Preventing Zika virus Infection during Pregnancy by Timing Conception Seasonally

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Summary

It has come to light that ZIKV infection during pregnancy can result in fetal death, damage to the central nervous system, and growth restrictions. In 2016 there are expected to be >8,600,000 births in countries with ongoing ZIKV transmission. In response to the ZIKV threat, the WHO is strategically targeting prevention of infection in pregnant women and funding contraception use in epidemic regions. I propose that the damaging effects of ZIKV can be curtailed by timing pregnancy seasonally to minimize maternal exposure to ZIKV. The ZIKV mosquito vector has seasonal changes in its abundance and *flavivirus* transmission competence. By seasonally planning pregnancy, this aspect of vector ecology can be leveraged to align sensitive periods of gestation with the low-transmission season.

Keywords. Zika, family-planning, season, infectious disease

Zika virus (ZIKV) is spreading rapidly across the globe [1]. Pregnant women infected with ZIKV risk severe fetal outcomes, including damage to the central nervous system (CNS) and death [2]. ZIKV is the suspected cause of the 2015/2016 outbreak of microcephaly in Brazil [3]. Two reports from February 2016 and a report from March 2016 provide strong evidence for a causal link. Most recently, 42 ZIKV-positive pregnant women were tested for fetal abnormalities. Adverse findings—including death, microcephaly, and CNS damage—were observed in 12 of the women. There were no abnormalities in ZIKV-negative women [2]. In addition, the complete ZIKV genome was recovered from the brain of a fetus with microcephaly aborted by an expectant mother infected during the 13^{th} week of gestation [4], and the CDC has reported four informative ZIKV-positive cases, two were newborns from Brazil with microcephaly who died shortly after birth, and two were miscarriages [5]. Recognizing the incomplete picture of ZIKV *in utero* pathology, in February 2016, the World Health Organization (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 [3]. Maternally-transmitted viral infections, such as ZIKV, can be achieved by protecting mothers from infection, but it is likely to be many years before the maternal transmission and molecular pathogenic mechanisms of ZIKV are understood sufficiently to develop treatments and/or vaccines. Alternative preventative measures are therefore needed to protect women and their children from this emerging pathogen.

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The WHO's ZIKV operational response plan includes control of the *Aedes aegypti* mosquito, which vectors ZIKV, and also financing contraceptive services in affected areas to manage pregnancy and mitigate the impact of ZIKV [3]. In addition, government officials in El Salvador, Colombia, and Ecuador have recommended women delay pregnancy while uncertainty surrounding ZIKV remains. 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 the ZIKV risk without requiring long-term delays of pregnancy. Specifically, I recommend that the public health community collectively considers (1) the seasonality of *Aedes aegypti* mosquitoes, (2) birth seasonality in humans, and (3) knowledge of infection-induced birth defects to develop regionally-tailored recommendations for seasonally-planned pregnancy that minimize the risk of ZIKV infection.

