatal ZIKV infection causes microcephaly and other forms of brain abnormalities. Upon maternal infection, however, the risk of such fetal outcomes remains unknown [5]. In April 2016, the causal link between ZIKV and microcephaly was inferred via several independent lines of evidence, including (1) microcephaly and brain abnormalities in infants born to mothers with suspected or confirmed ZIKV infection during the first or second trimester of pregnancy, (2) the rare form of microcephaly in infants with “congenital Zika syndrome”, distinguishing it from microcephaly resulting from other causes, and (3) birth defects occurring in women with travel-acquired ZIKV, coupled with the low probability that these events were coincident and not causal [5]. Several reports from February to May 2016 have now provided strong evidence for the causal link. A retrospective study of the 2013/2014 ZIKV outbreak in French Polynesia found a 14-fold increase in severe microcephaly in newborns and fetuses following the epidemic; amniotic fluid tested positive for ZIKV in 4 of 7 women sampled after identification of fetal abnormalities [6]. In addition, in Brazil, 42 ZIKV-positive pregnant women were tested for fetal abnormalities. Adverse findings—including fetal death, microcephaly, and CNS damage—were observed in 12 of the women. There were no abnormalities in ZIKV-negative women [2]. Lastly, the complete ZIKV genome was recovered from the brain of a fetus with microcephaly aborted by an expectant mother infected during the 13<sup>th</sup> week of gestation [7], and the CDC reported on two newborns from Brazil with microcephaly who died shortly after birth and two miscarriages, all tested positive for ZIKV [8]. In addition to the epidemiological evidence, newly developed mouse models of ZIKV have demonstrated that ZIKV strains from French Polynesia and Brazil can infect the fetus via the placenta and cause intrauterine growth restrictions and/or fetal loss [9,10], and culture models of early brain development have shown ZIKV can cause neural cell death [10,11]

Recognizing the incomplete picture of ZIKV *in utero* pathology, in February 2016, the WHO declared the cluster of microcephaly in Brazil to be a Public Health Emergency of International Concern, and the International Health Regulations Emergency Committee issued recommendations to reduce ZIKV infections in pregnant women [4]. In the U.S., \$1.9 billion has been requested of congress to respond to ZIKV domestically and internationally [12]. Maternally-transmitted viral infections, such as ZIKV, can be prevented by protecting pregnant women from infection, but it is likely to be many years before a ZIKV vaccine or treatment is developed. Alternative preventative measures are therefore needed to protect women and their children from this emerging pathogen.

Two key components of the ZIKV response by governments and health agencies are (1) vector control and (2) preventing infection in pregnant women. The WHO’s ZIKV operational response plan includes control of *Aedes aegypti* mosquitoes and financing contraceptive services in affected areas to manage pregnancy and mitigate the impact of ZIKV [4]. At the CDC’s April 2016 Zika Action Plan Summit, the CDC Director acknowledged “the control of *Aedes aegypti* is challenging” and declared that decreasing the risk of ZIKV to pregnant women and women of childbearing age is a key priority [13].

Government officials in El Salvador, Colombia, and Ecuador have recommended women delay pregnancy while uncertainty surrounding ZIKV remains. The WHO ZIKV Q&A website (updated regularly) states “Women wanting to postpone pregnancy should have access to a comprehensive range of reversible, long- or short-acting contraceptive options to the full extent of the law” [14]. The CDC has issued recommendations for ZIKV-exposed individuals to delay trying to get pregnant. Exposed women and exposed asymptomatic men are recommended to wait 8 weeks, and men with symptoms are recommended to wait 6 months [15]. No official stance on delaying pregnancy has been taken for unexposed women. Problematically, the public is receiving a mixed message,

highlighted by media coverage in Table 1. Given that extended delays of pregnancy may not be a viable option for millions of women living in ZIKV-epidemic regions, I propose a strategy that will reduce intrauterine ZIKV infection risk without requiring long-term delays of pregnancy. Specifically, I recommend that public health and research communities focus on three current ZIKV knowledge gaps:

1. seasonality of ZIKV transmission,
2. intrauterine transmission and pathology,
3. immunity.

