Comparative analysis of dengue and Zika outbreaks reveals differences by setting and virus

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Abstract

The pacific islands of Micronesia have experienced several outbreaks of mosquito-borne diseases over the past decade. In outbreaks on small islands, the susceptible population is usually well defined, and there is no co-circulation of pathogens. Because of this, analysing such outbreaks can be useful for understanding the transmission dynamics of the pathogens involved, and particularly so for yet understudied pathogens such as Zika virus. Here, we compared three outbreaks of dengue and Zika virus in two different island settings in Micronesia, the Yap Main Islands and Fais, using a mathematical model of transmission dynamics, making full use of commonalities in disease and setting between the outbreaks. We found that the estimated reproduction numbers for Zika and dengue were similar when considered in the same setting, but that, conversely, reproduction number for the same disease can vary considerably by setting. On the Yap Main Islands, we estimated a reproduction number of 8.0–16 (95% Credible Interval (CI)) for the dengue outbreak and 4.8–14 (95% CI) for the Zika outbreak, whereas for the dengue outbreak on Fais our estimate was 28–102 (95% CI). We further found that the proportion of cases of Zika reported was smaller (95% CI 1.4%–1.9%) than that of dengue (95% CI 47%–61%). We confirmed these results in extensive sensitivity analysis. They suggest that models for dengue transmission can be useful for estimating the predicted dynamics of Zika transmission, but care must be taken when extrapolating findings from one setting to another.

Author Summary

Dengue and Zika are related viruses and are both transmitted by mosquitoes. Dengue is well described and affects people around the world. Zika, on the other hand has only recently caused outbreak in human populations, and it has been suggested that its behaviour might similar dengue. To investigate this, we compared three outbreaks of dengue and Zika in island populations of the pacific: two dengue outbreaks and one Zika outbreak. Island outbreaks are useful laboratories for understanding the spread of

infections because they are usually short, well-identified episodes, whereas elsewhere it can be difficult to identify the properties of outbreaks when different viruses spread at the same time. In our investigation of the outbreaks in Micronesia we found that dengue and Zika virus did, indeed, behave similar in outbreaks they caused on the Yap Main Islands. A dengue outbreak on the smaller island of Fais, on the other hand, was different from the dengue outbreak on Yap in that transmission seems to have been more efficient. We conclude that dengue outbreaks are indeed a good model for Zika outbreaks when considered in the same setting, but that one must be careful when comparing outbreaks in different settings.

Introduction   1

Many infections of humans are transmitted by mosquitoes. Dengue virus is one of the   2
major pathogens infecting humans worldwide, causing an estimated 50–100 million cases   3
resulting in about 10,000 deaths annually [1]. Confined mainly to tropical regions   4
because of its reliance on transmission through *Aedes* mosquitoes, it is endemic in more   5
than 150 countries across the world [2]. Its four circulating serotypes cause a wide range   6
of clinical symptoms and severities, with most cases resolving without progressing to the   7
more severe forms, dengue hemorrhagic fever or dengue shock syndrome. Upon infection   8
following bite by an infectious female mosquito, the virus undergoes a period of   9
incubation before progressing to disease in an estimated 20-50% of infected people [3, 4],   10
with symptoms lasting approximately one week. The relative infectiousness of   11
symptomatically and asymptomatically infected people remains a topic of active study,   12
with recent evidence indicating that symptom-free people are more infectious to   13
mosquitoes than clinically symptomatic people [5, 6]. Infection results in lifelong   14
immunity to same serotype but subsequent infection with heterologous serotypes is   15
associated with higher rates of severe dengue [7].   16

  Zika virus, a member of the *Flaviviridae* family like dengue and also transmitted by   17
Aedes mosquitoes was discovered in Africa in 1947 [8]. Formerly believed to be mostly   18
confined to primate species, it has caused occasional cases in humans across Africa and   19
equatorial Asia in the decades after its discovery, before causing its first observed   20
outbreak in humans on the Yap Main Islands, Micronesia, in 2007 [9, 10]. Following   21
further outbreaks on Pacific islands in 2013/14 [11–13], cases of an illness characterised   22
by skin rash were reported from Brazil beginning in March 2015 and Zika virus   23
circulation confirmed in May 2015 [8, 14, 15]. Zika virus appears to largely cause   24
asymptomatic infection or mild disease and a non-itchy rash. However, it has recently   25
been linked to neurological issues in rare cases, particularly microcephaly when   26
contracted in pregnancy [16] and Guillain-Barré syndrome [17, 18]. A recent increase in   27
reported occurrences of microcephaly in Brazil has led to the declaration of a Public   28
Health Emergency of International Concern by the World Health Organization, to   29
"reduce infection with Zika virus, particularly among pregnant women and women of   30
childbearing age." [19].   31

