

Estimating Vector-borne Viral Infections in the Urban Setting of the 2020 Tokyo Olympics, Japan, Using Mathematical Modeling

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The first domestic outbreak of dengue fever in Japan since 1945 was reported in Tokyo in 2014. Meanwhile, daily mean summer temperatures are expected to continue to rise world-wide. Such conditions are expected to increase the risk of an arbovirus outbreak at the 2020 Tokyo Olympic Games.

To address this possibility, the present study compared estimates of the risk of infection by dengue, chikungunya, and Zika viruses in urban areas. To compare the risk of infection by arboviruses transmitted by *Ae. albopictus* mosquitoes, the reproduction number for each of three arboviruses was estimated under the environmental conditions associated with the 2014 dengue outbreak in Tokyo, and additionally under conditions assuming a daily mean temperature elevation of 2°C.

For dengue, chikungunya, and Zika, the estimated distributions of R_0 were independently fitted to gamma distributions yielding median R_0 values of 1.00, 0.46, and 0.36, respectively. If the daily mean temperature were to rise from 28°C to 30°C, our model predicts increases of the median R_0 of 18% for dengue, 4.3% for chikungunya, and 11.1% for Zika.

Strengthening of the public health responsivity for these emerging arboviral diseases will be needed in preparation for the 2020 Olympic Games in Tokyo.

Key words: Dengue virus, Chikungunya virus, Zika virus, Mathematical modeling, Urban area

INTRODUCTION

A Zika virus epidemic in Brazil has been locally observed starting from mid 2014, and the virus was initially detected in July of 2015; the virus subsequently spread to other Latin American countries in 2016 [1-4]. There was the speculation that the virus was introduced during the FIFA World Cup and in the World Sprint Championship Canoe Races in 2014 by phylogenetic and epidemiological investigation [5, 6].

The detection of this disease is reminiscent of the recent outbreak of dengue fever in Japan, a disease that is caused by a similar class of virus and also transmitted by *Aedes* mosquitoes. The first cases of the dengue outbreak, confirmed on 27 August 2014, represented the first autochthonous dengue infection reported in Japan since 1945 [7, 8]. Subsequently, a total of 160 dengue cases were reported in Japan through the end of October, 2014; the majority of these infections were transmitted by *Ae. albopictus* mosquitoes in Tokyo's Yoyogi Park [7, 8]. Like dengue, Zika virus and chikungunya virus also are transmitted by *Ae. albopictus*, and Japan will be at risk of outbreaks of these mosquito-borne diseases during the 2020 Tokyo Olympics, as many travelers from the epidemic areas of these mosquito-borne diseases will visit Tokyo, Japan. Simultaneous outbreaks of dengue, chikungunya, and Zika virus infections might occur in Japan, a country that does not currently have mosquito-borne disease transmission, due to expected delays between infection and diagnosis.

Moreover, monthly mean temperature in the summer of 2020 are assumed to rise by 2°C compared to the summer 2014 values according to the urban heat island effects. An urban heat island means that the air temperature at the city center is higher than that of the surrounding non-urban areas so that it looks like an island and this phenomenon is so called "urban heat island". Given that the mortality and biting rates of infected mosquitoes depend on ambient temperature, infection risk is expected to increase with this temperature elevation.

In the present study, I estimated and compared the risks of infection by dengue, chikungunya, and Zika viruses under the environmental conditions matching those that led to the 2014 dengue outbreak in Tokyo. I further investigated the additional infection risks of these vector-borne diseases that would be associated with the elevated temperatures predicted for urban heat islands.

MATERIALS AND METHODS

The basic reproduction number R_0 was calculated using the classic Ross-Macdonald model [8]:

$$R_0 = ma^2bc \exp(-\mu\tau_c) / (\mu\gamma)$$

where m is the number of female mosquitoes per person; a is the daily biting rate of the mosquitoes; b and c are the probabilities of viral transmission from an infected mosquito to a susceptible human, and from an infected human to a mosquito, respectively;