These aspects of ZIKV biology can be integrated with incidence data and mathematical models to inform interventions, including: reducing transmission (i.e., vector-to-human and sexual) via vector control and behavioral changes, planning pregnancy to avoid the high-transmission season, launching vaccines once developed, and reducing intrauterine transmission and pathology. Knowledge gap 3 (immunity) will be particularly important for understanding the recurrent epidemic dynamics of ZIKV and CZS. If ZIKV immunity either wanes or is not fully sterilizing, then we could expect women of childbearing age to be susceptible to ZIKV infection after their primary infection (which might occur during the first epidemic wave).

**Table 1. Recent New York Times articles about delaying pregnancy to avoid congenital Zika.**

Title	Date
Health Officials Split Over Advice on Pregnancy in Zika Areas	Apr 14, 2016
C.D.C. Offers Guidelines for Delaying Pregnancy After Zika Exposure	Mar 25, 2016
Growing Support Among Experts for Zika Advice to Delay Pregnancy	Feb 5, 2016

## Transmission Seasonality

Seasonality is a ubiquitous feature of acute infectious diseases [16–21], including *flaviviruses* like DENV, West Nile virus (WNV), Yellow fever virus (YFV), and other arboviruses vectored by *Aedes aegypti* (i.e., chikungunya virus, CHIKV) [22–26]. Although infectious diseases are seasonal, the timing of the high-transmission season can (1) vary among pathogens within a country and (2) vary among countries/regions for a given pathogen [27]. The drivers of DENV, WNV, YFV, and CHIKV seasonality are likely some combination of vector phenology, climate conditions, and additional host or environmental factors. In general, climatic, physiological, and behavioral factors that influence transmission seasonality include those that impact host and/or vector susceptibility to infection, host/vector infectiousness, virus viability, the transmission-relevant contact rate among hosts/vectors, the density of hosts, and vector abundance [16, 21, 27].

*Aedes aegypti* has seasonal variation in its ability to facilitate *flavivirus* transmission because its abundance and competence as a vector are affected by temperature and rainfall [28, 29]. Using data from Puerto Rico—one of the U.S. locations with ongoing ZIKV transmission—Fig 1a demonstrates the seasonal abundance of blood-fed female *Aedes aegypti*, which transmit ZIKV. *Aedes aegypti* seasonality affects seasonal transmission of DENV and CHIKV [28, 30] and it is likely to impact seasonal ZIKV

transmission. In regions with strong seasonal fluctuations in *Aedes aegypti*, seasonal changes in vector abundance and vectorial competence should be characterized and used to estimate the local timing of the high-transmission season.

A key reason for characterizing transmission seasonality and pinpointing the high transmission season is because its timing will affect the risk of microcephaly in birth cohorts. This is because births are seasonal across human populations, and there is a distinct birth pulse in most countries/regions that varies geographically in its seasonal timing [31,32]. Fig 1b shows the birth seasonality in Puerto Rico, with the birth peak from August-October. Due to birth seasonality, the percent of pregnancies experiencing a specific trimester is not evenly distributed throughout the year (Fig 1d). For any given country, the timing of the seasonal birth pulse, relative to the ZIKV transmission season, will therefore determine the fraction of pregnancies at risk for maternal infection and congenital ZIKV. For example, if a country has a birth pulse where sensitive gestational periods coincide with the ZIKV season, more pregnancies in that country will be at risk than elsewhere. Fortunately, if access to contraceptives and family planning practices are proactively targeted for intervention, then the birth pulse could be intentionally shifted and amplified regionally to minimize the risk of intrauterine ZIKV infection for entire birth cohorts.