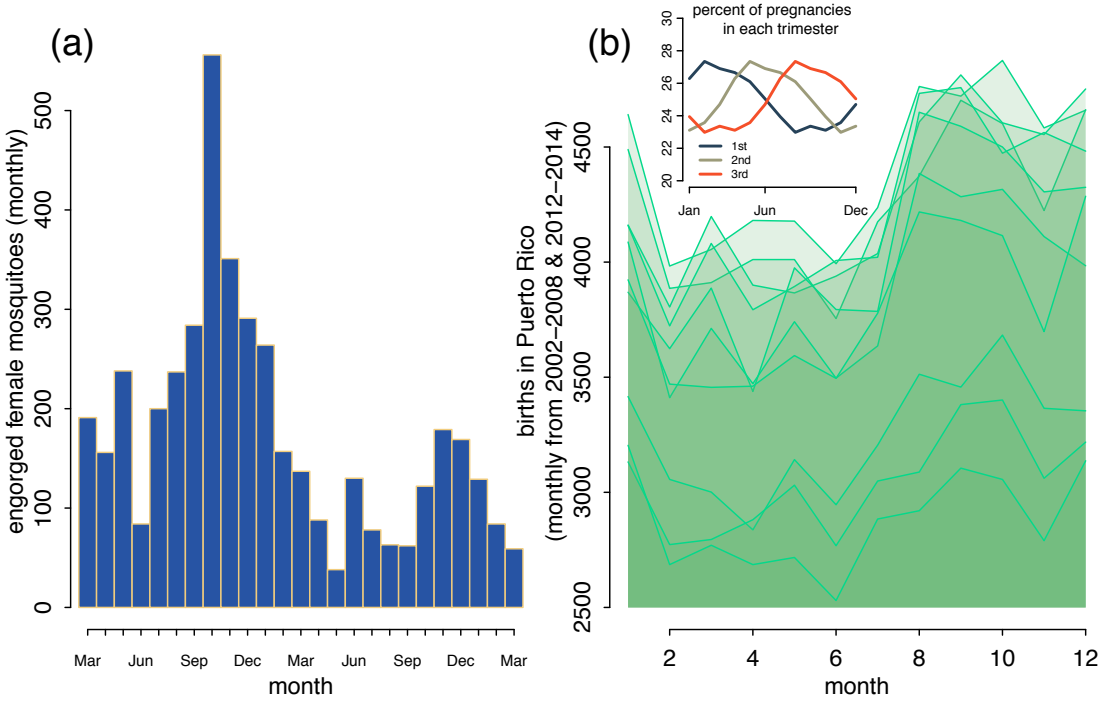

Figure 1: Seasonality of the ZIKV vector *Aedes Aegypti* and birth seasonality. (a) Monthly abundance of trapped female mosquitoes engorged with blood-meal in Puerto Rico. Data from [6]. (b) Monthly births in Puerto Rico. Births are seasonal around the world; the birth peak in Puerto Rico occurs around September each year. (b inset) The seasonal distribution of pregnancies by trimester. The timing of each trimester was estimated based on the birth data from Puerto Rico (data from [7]).

Seasonally-Timing Pregnancy. *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 [8, 9]. *Aedes aegypti* seasonality drives seasonal transmission of Dengue and Chikungunya virus [8, 10] and it is likely to result in seasonal ZIKV transmission. In regions with strong seasonal fluctuations in *Aedes aegypti*, the annual vector "low-season" should be characterized and pregnancy planned such that gestation is aligned with the vector low-season. This would minimize risk of maternal infection and subsequent damage to the fetus. In addition to vector seasonality, births are seasonal across human populations, and there is a distinct birth pulse in most countries/populations that varies geographically in its seasonal timing [11, 12]. 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 maternal

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infection with ZIKV for entire birth cohorts.

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 [13, 14, 15]. Fetal abnormalities have been found in women infected with ZIKV during weeks 8-35 of gestation [2], and miscarriages of ZIKV-positive fetuses have occurred at 11 and 13 weeks gestation [5]. A window of susceptibility (e.g., weeks 8-35) might also exist for ZIKV, and this window must be taken into account when planning the recommended seasonal timing of pregnancy. 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. Based on these data, the high transmission season in Puerto Rico is predicted to be October-December and the vector low-season is approximately April-June. Importantly, the high and low transmission seasons will be region-specific since they are tied to local climate conditions. 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 1b inset). Identifying the period of susceptibility for the fetus and using planned seasonal conception to redistribute births—i.e., to take advantage of the vector low season and ensure sensitive gestation occurs during the vector low season—would reduce risk to the fetus by minimizing maternal exposure. Based on the size of the 2014 birth cohort, 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 Puerto Rico. In a large country like Brazil, which had a birth cohort of approx. 3 million in 2015 [16], planned seasonal conception for 3% of births could reduce risk in >88,000 pregnancies.

Fig 2a shows the recommended timing of conception when the high transmission season lasts 13 weeks and the fetus is susceptible during either the full gestation period (weeks 1-40) or weeks 8-35 (based on the data from [2]). Assuming the window of susceptibility spans gestation weeks 8-35, Fig 2b shows how the seasonal distribution of pregnancy 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 minimize risk and provide an option for women as they wait for ZIKV epidemiology and clinical interventions to be hammered out. 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.