  In contrast to dengue, Zika virus has not been described in great detail, and its   32
epidemiology in human populations remains poorly understood. Here, we characterise   33
the epidemiology of dengue and Zika outbreaks in tropical island settings by comparing   34
three outbreaks in Yap State, Micronesia: the outbreak of Zika virus on the Yap Main   35
Islands in 2007, a dengue outbreak on the Yap Main Islands in 2011, and a dengue   36
outbreak on the island of Fais. Island outbreaks are a particularly useful vehicle for   37
understanding transmission dynamics as cases usually occur in episodic outbreaks,   38
limiting interaction between pathogens and reducing the chances of misclassification.   39
Moreover, all three outbreaks share particular characteristics: the two dengue outbreaks   40
share the infecting agent; the two outbreaks on the Yap Main Islands the setting; and   41

the Zika outbreak on the Yap Main Islands and the dengue outbreak on Fais that they probably struck immunologically naïve populations. Moreover, evidence suggest that both *Aedes aegypti* and *Aedes hensili* are important epidemic vectors in both settings, with the latter only recently having been implicated in outbreaks of arboviruses [20, 21]. We exploit these relationships to comparatively study the three outbreaks by simultaneously fitting a mathematical model to all three time series, holding the parameters constant between the outbreaks where they represent a common element.

Methods

Outbreak setting

Yap State is one of the four states of the Federal States of Micronesia, consisting of the Yap Main Islands (also called Yap Proper or simply Yap) and fourteen outer atolls spanning an area of approximately $120\,\text{km}^2$. The Yap Main Islands consist of four major inhabited islands and six smaller ones that form a contiguous land mass of approximately $79\,\text{km}^2$. The 7,370 inhabitants of the Yap Main Islands (2010 census, population density $93/\text{km}^2$) live in villages, the largest of which is the capital of Yap State, Colonia (population 3,126), with the remaining villages mostly located along the shore line. Fais is one of the outer islands of Yap State which lies about $270\,\text{km}$ to the East of the Yap Main Islands and has a much smaller land mass ($2.6\,\text{km}^2$). The population of 294 (2010 census, density $113/\text{km}^2$) is concentrated in a single population centre that spans approximately a quarter of the island's area (Fig. 1).

The Yap Main Islands have experienced several outbreaks of dengue in the past, including an outbreak of serotype 4 in 1995 [20] and an outbreak of serotype 1 in 2004 [22]. The outbreak of Zika in 2007, on the other hand, was the first observed outbreak of Zika overall [9]. The outbreak of dengue in Fais, too, is believed to have been the first ever on the island [23].

Because of its stable climate, mosquito numbers are not believed to vary seasonally in Micronesia [24].

Data

The dengue time series from the Yap Main Islands and Fais consist of suspect dengue cases as identified by the Yap Department of Health [23]. Clinically suspected dengue cases were identified using the WHO (2009) case definition. A small proportion of cases (9%) were reported on outer islands and included in the time series for the Yap Main Islands as we did not have access to a time series where the two were separated. Dengue virus serotype 2 was confirmed by reverse transcriptase polymerase chain reaction by the CDC Dengue Branch, Puerto Rico. The Zika time series from the Yap main islands consists of probable and confirmed cases as identified in a combination of prospective and retrospective surveillance at all health centres on Yap [9].