**Fig 1. Seasonality of the ZIKV vector and birth seasonality.** (a) Monthly abundance of trapped female mosquitoes engorged with blood-meal in Puerto Rico. Data from [33]. Mosquitoes were collected from 20 houses in heavily urbanized areas around San Juan Metropolitan area using battery-powered aspirators. Seasonal time series decomposition was used to extract the seasonal component of the time series (solid line). Red arrows indicate the inferred seasonal trough of engorged female mosquitoes, which occurred around April each year. (b) Monthly births in Puerto Rico for the years 2002-2008 and 2012-2014. Data from [34]. Time series from each year are stacked, with each line representing data from a single year. Births are seasonal around the world; the birth peak in Puerto Rico occurs around September each year. (c) Weekly reported DENV cases in Puerto Rico. Data are from [35]. Red arrows indicate the inferred DENV transmission trough in April, which coincides with the trough in mosquitoes. (d) The seasonal distribution of pregnancies by trimester. The timing of each trimester was estimated based on the birth data from Puerto Rico.

## Seasonally-Timing Pregnancy

At this time there are insufficient data to predict the seasonal timing and frequency (i.e., annual, biennial, triennial, etc.) at which ZIKV epidemics will occur. The ZIKV outbreak in Brazil peaked between July 12-18, 2015 [36] which is out-of-phase with DENV epidemics in Brazil, that consistently peak around March [37]. This suggests the seasonal timing of DENV epidemics might not be useful in predicting the timing of ZIKV. Importantly, however, the first epidemic wave of ZIKV may not reflect ZIKV's future recurrent epidemic timing. The first wave of the epidemic may differ from future recurrent epidemics because (1) clinical recognition and reporting of cases may lag far behind pathogen introduction, (2) the first wave occurs in a fully-susceptible population, which will alter the epidemic growth curve and the time until susceptible depletion, and (3) the timing of epidemic onset will be influenced by pathogen introduction, as opposed to recurrent epidemics in locations with unbroken transmission chains whose onset is influenced by the build-up of the susceptible population and seasonal transmission [17].

As ZIKV incidence data become available, the annual transmission "high-season"

and “low-season” should be characterized and pregnancy planned such that sensitive periods of gestation are aligned with the low-season. After the initial wave of the epidemic, ZIKV transmission models can be fit and transmission parameters estimated using time series data from ZIKV surveillance. Fig 2 provides a potential ZIKV Susceptible-Infected-Recovered transmission model developed with a focus on the demography relevant to congenital ZIKV. To estimate seasonal transmission parameters, this model would require extensive time series data on reported ZIKV cases, either weekly or monthly. To overcome data limitations, data from other ZIKV surveillance systems could be used in parallel to parameterize such a model. Surveillance data that could be used to study ZIKV transmission and pathology include: reported cases, registries of miscarriage and CZS, ZIKV serology data, and mosquito surveillance data. Models with similar levels of complexity in transmission, pathology, and demography have been parameterized for poliovirus and measles [32,38]; see [39] for statistical inference methods. By combining transmission models with reported ZIKV cases, data on vector abundance, and other covariates that could influence transmission (e.g., temperature, humidity, and human movement) the underlying mechanistic drivers of ZIKV transmission seasonality could be revealed (knowledge gap 1). Assuming vector abundance is an important driver of ZIKV seasonal transmission, based on the *Aedes aegypti* data from Puerto Rico, the high transmission season in Puerto Rico would occur between October-December and the trough would be April-June (Fig 1a). The impact of vector abundance on *flavivirus* transmission is indicated by the 2013 DENV epidemic in Puerto Rico, which had a trough in April (Fig 1c), as would be predicted based on vector seasonality. Importantly, the high and low transmission seasons are tied to local climate conditions and will therefore be region-specific.