Until the susceptible window of gestation is determined, all gestation weeks will need to be assumed susceptible (e.g., top line in Fig 2a). A conception planning calendar is provided as Supporting Information. This calendar assumes the high transmission season is $\leq$13 weeks, pregnancy lasts 40 weeks (full term), and the fetus is susceptible throughout gestation. To increase the effectiveness

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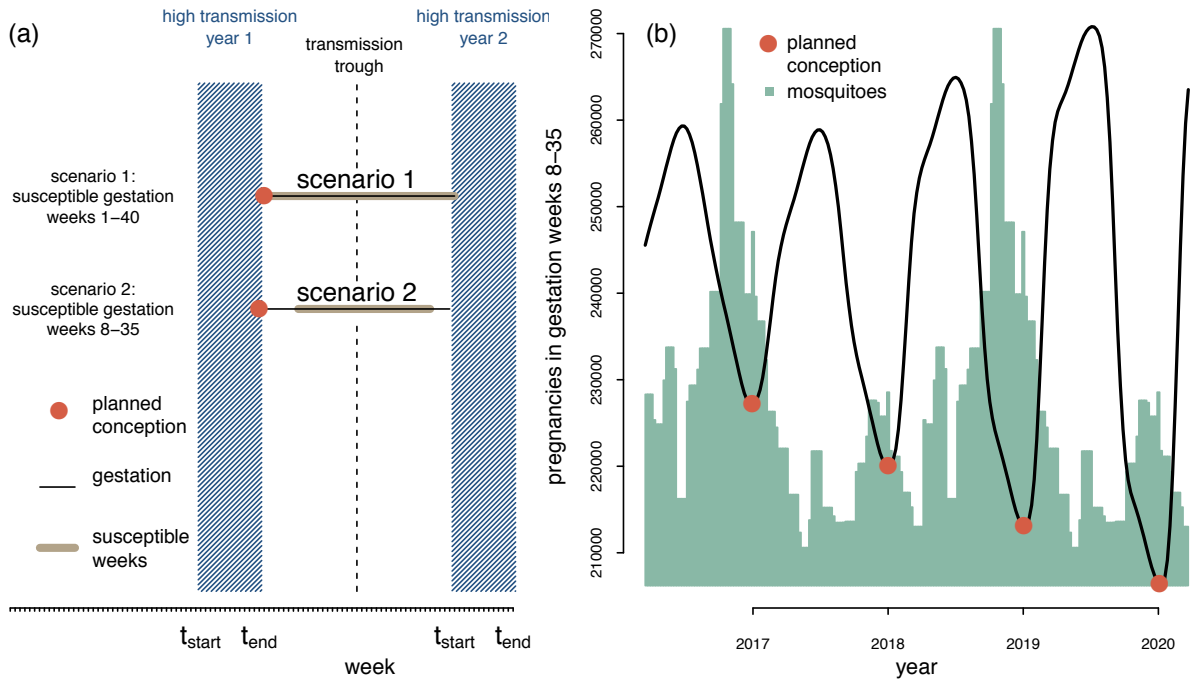

Figure 2: Planning pregnancy to take advantage of the low ZIKV transmission season. (a) The recommended timing of conception based on the region-specific transmission season. The high-transmission season is marked in blue, and the trough is indicated by the dashed line. Policy should encourage planned conception such that the susceptible gestation period is aligned with the transmission trough. This policy would minimize the risk of 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 pregnancies in gestation weeks 8-35 in Puerto Rico if conception were seasonally planned. Gestation weeks 8-35 were assumed to be susceptible (based on [2]). Conception was therefore encouraged at turn-of-the-year target weeks (weeks 51, 52, 1, and 2), 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 outside of target weeks being shifted to target weeks.