Table Parameters and parameter values

Parameter	Symbol	Dengue	Chikungunya	Zika
Host parameters				
Inverse of the duration of infectious period	γ	1/Gamma(25, 0.2) ⁸	1/Gamma(25, 0.2) ¹³	1/Gamma(100, 0.05) ¹⁰
Vector parameters (<i>Ae. albopictus</i>)				
Extrinsic incubation period for 28°C	$\tau_e(28)$	9.27	3.09	6.18
Extrinsic incubation period for 30°C	$\tau_e(30)$	6.09	2.03	4.06
Daily mortality rate for 28°C	$\mu(28)$	0.076	0.076	0.076
Daily mortality rate for 30°C	$\mu(30)$	0.085	0.085	0.085
Daily biting rate of mosquitoes for 28°C	$a(28)$	0.107	0.107	0.107
Daily biting rate of mosquitoes for 30°C	$a(30)$	0.112	0.112	0.112
Host and vector parameters				
Transmission probability (vector to host)	b	0.46 ⁸	0.33 ¹²	0.31 ¹⁰
Transmission probability (host to vector)	c	0.83 ⁸	0.33 ¹²	0.35 ¹⁰

Superscript numbers indicate references (sources of values).

Gamma (k, θ) shows gamma distribution with shape parameter k and scale parameter θ .

τ_e is the extrinsic incubation period; μ is the daily mortality rate of the vector; and γ is the inverse of the duration of the infectious period of the host.

Density of mosquito to person m was assumed at 7.13 per person based on the results of the investigation of *Ae. albopictus* mosquitoes collected in Yoyogi Park in September 2014 [9]. For other parameters, values for Zika virus were based on the values obtained in a modeling analysis of the outbreaks in the Pacific islands (Yap, Micronesia, 2007; Tahiti and Moorea, French Polynesia, 2013–2014; and New Caledonia, 2014) [10, 11], and those for chikungunya virus were based on the values obtained in a modeling analysis of a 2007 epidemic outbreak in Europe [12, 13]. The values for calculating R_0 estimates are summarized in Table. As *Ae. albopictus* may play a role in outbreaks of dengue and chikungunya viruses in Japan, vector parameters, and host and vector parameters were defined as specified by the previous reports about dengue and chikungunya epidemics with *Ae. albopictus*. The temperature-dependent mortality rate was defined by the following expression from previous reports based on laboratory and field data [14]:

$$1/(1.065 + \exp(32.2 - 0.92T)) + 0.0747 \text{ if } T \geq 26.3^\circ\text{C}$$

The temperature-dependent biting rate was given by the following equation [15, 16]:

$$0.5 \times (0.0043T + 0.0943).$$

The temperature-dependent extrinsic incubation period (EIP) for each virus in *Ae. aegypti* was given by the following equation [17];

$$\kappa_{28} \times \exp(-0.21(T - 28.0))$$

where a base value $\kappa_{28} = 9.0$ for dengue, 3.0 for chikungunya, and 6.0 for Zika (measured at 28°C). The EIP of each virus in *Ae. albopictus* mosquitoes was obtained from multiplying factor 1.03 and the EIP for *Ae. aegypti*.

Estimated R_0 values were obtained using a Monte Carlo simulation function in Oracle Crystal Ball soft-

ware (Oracle Corporation, Redwood Shores, CA, USA). The goodness of fit of R_0 distributions was tested using Anderson-Darling statistics.

For average temperatures in August in Tokyo, 27.7°C was observed in 2014 when dengue outbreak occurred, and 29.6°C in 2010 was highest from 1980 to 2016 [18]. In the first iteration, R_0 distributions were estimated assuming an average temperature of $T = 28^\circ\text{C}$; in the second iteration, R_0 distributions were estimated assuming an average temperature of $T = 30^\circ\text{C}$ under the assumption that average temperature during 2020 Tokyo Olympic would be 30°C. These two results then were compared.

This article does not contain any studies performed by the author with human participants.

RESULTS

For a daily average temperature of $T = 28^\circ\text{C}$, the estimated distribution of R_0 for dengue was fitted to a gamma distribution using location parameter -0.07, scale parameter 0.04, and shape parameter 28.43, yielding a median R_0 of 1.00. The estimated distribution of R_0 for chikungunya was fitted to a gamma distribution using location parameter -0.03, scale parameter 0.02, and shape parameter 28.43, yielding a median R_0 of 0.46. The estimated distribution of R_0 for Zika was fitted to a gamma distribution using location parameter -0.05, scale parameter 0.00, and shape parameter 132.20, yielding a median R_0 of 0.36.

