Potential for Zika virus to establish a sylvatic transmission cycle in the Americas

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Abstract

Zika virus (ZIKV) originated and continues to circulate in a sylvatic transmission cycle between non-human primate hosts and arboreal mosquitoes in tropical Africa. Recently ZIKV invaded the Americas, where it poses a threat to human health, especially to pregnant women and their infants. Here we examine the risk that ZIKV will establish a sylvatic cycle in the Americas, focusing on Brazil. We review the natural history of sylvatic ZIKV and present a mathematical dynamic transmission model to assess the probability of establishment of a sylvatic ZIKV transmission cycle in non-human primates and/or other mammals and arboreal mosquito vectors in Brazil. Brazil is home to multiple species of primates and mosquitoes potentially capable of ZIKV transmission, though direct assessment of host competence (ability to mount viremia sufficient to infect a feeding mosquito) and vector competence (ability to become infected with ZIKV and disseminate and transmit upon subsequent feedings) of New World species is lacking. Modeling reveals a high probability of establishment of sylvatic ZIKV across a large range of biologically plausible parameters. Probability of establishment is dependent on host population sizes and birthrates and ZIKV force of infection, but a network of as few as 6,000 primates with 10,000 mosquitoes is capable of supporting establishment of a ZIKV sylvatic cycle. Research on the susceptibility of New World monkeys or other small mammals to ZIKV, on the vector competence of New World *Aedes, Sabethes*, and *Haemagogus* mosquitoes for ZIKV, and on the geographic range of these species is urgently needed. A sylvatic cycle of ZIKV would make future elimination efforts in the Americas practically impossible, and paints a dire situation for the epidemiology of ZIKV and ending the ongoing outbreak of congenital Zika syndrome.

keywords

Zika virus, arbovirus, sylvatic transmission, enzootic transmission, mathematical modeling, primates, mosquitoes

Introduction

The invasion of Brazil by Zika virus (ZIKV) is the latest upheaval in a decade-long cataclysm in the epidemiology of viruses transmitted by the mosquito *Aedes aegypti* in the Americas [1, 2]. Dengue virus (DENV) made forays into Florida in 2009 [3], Arizona in 2014 and Hawaii in 2015 [4]; chikungunya virus (CHIKV) was introduced into the Caribbean in 2013 and hurtled across both Central and South America [5]; and, in 2015, Zika virus (ZIKV) was first detected in Brazil. With ZIKV came a spike in cases of congenital microcephaly and Guillain-Barre syndrome [2, 6]. The introduction of ZIKV to the Americas had been predicted well in advance of the event [7, 8], however, the association of ZIKV infection with neuropathology and teratogenicity were only revealed during the spread of the virus through the Pacific and into Brazil. Hayes [7] did warn in 2009 that the spread of ZIKV warranted concern despite lack of contemporary evidence for severe ZIKV disease. He reminded the scientific community that West Nile virus was also considered a "relatively innocuous pathogen" until it ushered outbreaks of neuroinvasive disease into Europe and the Americas. In response to a growing body of evidence linking ZIKV infection with teratogenic effects [9, 10, 11], the World Health Organization declared the ZIKV outbreak a public health emergency of international concern in February of 2016 [1, 12].

ZIKV is unusual among the arthropod-borne viruses (arboviruses) in its capacity for sustained transmission in a human-endemic cycle. This capacity is shared by three other arboviruses that are also, not coincidentally, transmitted in the human cycle by *Aedes aegypti*: DENV, CHIKV and yellow fever virus (YFV). For all four viruses, human-endemic lineages emerged from ecologically and evolutionarily distinct, sylvatic, enzootic cycles transmitted between mostly arboreal *Aedes* spp. vectors and non-human animal hosts [7, 13, 14]. While non-human primates (hereafter primates) have generally been considered the major reservoir hosts for the sylvatic transmission cycle of all four viruses, this paradigm is

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26 based on scant evidence and researchers in the field have repeatedly cautioned that other
27 animal species may play key roles in the transmission dynamics of these viruses [15, 16,
28 13, 7]. The ancestral sylvatic cycles of YFV, CHIKV and ZIKV occur in Africa, while the
29 DENV ancestral cycle occurs in Southeast Asia with later transport to West Africa and
30 enzootic establishment [17]. YFV was transported from Africa to the Americas in infected
31 humans and mosquitoes via the slave trade in the 17th and 18th centuries [18] and spilled
32 back into a sylvatic cycle, maintained in New World monkey species, which persists today.
33 Dengue virus, in contrast, has not spawned an established a sylvatic transmission cycle
34 in the Americas despite widespread circulation of the virus across the Americas in the
35 human-endemic cycle [13].

