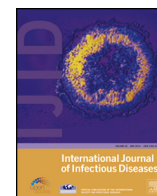




Title	Transmission potential of Zika virus infection in the South Pacific
Author(s)	Nishiura, Hiroshi; Kinoshita, Ryo; Mizumoto, Kenji; Yasuda, Yohei; Nah, Kyeongah
Citation	International journal of infectious diseases, 45, 95-97 <a href="https://doi.org/10.1016/j.ijid.2016.02.017">https://doi.org/10.1016/j.ijid.2016.02.017</a>
Issue Date	2016-04
Doc URL	<a href="http://hdl.handle.net/2115/62280">http://hdl.handle.net/2115/62280</a>
Rights(URL)	<a href="https://creativecommons.org/licenses/by-nc-nd/4.0/">https://creativecommons.org/licenses/by-nc-nd/4.0/</a>
Type	article
File Information	IntJInfectDis45_95.pdf



[Instructions for use](#)



## Short Communication

## Transmission potential of Zika virus infection in the South Pacific



Hiroshi Nishiura<sup>a,b,c,\*</sup>, Ryo Kinoshita<sup>a,b,c</sup>, Kenji Mizumoto<sup>a,c,d</sup>, Yohei Yasuda<sup>a</sup>, Kyeongah Nah<sup>a,b,c</sup>

<sup>a</sup> Graduate School of Medicine, Hokkaido University, Kita 15 Jo Nishi 7 Chome, Kita-ku, Sapporo-shi, Hokkaido 060-8638, Japan

<sup>b</sup> CREST, Japan Science and Technology Agency, Kawaguchi, Saitama, Japan

<sup>c</sup> Graduate School of Medicine, The University of Tokyo, Bunkyo-ku, Tokyo, 1130033, Japan

<sup>d</sup> Graduate School of Arts and Sciences, The University of Tokyo, Meguro-ku, Tokyo, Japan

## ARTICLE INFO

## Article history:

Received 31 January 2016

Received in revised form 22 February 2016

Accepted 22 February 2016

**Corresponding Editor:** Eskild Petersen, Aarhus, Denmark.

## Keywords:

Zika virus

Epidemic

Basic reproduction number

Statistical estimation

Transmissibility

## SUMMARY

**Objectives:** Zika virus has spread internationally through countries in the South Pacific and Americas. The present study aimed to estimate the basic reproduction number,  $R_0$ , of Zika virus infection as a measurement of the transmission potential, reanalyzing past epidemic data from the South Pacific.

**Methods:** Incidence data from two epidemics, one on Yap Island, Federal State of Micronesia in 2007 and the other in French Polynesia in 2013–2014, were reanalyzed.  $R_0$  of Zika virus infection was estimated from the early exponential growth rate of these two epidemics.

**Results:** The maximum likelihood estimate (MLE) of  $R_0$  for the Yap Island epidemic was in the order of 4.3–5.8 with broad uncertainty bounds due to the small sample size of confirmed and probable cases. The MLE of  $R_0$  for French Polynesia based on syndromic data ranged from 1.8 to 2.0 with narrow uncertainty bounds.

**Conclusions:** The transmissibility of Zika virus infection appears to be comparable to those of dengue and chikungunya viruses. Considering that *Aedes* species are a shared vector, this finding indicates that Zika virus replication within the vector is perhaps comparable to dengue and chikungunya.

© 2016 The Authors. Published by Elsevier Ltd on behalf of International Society for Infectious Diseases. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

## 1. Introduction

Zika virus is a mosquito-borne *Flavivirus* transmissible from human to human through bites of *Aedes* species mosquitoes. Zika virus not only shares a common vector species with dengue virus and chikungunya virus,<sup>1</sup> but the clinical signs and symptoms of Zika virus infection are also partly the same as those of dengue fever and chikungunya virus infection.<sup>2</sup> In recent years, the virus has spread internationally through countries in the South Pacific and Americas.<sup>3,4</sup> Due to growing concerns over the association between Zika virus infection in pregnant women and microcephaly in the fetus,<sup>5</sup> the risk assessment and management of infection has attracted global attention.

While the virus has spread geographically following the path of chikungunya virus along with the abundance of *Aedes spp.*,<sup>6–8</sup> the transmissibility of the virus has yet to be quantified statistically. This estimation is of the utmost importance, because the efforts required to control Zika virus infection will depend on the

transmission potential. The present study aimed to estimate the basic reproduction number ( $R_0$ ) of Zika virus infection – the average number of secondary human cases generated by a single primary human case – through an analysis of past epidemic data from the South Pacific.