### Fig 2. ZIKV transmission & pathology model schematic.

Susceptible-Infected-Recovered model of ZIKV transmission. (a) Transmission model. Births enter the population seasonally, as illustrated by Fig 1b. Susceptible individuals are categorized as infants and children ( $S_c$ ), adult males and women past reproductive age ( $S_a$ ), women of childbearing age ( $S_{wcb}$ ), and pregnant women ( $S_p$ ). There are three infected classes. The general infected class ( $I$ ) includes infants, children, adult males, and non-pregnant women. The infected class relevant to congenital ZIKV tracks pregnant women ( $I_p$ ), who can transmit trans-placentally to infect their fetus ( $I_f$ ). The recovered class (*Immune*) contains individuals who have recovered from infection and are immune from infection, but it is unknown how long immunity lasts and the nature of repeat infection, indicated by knowledge gap 3. The transmission process is unobserved because transmission events are not captured in surveillance. Interventions are indicated. (b) Surveillance model. Symptomatic ZIKV infections and past infections are observable through surveillance systems. The model assumes a subset of infected individuals will have symptoms and the infection of a fetus can result in miscarriage, CZS, or other forms of disease, the risk of which remains unknown (knowledge gap 2). Immunity in the host population can be observed through serology surveys, and mosquito abundance ( $V_S$  and  $V_I$ , susceptible and infected) can be measured based on vector surveillance. Vector abundance is seasonal as illustrated by Fig 1a and this likely affects seasonal transmission, indicated by knowledge gap 1.

With knowledge of regional transmission seasonality, seasonally-timing pregnancy would minimize risk of maternal infection and subsequent damage to the fetus. Birth defects resulting from *in utero* infection with CMV, herpes simplex, and rubella virus are reported to be highest when maternal infection occurs within the first 20 weeks of gestation [40–42]. Miscarriages of known ZIKV-positive fetuses have been reported at 11 and 13 weeks gestation [8]. Preliminary data suggest miscarriage and CZS are most likely when maternal infection occurs during the first or second trimester [5, 6, 43, 44],



but fetal abnormalities have been found in women infected with ZIKV during weeks 8-35 of gestation [2], indicating all three trimesters are vulnerable to some extent. The critical window of susceptibility for ZIKV-induced miscarriage and CZS needs to be identified and taken into account when planning the recommended seasonal timing of pregnancy. Identifying the period of susceptibility for the fetus and using planned seasonal conception to redistribute births—i.e., to take advantage of the transmission low season and ensure sensitive gestation occurs during the ZIKV low season—would reduce risk to the fetus by minimizing maternal exposure. Based on the size of the 2014 birth cohort in Puerto Rico, redistributing births even by a small amount, for example with as little as 3% fewer births experiencing a susceptible trimester during the high transmission season, would translate to reducing risk for approx. 1000 births annually. In a large country like Brazil, which had a birth cohort of approx. 3 million in 2015 [45], planned seasonal conception for 3% of births could reduce risk in > 88,000 pregnancies. The absolute reduction in risk, however, is unknown, as it will depend on the incidence of ZIKV infection in the population and the subsequent risk of trans-placental transmission and fetal abnormalities.

**Fig 3. Planning pregnancy to take advantage of the low ZIKV transmission season.** (a) Recommended timing of conception based on the region-specific transmission season and the susceptible period of gestation. The high-transmission season is marked in blue, and the transmission trough is indicated by the dashed line. The ZIKV-susceptible gestation period is unknown, but preliminary data suggest that all three trimesters are susceptible, but the first two trimesters are particularly vulnerable. The 6 scenarios depict the recommended seasonal timing of gestation under different windows of susceptibility. Scenario 1 is susceptibility during gestation weeks 1-20, similar to other congenital infections. Scenario 2 is susceptibility during weeks 1-26, i.e. the first and second trimester. Scenario 3 is susceptibility during weeks 1-40, all three trimesters. The A and B variants of each scenario indicate whether there is uniform susceptibility across the susceptible window of gestation, or if the first trimester is particularly vulnerable. Policy should encourage planned conception such that the susceptible gestation period is aligned with the transmission trough. This policy would minimize the risk of maternal exposure when the fetus is most vulnerable. The recommended timing of conception varies depending on when the high transmission season occurs. (b) Theoretical trajectory of conception in Puerto Rico if conception were seasonally planned. The percents indicate the monthly value based on pregnancies initiated that year. The transmission trough was assumed to be in April (based on the data in Fig1a and 1c) Gestation weeks 1-20 were assumed to be susceptible, with the first trimester being particularly vulnerable and given highest priority for protection. Conception was therefore encouraged in March, which had the effect of shifting and amplifying the birth pulse. The projection assumes that, each year, planned conception results in 3% of births that would have occurred in Jan, May, Jun, Jul, Aug, Sep, Oct, Nov, or Dec being redistributed to Feb (0.5%), Mar (2%), and Apr (0.5%). (c) The seasonal distribution of pregnancies in the first trimester based on the conception trajectory in b.