All three time series of cases are shown in Figure 3 and summarised in Table 1. The outbreak of Zika on the Yap Main Islands had its first cases reported with onset in mid-April 2007 and the last in July 2007. Overall, a total of 108 cases were classified as probable (59) and confirmed (49) in a population of 7,370, and 73% (95% CI 68–77) were later found with evidence of recent Zika infection in a household survey [9]. The outbreak of dengue on the Yap Main (and Outer) Islands began with a case with disease onset on 1 September, 2011, and two more onsets on the following day. The next case was reported with onset a week later, on 8 September, followed by another cluster around 15 September, and sustained spread beginning another week later, around 22 September, 2011. The peak of the outbreak occurred in the week beginning 24
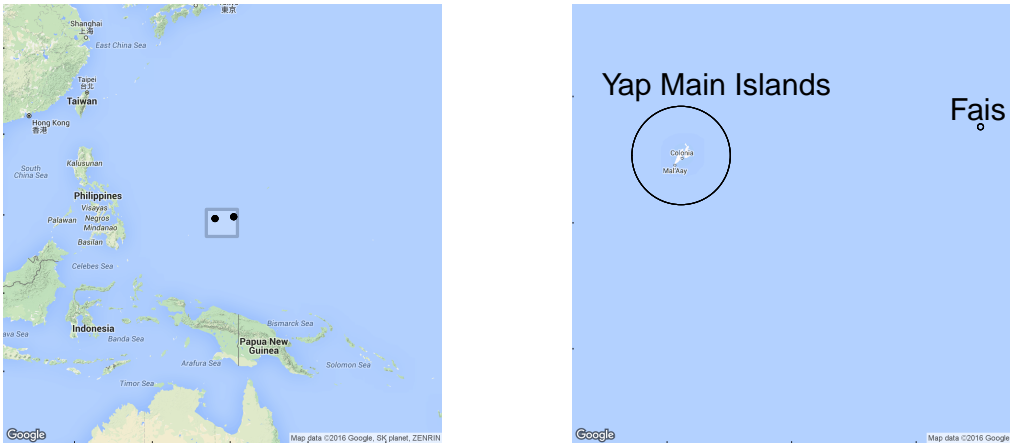
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Figure 1. Geographical location of the Yap Main Islands and Fais. The two islands are marked in the left panel with black dots, and shown in more detail on the enlarged map in the right panel.

November, 2011, with 142 cases reported with onset during that week. The last cases were reported with onset on 16 February, 2012.

Table 1. Outbreak characteristics. Summaries of the three outbreaks.

Location	Disease	Population	Reported cases	Duration (weeks)
Yap	Zika	7370	108	13
Yap	Dengue	7370	978	24
Fais	Dengue	294	155	6

The outbreak of dengue on Fais overlapped with the outbreak on the Yap Main Islands. It began on 10 November, 2011, with onset of disease in the likely index case. No further case was reported for 16 days, before cases started increasing after the second reported case (onset on 27 November, 2011) to a peak of 72 cases reported with disease onset in the week beginning 1 December, 2011. The last reported disease onsets were 2 cases on 20 December, 2011. Overall, 157 clinical cases were reported among the 294 residents.

Transmission model

We implemented a variant of the Ross-McDonald model [25, 26], schematically depicted in Fig. 2. The human population of size N_H was divided into susceptible (S_H), incubating or exposed (E_H), infectious (I_H) and recovered (R_H) compartments. The mosquito population of unknown size was divided into the proportion susceptible (s_M), incubating (e_M) or and infectious (i_M). We assumed that the size of the human (N_H) and vector populations did not vary over the course of the modelled outbreaks (i.e., we ignored birth and death rates in the human populations and assumed them to be the same in the vector populations), and that the symptomatic period in humans agrees with the infectious period [27]. We further assumed that infection results in immunity that lasts for at least the duration of the outbreak, and that vertical transmission in the mosquito population can be neglected [28].

In our model, everybody who gets infected can transmit the virus to mosquitoes [6]. Any lack of symptomatic disease is reflected in the mean proportion of cases reported r, as defined in the likelihood function below. The system of ordinary differential equations (ODEs) governing the outbreaks are:
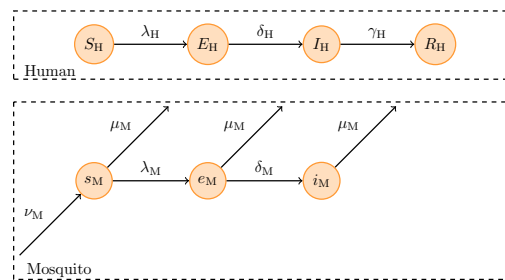
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Figure 2. Model structure. Only compartments that are relevant to the observed case series are depicted. For details of the parameter values, see text.

$$\frac{dS_{\mathrm{H}}}{dt} = -\lambda_{\mathrm{H}} S_{\mathrm{H}}$$
$$\frac{dE_{\mathrm{H}}}{dt} = +\lambda_{\mathrm{H}} S_{\mathrm{H}} - \delta_{\mathrm{H}} E_{\mathrm{H}}$$
$$\frac{dI_{\mathrm{H}}}{dt} = +\delta_{\mathrm{H}} E_{\mathrm{H}} - \gamma_{\mathrm{H}} I_{\mathrm{H}}$$
$$\frac{dR_{\mathrm{H}}}{dt} = +\gamma_{\mathrm{H}} I_{\mathrm{H}} \qquad (1)$$
$$\frac{ds_{\mathrm{M}}}{dt} = +\nu_{\mathrm{M}} - \lambda_{\mathrm{M}} s_{\mathrm{M}} - \mu_{\mathrm{M}} s_{\mathrm{M}}$$
$$\frac{de_{\mathrm{M}}}{dt} = +\lambda_{\mathrm{M}} s_{\mathrm{M}} - (\delta_{\mathrm{M}} + \mu_{\mathrm{M}}) e_{\mathrm{M}}$$
$$\frac{di_{\mathrm{M}}}{dt} = +\delta_{\mathrm{M}} e_{\mathrm{M}} - \mu_{\mathrm{M}} i_{\mathrm{M}}$$