## 2. Materials and methods

Time-dependent incidence data were retrieved from two published studies.<sup>2,9</sup> One occurred on Yap Island, Federal State of Micronesia in 2007,<sup>9</sup> while the other occurred in French Polynesia in 2013–2014.<sup>2</sup> Case data of the earlier epidemic were collected based on laboratory diagnosis (either by detecting Zika virus RNA or antibody;  $n = 108$ ), while the later epidemic data were derived from syndromic surveillance of suspected cases ( $n = 8581$ ). The number of new cases in every week could be yielded from both studies.

$R_0$  was estimated from the early exponential growth rate. First, the exponential growth rate was estimated from the weekly data using the Poisson distributed likelihood function, as proposed by Nishiura et al.<sup>10</sup> Subsequently, the estimated growth rate ' $r$ ' was converted into  $R_0$  using the following renewal equations that

\* Corresponding author. Tel.: +81 11 706 5066; fax: +81 11 706 7819.  
E-mail address: [nishiurah@gmail.com](mailto:nishiurah@gmail.com) (H. Nishiura).

describe the incidence in humans  $j_h(t)$  and vectors  $j_v(t)$ :

$$j_h(t) = R_{hv} \int_0^\infty g_{hv}(\tau) j_v(t-\tau) d\tau \quad (1)$$

$$j_v(t) = R_{vh} \int_0^\infty g_{vh}(\tau) j_h(t-\tau) d\tau \quad (2)$$

where  $R_{hv}$  and  $R_{vh}$  are the average number of human cases generated by a single infected vector and vector infections generated by a single human case, respectively.  $g_{hv}(\tau)$  and  $g_{vh}(\tau)$  are density functions of the time from vector infection to human infection and from human infection to vector infection, respectively. Assuming that the incidence of both humans  $j_h(t)$  and vectors  $j_v(t)$  grow exponentially with the rate  $r$  in a fully susceptible population, we obtain

$$R_0 = \sqrt{R_{hv}R_{vh}} = \sqrt{\frac{1}{M_{vh}(-r)M_{hv}(-r)}} \quad (3)$$

where  $M_{vh}(-r)$  and  $M_{hv}(-r)$  are the moment-generating functions of human to vector and vector to human transmissions, respectively, given growth rate  $r$ .<sup>11,12</sup> Table 1 shows published estimates that parameterized  $M_{vh}(-r)$  and  $M_{hv}(-r)$ . Assuming that each distribution is exponential with the mean values in Table 1, equation 3 agrees with Pinho et al.<sup>13</sup> The impact of

parameter uncertainty on  $R_0$  was examined using Latin hypercube sampling (LHS) with uniformly distributed parameters (Table 1).<sup>14,15</sup>

### 3. Results

Figures 1A and 1B compare the observed and predicted early growth of cases, assuming that the exponential growth has continued for the first 3–5 weeks. From Yap Island data, the maximum likelihood estimate (MLE) of  $R_0$  was 4.5 and 5.8 for the assumed 4-week and 5-week exponential growth period. Due to the scarcity of data, only an upper bound ( $R_0 \leq 2.7$ ) was obtained for the 3-week exponential window. Analyzing the data from French Polynesia,  $R_0$  was estimated at 1.8, 2.0, and 2.0 for 3-week, 4-week, and 5-week exponential growth, respectively (Figure 1C). The uncertainty analysis indicated that MLE of  $R_0$  for Yap Island could range from 2.8 to 12.5 depending on the length of generation time.<sup>15</sup> Similarly,  $R_0$  for French Polynesia could range from 1.5 to 3.1.