Fig 2a shows the recommended timing of conception when the high transmission season lasts 13 weeks and the fetus is susceptible during various periods of gestation. The recommended timing of conception depends on three key factors, (1) the timing of the transmission trough (i.e., the week(s) or month of the year when transmission is lowest), (2) the susceptible period of gestation, and (3) whether the severity of congenital ZIKV infection varies during the susceptible period of gestation. For example, it may be that the first two trimesters are susceptible to fetal abnormalities, but the first trimester is the most vulnerable. Knowing the distribution of susceptibility

throughout the gestational weeks would impact the timing of planned conception. Assuming the window of susceptibility spans gestation weeks 1-20, with the first trimester being highly susceptible and therefore given high priority for protection, Figs 2b-c show how the seasonal distribution of conception could be shifted and amplified to reduce ZIKV risk in Puerto Rico. In general, although tailoring conception seasonally will not alleviate risk of maternal exposure to ZIKV, it could reduce risk and provide an option for women as they wait for a ZIKV vaccine and/or clinical interventions. Planned seasonal conception would be an effective low-cost means of empowering women to protect themselves and their children.

The feasibility and implementation of this strategy would require collaboration among vector ecologists, epidemiologists, and social scientists. In order to seasonally-time pregnancy:

1. each country will need to identify their region-specific high and low ZIKV transmission season,
2. women and health care providers will need to be educated about seasonal conception, and
3. women will need access to contraception.

A key unknown is the susceptible window of gestation, when this is determined then seasonally-planning pregnancy could be intergrated into the growing portfolio of ZIKV interventions. The feasibility and acceptability of planning conception seasonally will need to be addressed regionally with careful consideration of women's reproductive rights and personal values. An R package including data used in this manuscript and a conception planning calendar is provided as Supporting Information. The conception planner requires user defined (1) timing of the transmission trough, (2) susceptible weeks of gestation, and (3) a statement of whether the first trimester is particularly vulnerable. To increase the effectiveness of seasonally planning conception, vector control campaigns could be used to restrict the mosquito season and minimize the duration of the high-transmission season and expand the window for "safe gestation". The integration of epidemiology and family planning can be an effective tool for seasonally-timing pregnancy to reduce women's risk of ZIKV infection during pregnancy.