Here, λ_{H} and λ_{M} are the forces of infection acting on humans and mosquitoes, respectively, $\delta_{\mathrm{H}} = 1/D_{\mathrm{inc,H}}$ and $\delta_{\mathrm{M}} = 1/D_{\mathrm{inc,M}}$ are the incubation rates, defined as the inverse of the average incubation periods $D_{\mathrm{inc,H}}$ and $D_{\mathrm{inc,M}}$ in humans and mosquitoes, respectively, $\gamma_{\mathrm{H}} = 1/D_{\mathrm{inf,H}}$ is the recovery rate in humans, defined as the inverse of the average duration of infectiousness, ν_{M} is the birth rate of female mosquitoes or number of susceptible female mosquitoes born per female mosquito per unit time, here assumed to be equal to the mosquito death rate $\mu_{\mathrm{M}} = 1/D_{\mathrm{life,M}}$, defined as the inverse of the average mosquito life span $D_{\mathrm{life,M}}$. This ensured that mosquito population sizes remained constant over the course of each outbreak.

The forces of infection can be written as

$$\lambda_H = \tau b_{\mathrm{H}} m i_{\mathrm{M}}$$
$$\lambda_M = \tau b_{\mathrm{M}} \frac{I_{\mathrm{H}}}{N_{\mathrm{H}}} \qquad (2)$$

where τ is the number of human blood meals taken by a single female mosquito per unit time, b_{H} and b_{M} are the probabilities that a bite by an infectious female mosquito leads to infection in a human and a bite on an infectious human leads to infection in a mosquito, respectively, and m is the number of female mosquitoes per human.

The human-to-human reproduction number of this model is

$$R_{\mathrm{H}\to\mathrm{H}} = R_{\mathrm{H}\to\mathrm{M}} \times R_{\mathrm{M}\to\mathrm{H}} = \frac{\tau b_{\mathrm{M}}}{\gamma_{\mathrm{H}}} \times \frac{\tau m b_{\mathrm{H}}}{\mu_{\mathrm{M}}} \frac{\delta_{\mathrm{M}}}{\mu_{\mathrm{M}} + \delta_{\mathrm{M}}} \qquad (3)$$

The basic reproduction number of the system, or the average number of secondary infections (in human or mosquito) from a primary infectious bite can be calculated from

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the next-generation matrix [29], and is the square root of the human-to-human reproduction number given in Eq. 3.

Generation Intervals

The equilibrium generation interval, or the mean time between the infection of a primary case and its secondary cases, relates reproduction numbers (which only describe reproduction per generation, without an explicit time scale) to the time scale of transmission. For our model, in an equilibrium situation it would be [30]:

$$G_{\text{eq}} = D_{\text{inc,H}} + D_{\text{inf,H}} + D_{\text{inc,M}} + D_{\text{life,M}} \qquad (4)$$

In an outbreak situation, observed generation intervals deviate from the theoretical value at equilibrium and change over time. When new infections are generated at approximately exponential rate, observed mean generations interval are smaller than the equilibrium value as most infectious people will only just have been infected [31]. This issue has recently been generalised to the whole distribution of generation intervals, and beyond assumptions of exponential growth [32].

For Zika, the generation interval has been estimated to be between 10 and 23 days [33], combining estimates for $D_{\text{inc,H}}$ of 3–12 days, $D_{\text{inc,M}}$ of 4–6 days, assuming $D_{\text{inf,H}} = D_{\text{life,M}} = 0$, that is that mosquitoes are infected by humans and vice versa just after their infectious period started, as well as an additional delay before symptomatic humans become viraemic of 3–5 days. If humans are, instead, taken to be viraemic for the first 3–5 days from symptoms onset [34], the estimated range shortens to 7–18 days. This should be taken as a lower limit for observed generation intervals, as in reality some infections will be caused by humans/mosquitoes that have been infectious for some time.