For a daily average temperature of $T = 30^\circ\text{C}$, as would be expected in the summer of 2020, the estimated distribution of R_0 for dengue was fitted to a gamma distribution using location parameter -0.08, scale parameter 0.04, and shape parameter 28.43, yielding a median R_0 of 1.18, representing an 18% increase relative to the value obtained for $T = 28^\circ\text{C}$. The estimated distribution of R_0 for chikungunya was fitted to a gamma distribution using location parameter -0.03, scale parameter 0.02, and shape parameter 28.43, yielding a median R_0 of 0.48, representing a 4.3% increase relative to the value obtained for $T = 28^\circ\text{C}$. The estimated distribution of R_0 for Zika was obtained by fitting to a gamma distribution using location parameter -0.05, scale parameter 0.00, and shape parameter

132.20, yielding a median R_0 of 0.40, representing a 11.1% increase relative to the value obtained for $T = 28^\circ\text{C}$.

DISCUSSION

Dengue virus and Zika virus are members of the family *Flaviviridae*, and chikungunya virus is a member of the family *Togaviridae*. These viruses are transmitted by *Ae. albopictus* mosquitoes living in Japan, and cause arboviral diseases.

The first autochthonous case of dengue fever in Japan since 1945 was reported on 27 August 2014, and a subsequent outbreak demonstrated how dengue might be imported by such travelers [9]. The expectations of the risks of outbreak for these arboviral diseases will be useful for building prevention plans in preparation for mosquito breeding season and ongoing human travel, notably the upcoming traffic to Japan expected for the 2020 Olympics.

A Zika virus epidemic in Brazil has been observed starting from July of 2015; the virus subsequently has spread to other Latin American countries in 2016 [1-4]. At the same time, a major increase in the number of infants born with congenital microcephaly has been observed in Brazil, and some researchers have suggested that microcephaly is the result of Zika virus infection of mothers during pregnancy [19-21]. In response, on 1 February 2016 the WHO declared a Public Health Emergency of International Concern regarding the spread of Zika virus [22]. In Singapore, the Ministry of Health announced the first locally transmitted Zika virus infection on 27 August 2016, and its origin was considered as Asian lineage [23]. Additional cases have been reported through the end of September. A report about the first cases in Southeast Asia (in Thailand, specifically) of microcephaly linked to Zika infection was announced on 30 September 2016 [24], and fears of the spread of a Zika virus epidemic into Southeast Asia are increasing.

In Japan, Zika virus infection was confirmed on 24 February 2016 in a male high school student who had recently returned from Brazil; this event was the first confirmed case in Japan since the start of the previous year's epidemic in Brazil [25]. Subsequently, another 8 Zika cases have been imported to Japan through the end of September 2016 [25].

Model for different arboviruses and mosquito vectors

Funk *et al.* [26] investigated dengue and Zika virus outbreaks in the Pacific islands of Micronesia, with an estimated mean R_0 of 4.3 (95% credible interval: 3.1-6.1) for the dengue outbreak and 4.8 (2.9-8.1) for the Zika outbreak. Those authors also observed that the ranges of most disease-specific parameters largely overlap between dengue and Zika. Based on those results, Funk *et al.* [26] suggested that models for dengue transmission could be readily adapted to study Zika outbreaks. Thus, the dengue transmission model was used in the present work to estimate a potential Zika outbreak.

Sawabe *et al.* [27] investigated host-feeding habits of *Culex pipens* and *Ae. albopictus* collected in urban and suburban residential areas of Japan during 2003-2006. Those authors observed that *Ae. albopictus* was the predominant mosquito in urban areas and showed

that this species fed predominantly on humans. Hence, the same environmental conditions as those that led to the 2014 dengue outbreak in Tokyo are expected to apply in other urban areas in Japan.

Chouin-Carneiro *et al.* [28] investigated the susceptibilities to Zika virus of *Ae. aegypti* and *Ae. albopictus* from the Americas, and these authors showed similar transmission potential between these two mosquito species. Chouin-Carneiro *et al.* [28] also showed that different populations of *Ae. albopictus* exhibit different susceptibilities to Zika virus. These arboviruses' principal vector in Japan is *Ae. albopictus*; hence *Ae. albopictus* parameters were used here for the modeling of dengue and chikungunya outbreaks. In contrast, *Ae. aegypti* host and vector parameters were used here for the modeling of a Zika outbreak, while assuming a transmission potential similar to that of *Ae. albopictus*.