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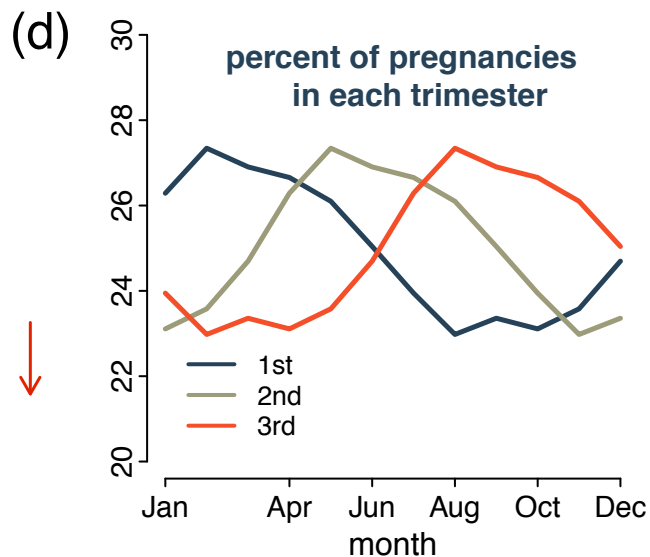
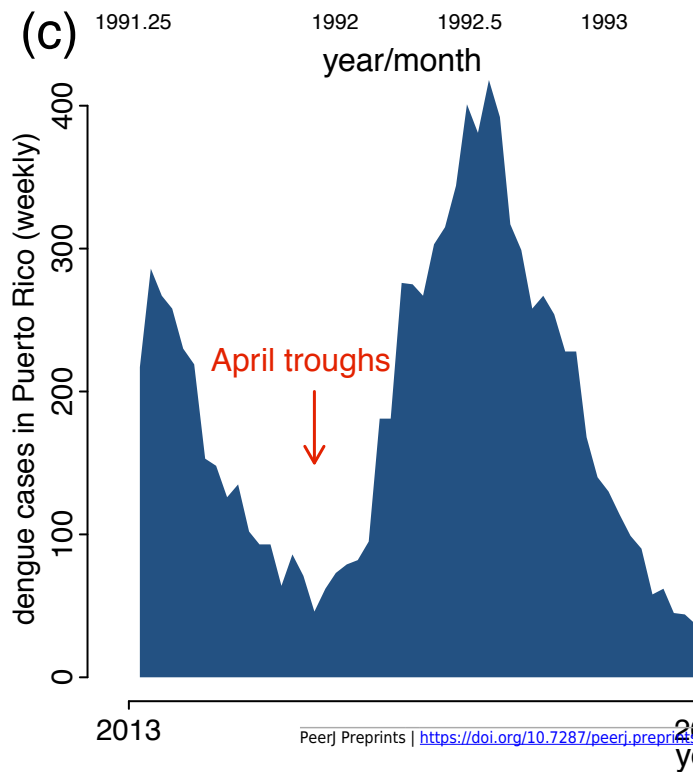
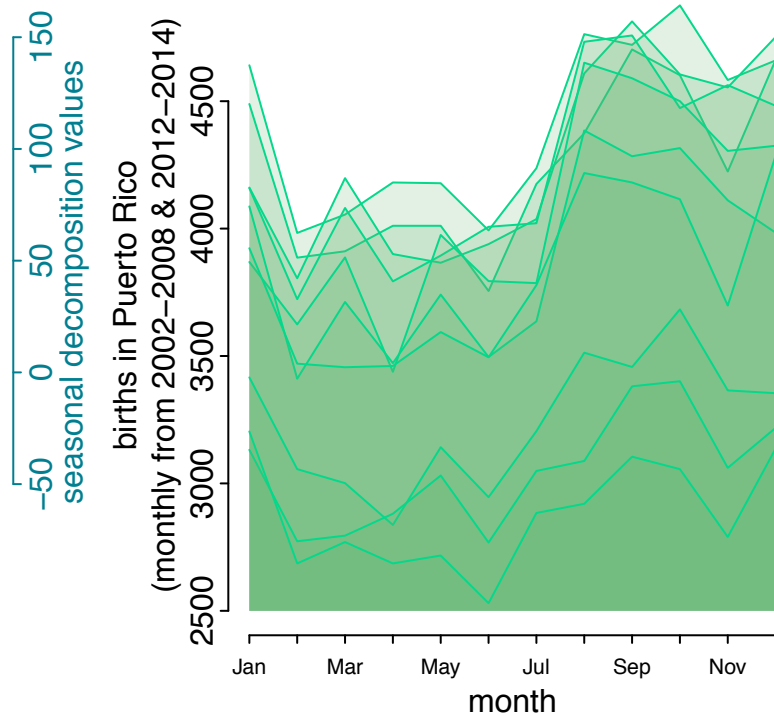
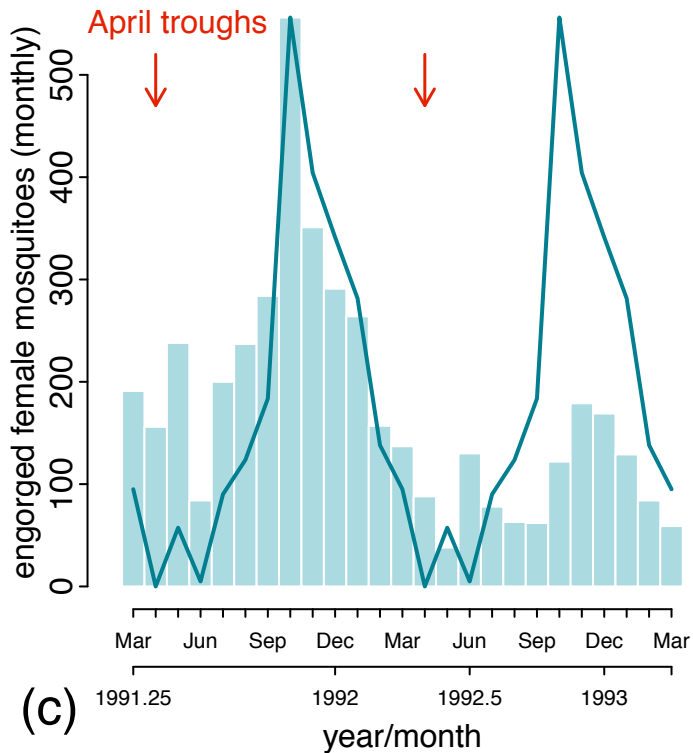