36   Whether ZIKV will emulate YFV or DENV is an open and urgent question. If the virus
37 establishes a sylvatic cycle in the Americas, then mosquito control and even vaccination
38 will not suffice to eradicate it from the region. ZIKV was first isolated in 1947 from a
39 sentinel monkey in the Ziika forest of Uganda. Intriguingly the sentinel species used was
40 the rhesus macaque, demonstrating the susceptibility of Asian primates to ZIKV. The
41 next year ZIKV was isolated from *Ae. africanus* in the area, suggesting mosquito-borne
42 transmission of the virus. As laid out in the comprehensive review by Hayes, the virus was
43 subsequently detected across a wide swath of tropical Africa via serosurveys of monkeys
44 as well as virus isolation from monkeys and several species of sylvatic *Aedes* [7]. Notably
45 these mosquitoes were collected in the forest canopy but also on the forest floor. Infection
46 of humans living in proximity to sylvatic cycles was detected via serosurveys and clinical
47 surveillance. Seroprevalence was variable and quite high (up to 40%) in some human
48 populations, but disease was invariably mild, generally manifesting as fever, headache,
49 rash and conjunctivitis. In 2007, an outbreak of ZIKV in Libreville, the capital of Gabon
50 was thought to have been vectored by the peri-urban mosquito species *Aedes albopictus* [19].

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51 Importantly, experimental studies of the interaction among different African arboviruses

52 have shown evidence for both enhancement [20, 21] and interference [7].

53   Over the same time period that the ZIKV transmission cycle was being investigated in

54 Africa, circulation of ZIKV was documented in several countries in Asia. Albert Rudnick,

55 the pioneer of sylvatic DENV research, isolated the virus from *Ae. aegypti* in Malaysia [22].

56 A serological study in 1977-78 in Central Java revealed that a high percentage of febrile

57 patients had antibodies against ZIKV [23]. Subsequently ZIKV infection was documented

58 in travellers returning from Indonesia [24], Thailand [25], and Malaysia [26] and in residents

59 of Indonesia [27], Cambodia [28], the Philippines [29], and Thailand [30]. One of the cases

60 of Zika infection in a traveller was notable as disease onset occurred five days after being

61 bitten by a monkey in Indonesia [31]. Anti-ZIKV antibodies have also been detected

62 semi-captive orangutans in Malaysia [32] To date there has been no solid evidence of an

63 Asian sylvatic cycle of ZIKV, but such a sylvatic cycle could be widespread and still go

64 undetected due to the lack of surveillance for sylvatic arboviruses in Southeast Asia [33].

65 Thus it remains uncertain whether all human ZIKV infections in Asia derive from the

66 human-endemic cycle or whether some may occur due to spillover from an as-yet unknown

67 sylvatic cycle in the region. The lineage of ZIKV that circulates in Asia is distinct from

68 the African lineages of the virus, and it is the Asian lineage that spread across the Pacific

69 and into Brazil [34].

70   Research on the sylvatic cycle of ZIKV since 2007 has focused primarily on West Africa.

71 Phylogenetic analysis indicates that the virus has been introduced into West Africa at least

72 twice in the twentieth century [35] and that West Africa contains ZIKV strains that are

73 distinct from those elsewhere in Africa [36]. Analyses of mosquitoes collected annually

74 over the last fifty years in Kedougou, Senegal demonstrated that ZIKV is amplified in

75 mosquito collections at four year intervals, that rainfall is a positive predictor of ZIKV