of planned seasonal conception, vector control campaigns could be used to restrict the mosquito season, which would 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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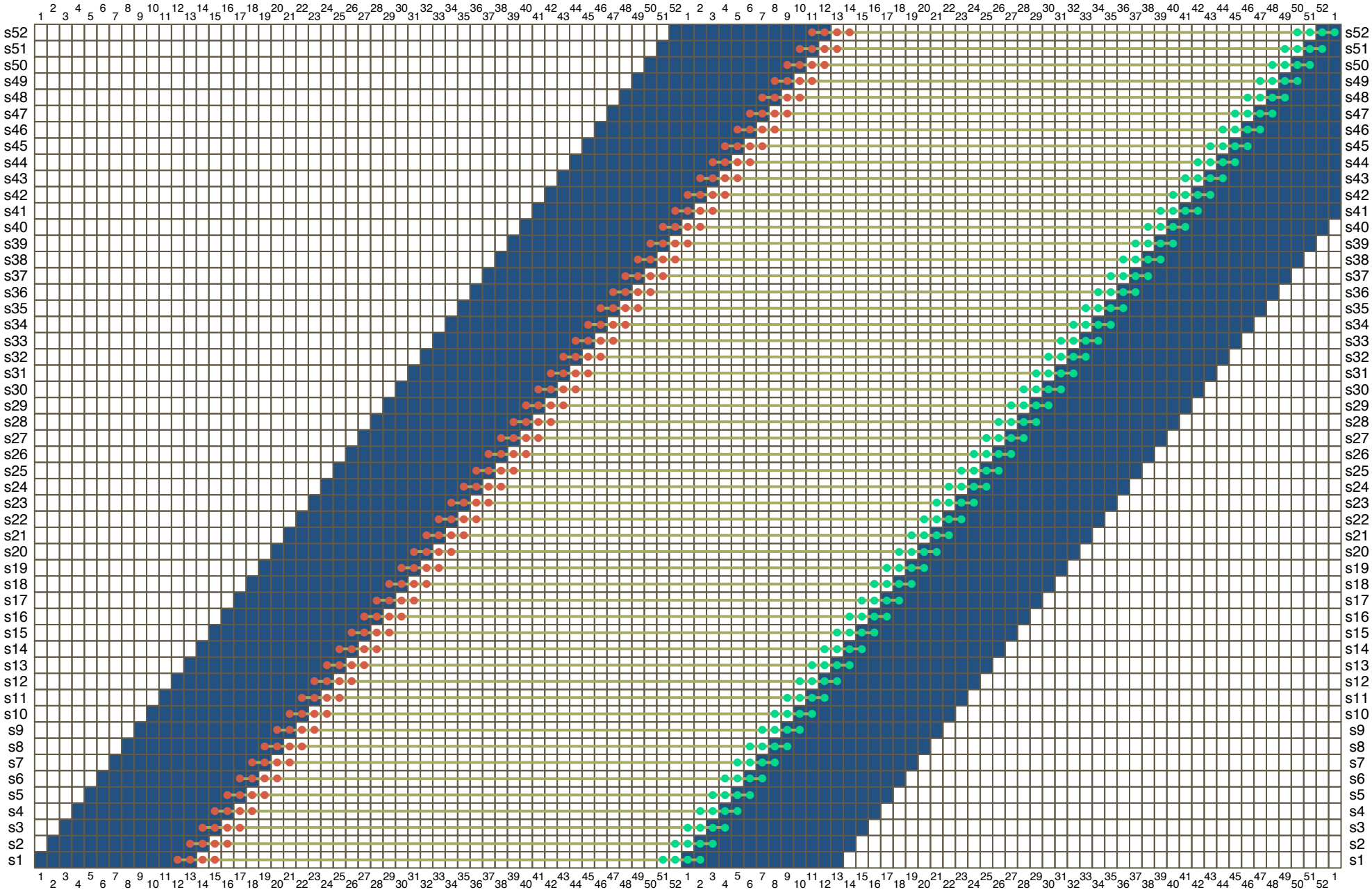
week of the year



Step 1: Is the high−transmission season < 14 weeks long?
(if yes, Step 2)
Step 2: Identify the high−transmission season scenario
Step 3: Identify the planned conception weeks for that scenario

high transmission season
planned conception
gestation
delivery

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