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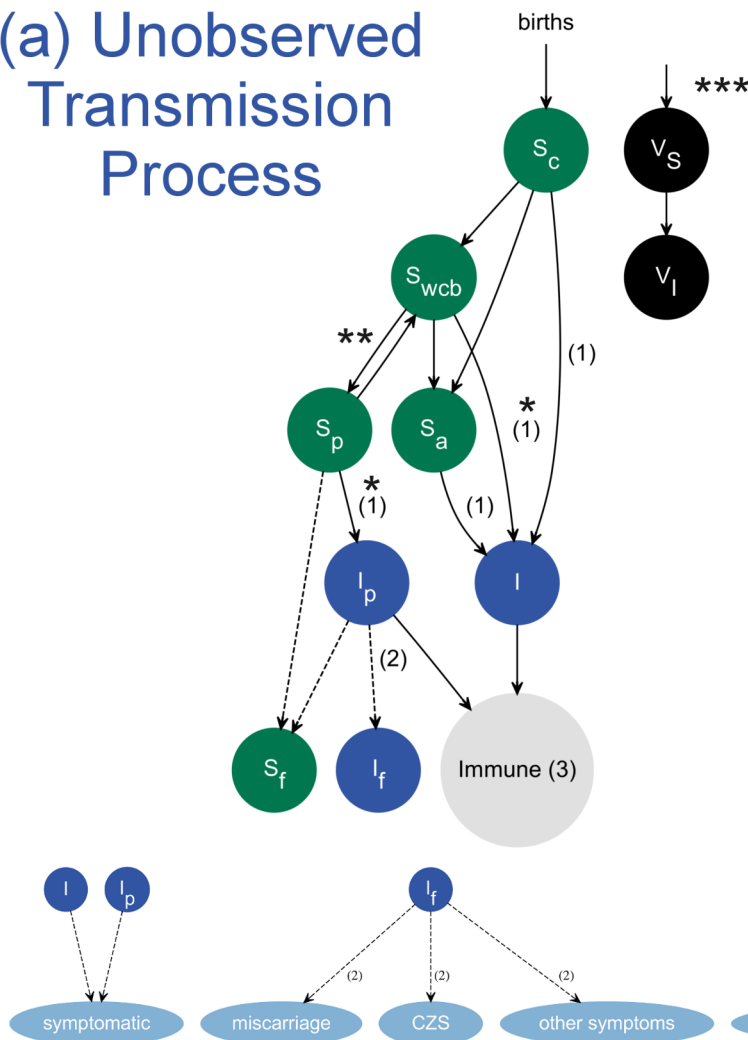
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## (a) Unobserved Transmission Process