A second study that estimated the equilibrium generation interval using all the components of Eq. 4 and drawing from a systematic review of the natural history of the infection [35]. Assuming that humans or mosquito are equally likely to cause infection in mosquitoes or humans, respectively, the generation interval was estimated to be 20 days (mean, 95% CI 15.6–25.6), with a standard deviation of 7.4 days (mean, 95% CI 5.0 – 11.2), using an average mosquito life time of 5 days with standard deviation of 1.7 days [36].

Parameter estimation

To fit the model to the data sets, we used a Bayesian framework, generating samples from the posterior distribution using Markov-chain Monte Carlo (MCMC). The observation likelihood at each data point was assumed to be distributed approximately according to a Poisson distribution with rate rZ_{H}, where Z_{H} is the number of new human infections of Zika per reporting interval r is the proportion of these infections that get reported, estimated using a normal approximation with mean and variance both equal to rZ_{H}. We only had access to a weekly time series of Zika on the Yap Main Islands, and therefore aggregated the daily time series of dengue cases to weekly numbers to make estimates comparable between time series.

We fixed the biting rate to 1 per day [37]. Since we did not have enough information on mosquito life span to inform a full prior distribution, we further fixed the life span of the mosquito to either 1 week [36] or 2 weeks [38], and compared the two sets of fits using the Deviance Information Criterion or DIC [39]. We modelled the other natural history parameters (intrinsic and extrinsic incubation periods and infectious period in humans) with dengue-like priors, assuming that infectiousness starts 1.5 days before symptom onset [36, 40] and ends 1.5 days before their end. These prior distributions overlap with ones that have recently been estimated from the available data for Zika virus infections [35, 36].

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We estimated the remaining parameters of the model by fitting to all three time series simultaneously, with the following constraints: probabilities of infection from a potentially infectious bite, proportion reported, intrinsic and extrinsic incubation periods and human infectious periods were all to be disease-specific but the same across settings; mosquito densities, on the other hand were to be setting-specific but the same across the two pathogens, reflecting potential differences in the sizes of vector populations but also in human population density and behaviour.

For the outbreak of dengue the Yap Main Islands, we assumed that only a proportion q of the population was susceptible to infection. For the Zika outbreak on the Yap Main Islands, we assumed that the whole population was susceptible to infection. In other words, our Zika model is the assumed equivalent of a single-serotype dengue model not incorporating cross-reactivity between heterologous viruses or serotypes. The dengue outbreak in Fais, too, was assumed to strike a fully susceptible population, as it was the first known outbreak of dengue on the island. All outbreaks were started with a single infectious case, and date at which that case became infectious fitted as a separate parameter (rounded to the week) for all three outbreaks.

The MCMC procedure for parameter estimation was implemented using the *libbi* software package [42], run from the statistical package R [43] using the *RBi* [44] and *RBi.helpers* [45] packages. After adapting the size and shape of the multivariate normal proposal distribution in trial runs, the algorithm was run for 10 million iterations and convergence confirmed visually. All code and data used to generate the results are available at `http://github.com/sbfnk/vbd`.

Alternative models

We fitted two modified models to a data set containing an additional data point included in the fit to reflect the final outbreak size observed in a serological study on the Yap Main Islands [9]. The likelihood at this data point was given by a normal distribution centred around the final size, with a standard deviation of 2.2% to reflect the 95% confidence interval reported in the serological study. In one model, the population size of Yap Main Islands would be reduced by a factor ρ [41], whereas in the other one the initial proportion susceptible would be a proportion q of the whole population but everybody susceptible to mosquito bites, as in our model for the dengue outbreak on the Yap Main Islands.

We further fitted a two-patch metapopulation model to the outbreaks on the Yap Main Islands. While we did not have any spatially resolved data to inform such a model, the outbreak of Zika on the Yap Main Islands could be interpreted to consist of two peaks, a structure that would be expected to reproducible by a two-patch model. In this model, the outbreak starts in a patch which contains a proportion ϕ of the total population. This and another patch share the same parameters, and human in each patch exert a force of infection on mosquitoes in the other (representing human movement) that is reduced by a factor σ with respect to the force of infection within each patch.