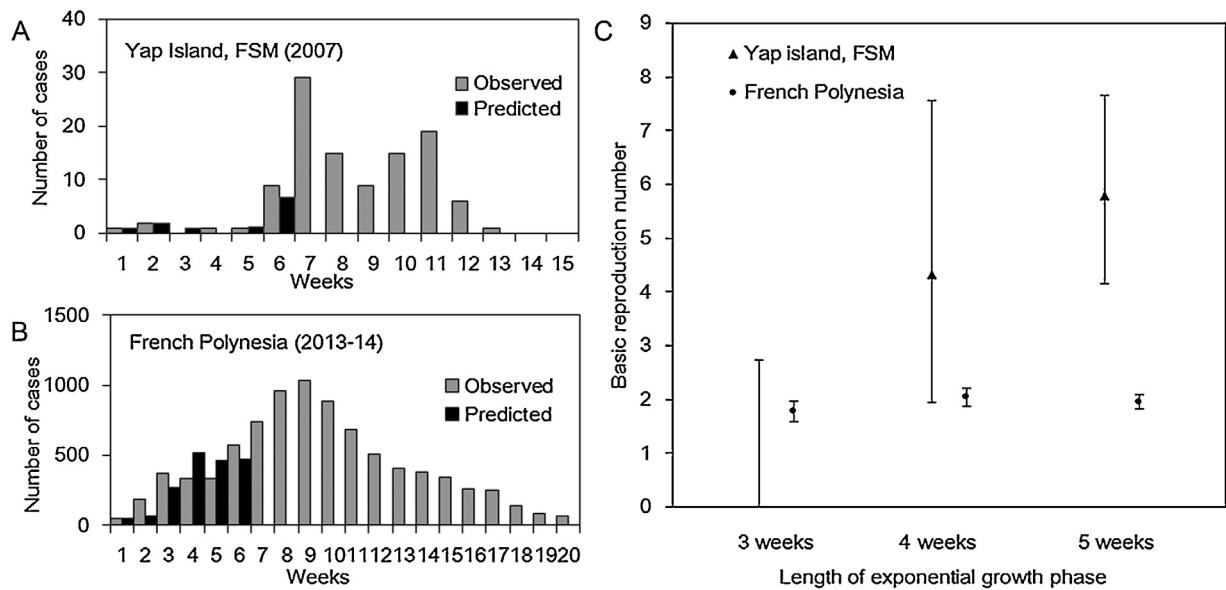
### 4. Discussion

$R_0$  of Zika virus infection was estimated analyzing datasets from the South Pacific. MLE of  $R_0$  for the Yap Island epidemic was in the order of 4.3–5.8 with broad uncertainty bounds due to the small

**Table 1**  
Parameters used in the model of Zika virus transmission

Parameter	Biological meaning	Value (per day)	Reference	Assumed range
$\mu_h$	Human mortality rate	1/(365 × 60)	Assumed	N/A
$\epsilon_h$	Rate of acquiring infectiousness	1/5	15, 19	1/12–1/3
$\gamma_h$	Recovery rate	1/11	15, 20	1/17–1/6
$\mu_m$	Mosquito mortality rate	1/14	15, 21	1/23–1/10
$\epsilon_m$	Extrinsic incubation rate	1/10	15, 19	1/23–1/6

N/A, not applicable.



**Figure 1.** Transmission dynamics of Zika virus infection on Yap Island, 2007 and French Polynesia, 2013–2014. (A) (B) Comparison of observed and predicted weekly numbers of new cases during the early period of the Zika virus epidemic. Predictions are shown when an exponential growth was assumed to continue for the first 4 weeks. (C) Estimates of the basic reproduction number. Dots represent the maximum likelihood estimates, while whiskers extend from the lower to upper 95% confidence intervals as derived from profile likelihood. For Yap Island, the maximum likelihood estimate was not calculable using only the first 3 weeks due to the scarcity of cases. Case data for the Yap Island epidemic were collected based on laboratory diagnosis (either by detection of Zika virus RNA or antibody;  $n = 108$ ), while data for French Polynesia were derived from the syndromic surveillance of suspected cases ( $n = 8581$ ).

sample size. The MLE of  $R_0$  for French Polynesia ranged from 1.8 to 2.0 with narrow uncertainty bounds. Both values are broadly consistent with empirical estimates of  $R_0$  for dengue and chikungunya virus infections.<sup>16,17</sup> Considering that *Aedes spp* are a shared vector, this finding indicates that Zika virus replication within the vector is perhaps comparable to that of dengue and chikungunya viruses.

Caution must be exercised in the interpretation of these estimates. First, the  $R_0$  of a vector-borne disease is not universally applicable to any other setting in the world. In particular, the abundance of *Aedes spp* is not substantial in temperate countries and thus these estimates will only help to understand the transmission potential in geographic areas where Zika virus transmission could be sustained. In addition, it should be noted that the implications for control could also depend on the fraction of sexual transmission among all secondary transmissions.<sup>18</sup> Second, both datasets involved an issue of under-ascertainment, and syndromic data are non-specific. To overcome these issues, sero-epidemiological surveys should ideally be implemented to capture the overall transmission dynamics. Third, the present approach might not have sufficiently captured demographic stochasticity due to the absence of finer time-scale data than weekly counts of cases.<sup>19,20,21</sup>

In conclusion, the transmission potential of Zika virus infection in the South Pacific was quantified, demonstrating that the transmissibility of this emerging virus is comparable to those of dengue and chikungunya viruses. Vector control programs should be planned with reference to these estimates.

#### Acknowledgements

HN received funding support from the Japanese Society for the Promotion of Science (JSPS) KAKENHI (grant numbers 26670308 and 26700028), Japan Agency for Medical Research and Development, the Japan Science and Technology Agency (JST) CREST program, and RISTEX program for Science of Science, Technology and Innovation Policy. The funders had no role in the study design, data collection and analysis, decision to publish, or preparation of the manuscript.