### Knowledge Gaps:

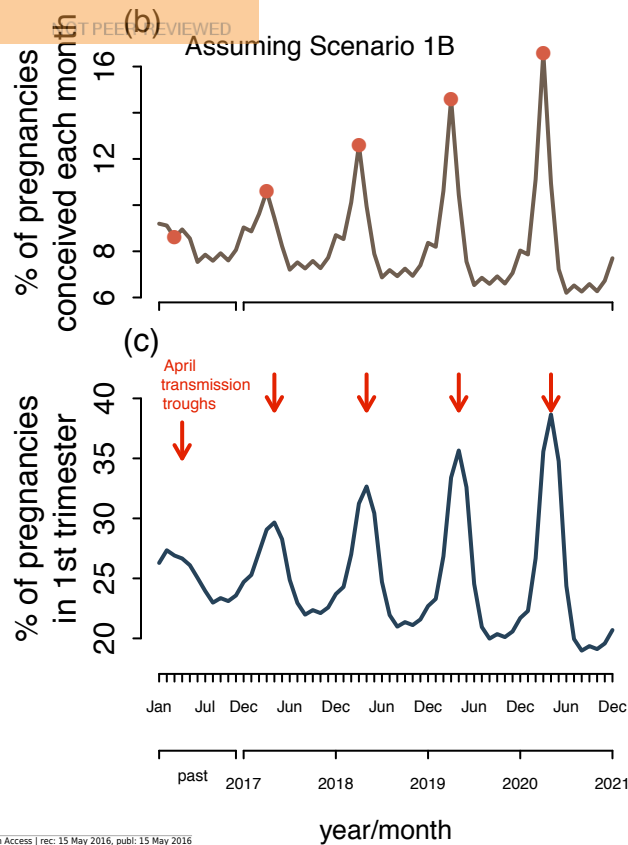
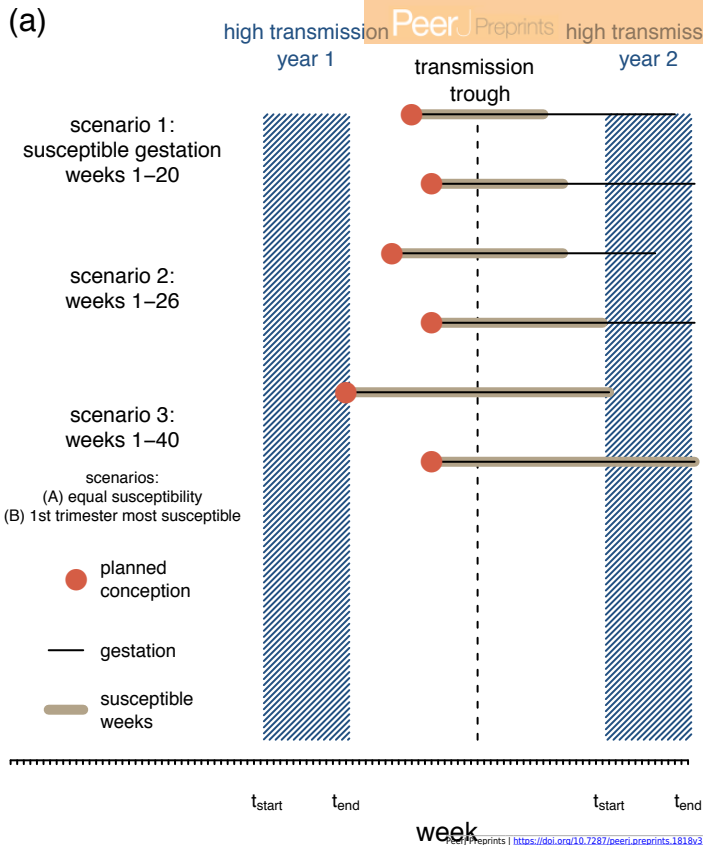
- (1) Seasonality of ZIKV transmission
- (2) intrauterine transmission & pathology
- (3) immunity (mode & duration of protection)

### Interventions:

- \* Protect pregnant women & those of childbearing age
- \*\* Delay pregnancy
- \*\*\* Vector control

## (b) Surveillance Systems





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