Results

The models with mosquito life spans of 1 week vs 2 weeks fit the data equally well (DIC difference < 1). Assuming that both were equally likely to be true and combining the posterior distributions, the estimated disease-specific durations of infection and incubation largely corresponded to the given prior distributions (Table 2). There was, however, a more than twenty-fold difference in the proportion of infectious people reported, between a median estimate of 53% (IQR 51–56, 95% CI 47–61) for dengue and
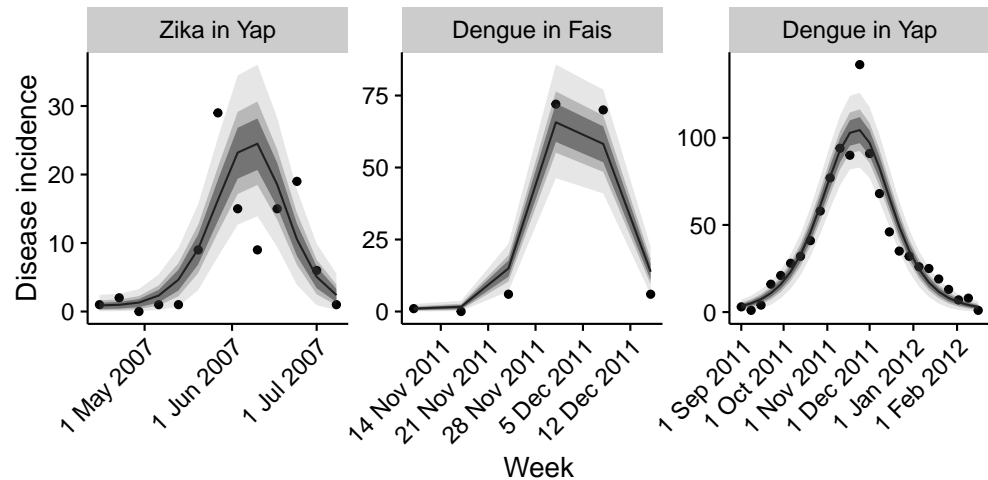
Figure 3. Time-lines of the outbreaks. Left to right: Zika virus on the Yap Main Islands, 2007; dengue outbreak on the Yap Main (and Outer) Islands, 2011 and Fais, 2011. Shown are the data (weekly incidence) as dots, and model fits (median, line; interquartile range, dark grey; 72% and 95% credible intervals, lighter shades of grey).

1.6% (IQR 1.5–1.7, 95% CI 1.4–1.9) for Zika. Location-specific parameters indicated a considerable difference in the number of female mosquitoes per person, with a mean estimate of 1.0 (IQR 0.69–1.5, 95% CI 0.38–8.4) on the Yap Main Islands and 4.7 (IQR 3.4–7.2, 95% CI 2.1–30) on Fais. The proportion of the population initially susceptible to dengue on the Yap Main Islands was estimated to be 27% (IQR 26–29, 95% CI 24–32).

The median estimates of the human-to-human reproduction number, $R_{H \to H}$ were 11 (IQR 9.7–13, 95% CI 8.0–16) for dengue on the Yap Main Islands, 7.6 (IQR 6.3–9.6, 95% CI 4.8–14) for Zika on the Yap Main Islands, and 51 (IQR 40 – 71, 95% CI 28–102) for dengue on Fais (Fig. 4). By combining the estimated parameters between settings and disease, we estimated R_0 for Zika on Fais to be 35 (posterior mean, IQR 26–52, 95% CI 18-79). The differences in R_0 between Yap and Fais are reflected in the different estimated differences in the number of female mosquitoes per person, which results in differences in the number of bites experienced per person.

Much of the variation in R_0 is explained by the different lengths of the generation interval which was poorly identified from the data (Fig. 4, Table 3). This is particularly the case for dengue in Fais, where all infections occurred in one or two generations, depending on the length of the generation interval (Fig. 5).

The alternative models with reduced population size or reduced susceptibility against Zika on the Yap Main Islands were both able to reproduce the observed proportion infected of 73% (see Supporting Information S1 Text). In the model with reduced population size the initial proportion susceptible to dengue on the Yap Main Islands was estimated to 37% (median, IQR 35–39, 95% CI 32–44), leading to a smaller human-to-human reproduction number of 8.7 (median, IQR 7.3–10, 95% CI 6.0–13) and greater proportion of Zika cases reported of 2.2% (median, IQR 2.1–2.3, 95% CI 1.9–2.7). In the model where only a proportion of the population q was susceptible to infection with Zika on the Yap Main Islands, the estimate of the proportion susceptible to dengue and human-to-human reproduction numbers were unchanged, while the proportion of Zika cases reported increased to 2.2% (median, IQR 2.1–2.4, 95% CI 1.8–2.7) The two models described the data equally well (DIC difference < 1). The alternative two-patch metapopulation model produced very similar parameter fits to the

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Table 2. Posterior means, 95% credible intervals (CIs) and prior distributions of estimated parameters. Yap: Yap Main Islands. Parameters given for the distributions are the lower and upper bound for (Log-)uniform distributions, and mean and standard deviation for (Log-)normal distributions. Durations are given in units of days and rates in unite of days^{-1}. CI: credible interval.