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isolations in mosquitoes, and that there was little positive or negative association between amplification of ZIKV and of three other *Aedes*-borne arboviruses that circulate in the region, YFV, DENV-2 and CHIKV [37]. Moreover our field studies in Kedougou during the 2011 ZIKV amplification showed that the virus was present in all major land cover classes in the region but was detected significantly more often in the forest than in other land cover types [38]. In this study, ZIKV was detected in ten separate species of *Aedes*, with *Ae. hirsutus*, *Ae. unilineatus*, *Ae. metallicus*, and *Ae. africanus* having the highest minimum infection rates of collected species. In addition, one pool of male *Ae. furcifer* was found to be positive, indicating possible vertical transmission of ZIKV. To follow up these field observations, Diagne et al. tested the vector competence of multiple Senegalese *Aedes* species for ZIKV in the laboratory and found that only *Ae. luteocephalus* and *Ae. vittatus* were capable of transmitting the virus [39]. ZIKV has previously been isolated from two of the three monkeys species resident in Kedougou: African green monkeys (*Chlorocebus sabaeus*) and patas monkeys (*Erythrocebus patas*) (reviewed in [40]) In combination with previous field studies in Africa, these findings demonstrate that the transmission dynamics of ZIKV are complex and that a diverse network of *Aedes* vector species and primate host species participate in the maintenance of the sylvatic ZIKV cycle.

Here, we used a mathematical model that we have previously employed to study the sylvatic DENV cycle in Senegal [41] to identify the conditions of host and vector density and connectivity that would permit the establishment of an American sylvatic cycle of ZIKV.

Establishing a sylvatic ZIKV cycle

Our model extends, to our knowledge, the only previous dynamic model of mosquito-borne viruses in non-human primate hosts [41, 42]. While the Althouse et al. (2012)

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study was focused on sylvatic DENV, the strong similarities between sylvatic DENV and sylvatic ZIKV transmission cycle make the model a good fit for both viruses. Here we use the model to ask whether ZIKV will establish a self-sustaining transmission cycle in a network of two susceptible host populations with two corresponding competent vector mosquito populations after introduction of a single ZIKV-infected host. We assume host and vector species interact as separate populations, and thus populations correspond to separate species. Further, we assume that each host population has a vector population that is source of the largest number of bites that could transmit ZIKV, indicating vector preference, with a vector biting its preferred host 100 times more frequently than its non-preferred hosts. Our previous work suggests that this non-preferred biting synchronizes transmission in the two populations and the synchrony is qualitatively unrelated to the ratio of preferred to non-preferred biting [41]. Here we explore primates and mosquitoes as the hosts and vectors, with Althouse et al. (2012) and Althouse and Hanley (2015) giving full model details.

Briefly, mosquitoes and primates are born susceptible to ZIKV infection, and are infected at a rate proportional to the number of bites given or received per day and a probability of infection. Primate species differ in their life history, particularly birthrate and lifespan. We assume birthrate = 1/lifespan, which is conservative as age of fertility completion is younger than age of mortality for many primates [43]. Transmission probabilities vary seasonally due to differences in rainfall and temperature [37]. We explore three per-bite infection probabilities (0.3, 0.6, 0.9) with an average of 0.5 infectious bites per day. This gives forces of infection 0.15, 0.3, 0.45, which is in line with observed sylvatic DENV forces of infection from primate collections in Kedougou, Senegal in 2010-2012 (Sall, Diallo, Althouse, Hanley, Weaver, unpublished data). These forces of infection ranged from 0.09 (95% CI: 0.07, 0.11) for Guinea baboons (*Papio papio*) in 2012, to 0.41 (95% CI: 0.26,

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125 0.76) for African green monkeys (*Chlorocebus sabaeus*) in 2012. After infection, primates

126 recover at a fixed rate (4 days [44]) while mosquitoes are infected for the remainder of their

127 life. We employ the stochastic version of the model simulated using a Gillespie stochastic

128 simulation algorithm with the Binomial Tau leap approximation (BTL) to examine the

129 effects of population size, primate birthrate, and force of infection on the probability of

130 ZIKV establishment. Simulations were run and we calculated the proportion of simulations

131 not becoming extinct after introduction of a ZIKV infected host (ie, establishing a sylvatic

132 cycle).