Estimated basic reproduction number for each arbovirus with different average temperatures

In the present study, the median of the estimated distribution of R_0 was 1.18 for a dengue outbreak, 0.48 for a chikungunya outbreak and 0.40 for a Zika outbreak at a daily average temperature of $T = 30^\circ\text{C}$. Manore *et al.* [29] showed the median estimates for the basic reproduction number R_0 for the Zika virus infection was 0.82, and the median estimates for R_0 for the chikungunya virus infection was 0.68 spreading across 4 urban cities in the Eastern United States by the infected *Ae. albopictus*. Estimated basic reproduction numbers for Zika and chikungunya virus are less than one in their and this studies.

Kucharski *et al.* [11] investigated the transmission dynamics of the Zika virus in island populations using a compartmental mathematical model based on the 2013-14 French Polynesia outbreak. Those authors showed that the median estimates for the basic reproduction number R_0 ranged from 2.6-4.8. Nishiura *et al.* [30] investigated two Zika epidemics (one on Yap Island in 2007, and the other in French Polynesia in 2013-14) and estimated R_0 for the Zika virus infection from the early exponential growth rate of these epidemics. The resulting estimate of R_0 on Yap Island had a wide uncertainty range of 4.5-5.8, whereas the estimate of R_0 in French Polynesia had a narrower uncertainty range of 1.8-2.0. For an outbreak in Colombia, Nishiura *et al.* [30] estimated an exponential growth rate over the first 3-5 weeks of 3.0 to 6.6. In both of these reports, Nishiura *et al.* [31] found that the ranges of estimated R_0 for the Zika virus epidemics were similar to the ranges of estimated R_0 for dengue virus epidemics previously observed in the same areas. In this study, the median of the estimated distribution of R_0 for dengue virus infection risk was higher than the value for Zika virus infection. One reason is that dengue and Zika viruses in epidemics of the Pacific and the Americas were principally transferred by *Ae. aegypti*, and these arboviruses' principal vector in Japan is *Ae. albopictus*.

Tsetsarkin *et al.* [32] showed that a single amino-acid substitution might have influenced mosquitoes' specificity, increasing fitness of chikungunya virus for *Ae. albopictus* compared to that for *Ae. aegypti*. Mouttailler *et al.* [33] showed that chikungunya virus had a faster virus replication rate in *Ae. albopictus* than did dengue

virus in this species. Consequently, this adaptation yielded efficient chikungunya virus transmission, and the same variant was observed in the outbreaks in the Indian Ocean islands and India, and was the cause of the outbreak transmitted by *Ae. albopictus* in north-eastern Italy [34]. Therefore, chikungunya will represent a higher risk in naïve areas with high densities of *Ae. albopictus*.

Under conditions of increased daily average temperature, the R_0 estimate obtained for dengue virus in the present work was predicted to be 18% higher than the value obtained at $T = 28^\circ\text{C}$; the value obtained for dengue virus also was higher than that for the other 2 viruses.

Limitations of this study include the fact that asymptomatic cases of infection by these arboviral diseases were not included in these models. Based on serosurveys, Appassakij *et al.* [35] estimated that 3% to 28% of infected persons remain asymptomatic for chikungunya infection, and Chastel [36] concluded that the number of asymptomatic dengue virus infection cases exceeds the number of symptomatic cases, in some instances representing a 14-fold excess. Duffy *et al.* [37] reported that an estimated 80% of persons infected with Zika virus remain asymptomatic.

An increase in the incidence of Guillain-Barré syndrome was observed in the French Polynesian Zika virus outbreak of 2013 [38], and this effect has also been observed in Brazil [39]. Association between *in utero* exposure to Zika virus and microcephaly is the focus of ongoing investigation, but has not yet been proven [40]. These reports showed that the potential burden of Zika virus infection exceeds those of dengue and chikungunya. Infected travelers or tourists are often visitors to urban areas, and international sporting events such as the Olympics are expected to accelerate the number of imported cases. Given that all Zika cases imported to Japan lived in urban and suburban areas, this country will need to strengthen its public health responsiveness for these emerging arboviral diseases, especially for dengue in urban areas.

Further studies will be needed, including the identification of environmental factors that may contribute to these viral epidemics.

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AUTHORS' CONTRIBUTIONS

Author had study idea, calculated the model, and wrote this paper.

CONFLICT OF INTEREST

There are no other conflicts of conflicts of interest to declare.

ETHICS AND CONSENT

Not required

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