Disease-specific parameters						
	Dengue		Zika			
	Median	95% CI	Median	95% CI	Prior	Reference
$D_{\mathrm{inf,H}}$	4.2	(3.7, 4.5)	4.4	(4.0, 4.8)	Normal(4.5, 1.75)	[46]
$D_{\mathrm{inc,H}}$	4.7	(1.6, 7.6)	4.9	(2.2, 7.7)	Normal(4.4, 0.25)	[27, 40]
$D_{\mathrm{inc,M}}$	8.6	(4.3, 15)	9.1	(4.4, 17)	Normal(6.5, 1.15)	[27]
b_{H}	0.63	(0.17, 0.98)	0.59	(0.14, 0.97)	Uniform(0,1)	n/a
b_{M}	0.77	(0.16, 0.99)	0.58	(0.07, 0.98)	Uniform(0,1)	n/a
r	0.53	(0.47, 0.61)	0.016	(0.014, 0.019)	Uniform(0,1)	n/a
Location-specific parameter						
	Yap		Fais			
	Median	95% CI	Median	95% CI	Prior	Reference
m	1.0	(0.38, 8.4)	4.7	(2.1, 30)	Log-uniform(0.1, 100)	n/a
τ	1	–	1	–	fixed	[37]
q	0.27	(0.24, 0.32)			Uniform(0, 1)	n/a
Common parameter						
	Mean	95% CI			Prior	Reference
$D_{\mathrm{life,M}}$	7 or 14				fixed	[36, 38]

single-patch model. In particular, the fit to the outbreak of Zika on the Yap Main Islands produced a single peak unless it was viewed in isolation.

Discussion

We have analysed three outbreaks of mosquito-borne disease on small islands of Micronesia using a mathematical model. We exploited the overlap between those outbreaks in setting and disease to constrain parameter values and used this to investigate differences in transmission dynamics. While we found large difference between the reproduction numbers for dengue in two different island settings, our estimates of the reproduction numbers for dengue within the same settings are similar.

Our approach of fitting three time series concurrently and with common parameters helped identify some parameters that would not be identifiable by observing the

Table 3. Posterior mean, IQR and 95% credible interval (CIs) of the human-to-human reproduction number for different generation intervals (± 0.1 weeks) from samples of the posterior distribution.

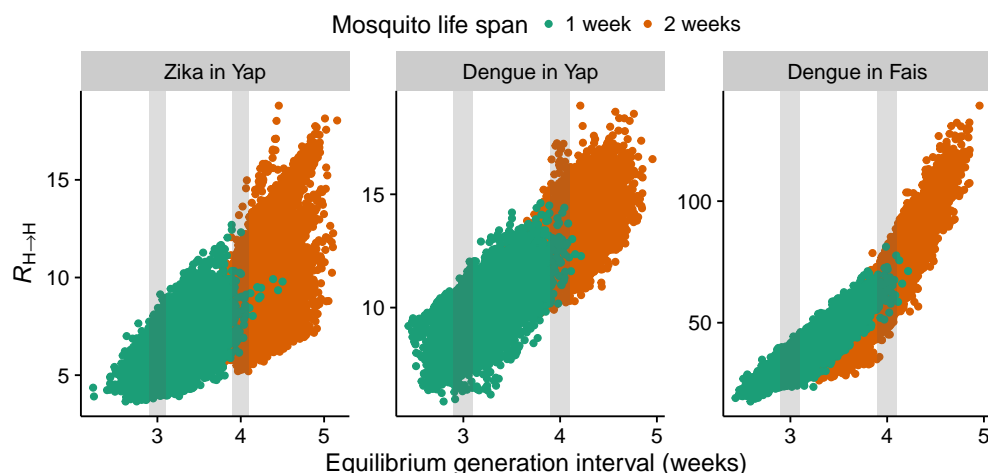| Disease	Setting	Generation interval (weeks)	median	$R_{\mathrm{H \to H}}$ IQR	95% CI
Zika	Yap	3	5.7	(5.2,6.3)	(4.4,7.6)
		4	8.4	(7.5,9.5)	(6.2,12)
Dengue	Yap	3	9.0	(8.4,9.6)	(7.4,11)
		4	13	(12,14)	(11,15)
Dengue	Fais	3	34	(31,36)	(27,41)
		4	65	(60,70)	(51,79)