133   Model simulations suggest the probability of establishment is highly dependent on the

134 primate birthrate (Figure 1). In low and medium force of infection settings (0.15 and

135 0.3) primates with lifespans of 15 and 25 years show little probability of sylvatic estab-

136 lishment (panels d, g, h). However, if there exists a rapidly reproducing primate (lifespan

137 of 5 years), establishment of a sylvatic cycle is nearly assured (panels a, b, c). Generally,

138 increasing numbers of primates relative to mosquitoes lowers the probability of establish-

139 ment, as might be expected as the force of infection is directly proportional to the number

140 of mosquitoes and inversely proportional to the number of primates [37]. A network of as

141 few as 6,000 primates with 10,000 mosquitoes is capable of supporting the establishment

142 of a ZIKV sylvatic cycle.

Outlook

144 To our knowledge, the susceptibility of New World monkeys to ZIKV has never been tested,

145 and it is possible that they are insusceptible to ZIKV infection or generate only low levels

146 of viremia insufficient to infect potential sylvatic vectors. However, as we have pointed out

147 in a previous review, there are free-living populations of several Old World monkey species

148 in the Americas, some of which, notably African green monkeys (which as noted above had

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149 high forces of sylvatic DENV infection in Senegal) are known to be hosts of sylvatic ZIKV in

150 Africa [13]. Our model predicts that the presence of a rapidly reproducing primate or other

151 mammal that is a competent host for ZIKV vastly increases the chances of establishment.

152 There is some serological evidence that vertebrates other than primates may also serve as

153 enzootic reservoirs of ZIKV [27, 45]. Again, ZIKV susceptibility testing of potential small

154 mammal hosts is lacking and should be a high priority for future research.

155 We also do not know the susceptibility of most New World *Aedes* species for ZIKV.

156 However, it has recently been shown that *Ae. albopictus* was likely the primary vector of

157 a ZIKV outbreak in humans in Gabon [19]. This mosquito species, which is common in

158 the Americas, has a broad host range and has high potential to serve as a bridge vector

159 to transfer the virus from humans to non-human animals [46]. Additionally, *Sabethes* and

160 *Haemagogus* spp mosquitoes are tropical New World vectors of sylvatic YFV and thus may

161 be likely vectors of sylvatic ZIKV as well [13].

162 The current work is limited by gaps in knowledge, and relies on sylvatic ZIKV trans-

163 mission dynamics being similar to sylvatic DENV transmission – a reasonable assumption

164 given the extensive overlap of the two viruses in the hosts and vectors used in West African

165 sylvatic cycles [7, 13, 38]. We note that our model calculates the probability of ZIKV estab-

166 lishment starting from a single infectious introduction without further importation, and

167 does not include vertical transmission of ZIKV within mosquitoes. These features both

168 make our estimates conservative and potentially paint a dire situation for the epidemi-

169 ology of ZIKV and for prospects of extinguishing the ongoing congenital Zika syndrome

170 outbreak in Brazil.

171 The International Task Force for Disease Eradication identifies a key factor for consid-

172 ering a disease eradicable as epidemiologic vulnerability, including not having the presence

173 of an animal reservoir [47]. Establishment of a sylvatic cycle of ZIKV would make future

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174 elimination efforts in the Americas extremely difficult if not impossible. Taking lessons

175 from sylvatic YFV in Brazil, reactive, and massive vaccination efforts will be necessary

176 when a ZIKV vaccine becomes available to control ZIKV transmission [48], decrease mor-

177 bidity, and protect unborn infants from potential teratogenic effects. We use this work to

178 identify and highlight key lines of research that would enable the public health community

179 to understand ZIKV transmission going forward and target surveillance for enzootic ZIKV

180 to those animal populations most likely to sustain virus transmission.