*Conflict of interest:* The authors declare no conflicts of interest.

#### References

- Musso D, Nilles EJ, Cao-Lormeau VM. Rapid spread of emerging Zika virus in the Pacific area. *Clin Microbiol Infect* 2014;**20**: O595–6.
- Ioos S, Mallet HP, Leparc Goffart I, Gauthier V, Cardoso T, Herida M. Current Zika virus epidemiology and recent epidemics. *Med Mal Infect* 2014;**44**:302–7.
- Fauci AS, Morens DM. Zika virus in the Americas—yet another arbovirus threat. *N Engl J Med* 2016;**374**:601–4. <http://dx.doi.org/10.1056/NEJMp1600297>
- Lucey DR, Gostin LO. The emerging Zika pandemic: enhancing preparedness. *JAMA* 2016;**315**:865–6. <http://dx.doi.org/10.1001/jama.2016.0904>
- Staples JE, Dziuban EJ, Fischer M, Cragan JD, Rasmussen SA, Cannon MJ, et al. Interim guidelines for the evaluation and testing of infants with possible congenital Zika virus infection—United States, 2016. *Morb Mortal Wkly Rep* 2016;**65**:63–7.
- Musso D, Cao-Lormeau VM, Gubler DJ. Zika virus: following the path of dengue and chikungunya? *Lancet* 2015;**386**:243–4.
- Faye O, Freire CC, Iamarino A, Faye O, de Oliveira JV, Diallo M, et al. Molecular evolution of Zika virus during its emergence in the 20th century. *PLoS Negl Trop Dis* 2014;**8**:e2636.
- Bogoch II, Brady OJ, Kraemer MU, German M, Creatore MI, Kulkarni MA, et al. Anticipating the international spread of Zika virus from Brazil. *Lancet* 2016;**387**:335–6. [http://dx.doi.org/10.1016/S0140-6736\(16\)00080-5](http://dx.doi.org/10.1016/S0140-6736(16)00080-5)
- Duffy MR, Chen TH, Hancock WT, Powers AM, Kool JL, Lanciotti RS, et al. Zika virus outbreak on Yap Island, Federated States of Micronesia. *N Engl J Med* 2009;**360**:2536–43.
- Nishiura H, Chowell G, Heesterbeek H, Wallinga J. The ideal reporting interval for an epidemic to objectively interpret the epidemiological time course. *J R Soc Interface* 2010;**7**:297–307.
- Keyfitz N. Introduction to the mathematics of population. London: Addison-Wesley; 1968.
- Wallinga J, Lipsitch M. How generation intervals shape the relationship between growth rates and reproductive numbers. *Proc R Soc Lond Ser B* 2007;**274**:599–604.
- Pinho ST, Ferreira CP, Esteva L, Barreto FR, Morato e Silva VC, Teixeira MG. Modelling the dynamics of dengue real epidemics. *Philos Trans A Math Phys Eng Sci* 2010;**368**:5679–93.
- Sanchez MA, Blower SM. Uncertainty and sensitivity analysis of the basic reproductive rate. Tuberculosis as an example. *Am J Epidemiol* 1997;**145**:1127–37.
- Majumder MS, Cohn E, Fish D, Brownstein JS. Estimating a feasible serial interval range for Zika fever. *Bull World Health Organ* 2016; in press. doi: <http://dx.doi.org/10.2471/BLT.16.171009>.
- Imai N, Dorigatti I, Cauchemez S, Ferguson NM. Estimating dengue transmission intensity from sero-prevalence surveys in multiple countries. *PLoS Negl Trop Dis* 2015;**9**:e0003719.
- Perkins TA, Metcalf CJ, Grenfell BT, Tatem AJ. Estimating drivers of autochthonous transmission of chikungunya virus in its invasion of the Americas. *PLoS Curr* 2015;**7**. pii: ecurrents.outbreaks.a4c7b6ac10e0420b1788c9767946d1fc.
- Adams B, Boots M. How important is vertical transmission in mosquitoes for the persistence of dengue? Insights from a mathematical model. *Epidemics* 2010;**2**:1–10.
- Hayes EB. Zika virus outside Africa. *Emerg Infect Dis* 2009;**15**:1347–50.
- Centers for Disease Control and Prevention (CDC). Zika virus. Atlanta, GA: CDC; 2016. Available at: <http://www.cdc.gov/zika/index.html> (accessed March 2, 2016).
- Dengue Virus Net. [DengueVirusNet.com](http://www.denguevirusnet.com/); 2016. Available at: <http://www.denguevirusnet.com/> (accessed March 2, 2016).