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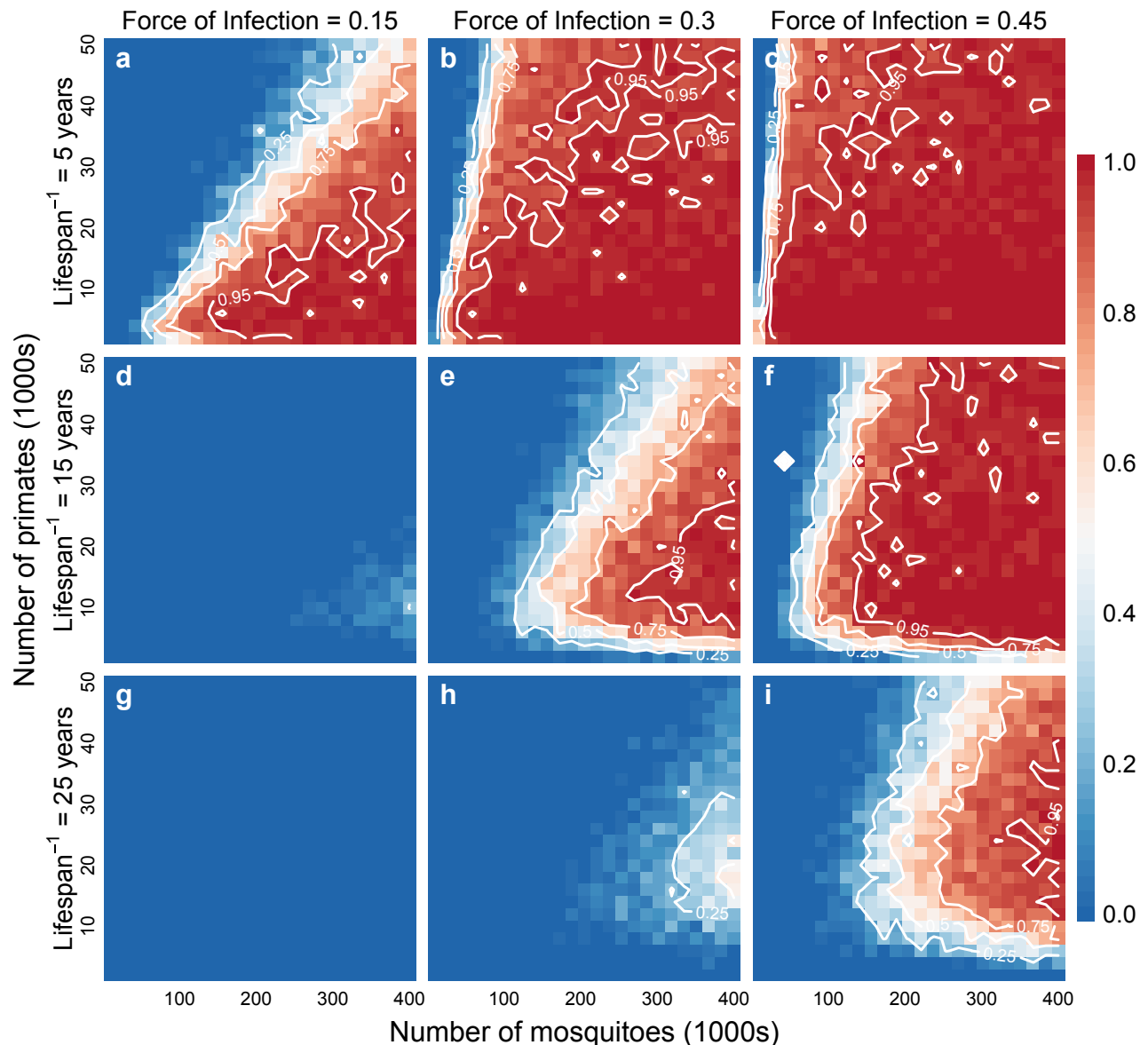325   2014.

Figure 1: **Figure 1 Probability of establishing a sylvatic ZIKV transmission cycle.** Figure shows heat maps of the probability of ZIKV establishment in 50 simulations per parameter set with colors ranging from blue (0 simulations establishing) to red (all simulations establishing). Contour lines show 0.25, 0.5, 0.75, and 0.95 probability of establishment. For each plot, the x-axis shows the total number of mosquitoes (in two populations) and the y-axis shows the total number of non-human primates (in two populations). Left to right the panels indicate increasing in force of infection, and top to bottom decreasing non-human primate birthrate (as 1/lifespan). Other parameters: mean mosquito lifespan = 7 days; mean ZIKV recovery in NHP = 4 days; mosquito vertical transmission of ZIKV = 0; rate of yearly ZIKV introduction = 0.