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Figure 4. Relationship between the human-to-human reproduction number and the equilibrium generation interval. Human-to-human reproduction number $R_{\mathrm{H}\to\mathrm{H}}$ and equilibrium generation interval G_{eq} in posterior samples split by whether mosquito life spans $D_{\mathrm{life,M}}$ was 1 week (green) or 2 weeks (brown). Regions used to estimate the reproduction number in Table 3 are shaded in grey.

outbreak in isolation. The proportion of cases of dengue reported was informed by the final size of the dengue outbreak in Fais which, in turn, enabled estimation of the initial proportion susceptible of the dengue outbreak on the Yap Main Islands, again from the final outbreak size. With these two parameters established, the reproduction number of dengue in the two settings could be estimated from initial growth rate and outbreak duration, as a function of the generation interval. The generation intervals themselves were poorly identified in the data, and the corresponding marginal posterior distributions largely overlapping with the prior distributions.

Parameters for the Zika outbreak on the Yap Main Islands were similarly identified. With the reproduction number given by the initial growth rate and outbreak duration, the proportion of cases reported could be estimated from the reported final outbreak size of the epidemic. In this context it should be noted that with the values of the reproduction number we estimated, one would expect nearly all of the population to get infected, in contrast to the 73% (68–77) estimated to have been infected in a serological study after the outbreak [9]. It remains an open question how to best reconcile a rapidly growing epidemic that spreads through large parts of a population in a few generations without rendering everybody seropositive, a phenomenon also observed in the 2013–14 Zika outbreak in French Polynesia [13, 41, 47]. In the case of Zika on the Yap Main Islands, there might be several reasons for the discrepancy between modelled outbreak sizes and observed serology, such as the sensitivity of the used diagnostic test or lack of seroconversion at low-level exposure. If, on the other hand, the measured seropositivity reflects true infection history, its discrepancy with our modelled outbreak sizes could be because some individuals were not exposed to infectious mosquito bites due to spatial heterogeneity or because behavioural factors prevented them from getting bitten, which would not be captured in our model of a homogeneously mixing population. Fitting a model that included a factor to reflect this produced qualitatively the same results as the original model while lowering the reproduction number of dengue in Yap and increasing the proportion estimated to be initially susceptible to dengue infection in Yap as well as the reporting proportion of cases of Zika that were reported. Lastly, the discrepancy could be because some of the population was protected from infection
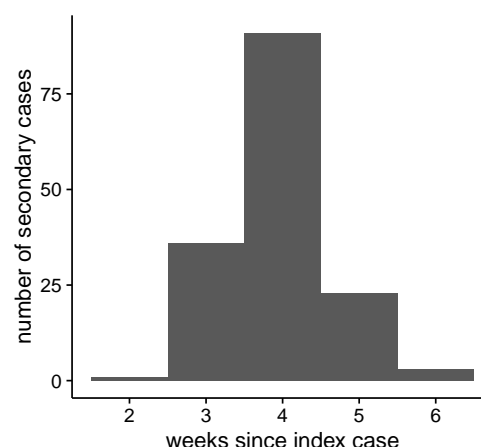
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Figure 5. Distribution of secondary cases for the dengue outbreak in Fais.
Time is measured in weeks since the index case (all symptom onset).

because of cross-immunity from prior infection with another virus, although current   298
evidence points to an opposite effect of antibody-dependent enhancement due to prior   299
dengue infection [48,49]. In the model fits with in this scenario, only the proportion of 300
cases of Zika reported increased. In all cases, this proportion remained well below the   301
equivalent number for dengue.   302

 The case series for Zika in Yap could be interpreted to consist of two peaks. In our   303
basic model, we did not include a mechanism that could have produced these peaks, as   304
we did not have access to any (for example, spatially resolved) data that could have   305
informed such a choice. Whilst two peaks could be produced by a model with spatial   306
heterogeneity, this would have been expected to produce a similar pattern in the dengue   307
outbreak, which consisted of a single peak. Because this is not the case, fits with a   308
two-patch model still yielded a single peak for Zika on the Yap Main Islands. Fitting   309
the Zika outbreak on the Yap Main Islands in isolation using a two-patch model did   310
reproduce two peaks, but ignored the additional information contained in the dengue   311
outbreaks, giving less credence to the fits. In this context, it is worth noting that our 312
model is deterministic and ignores any underlying stochasticity that may have played a   313
role especially early and late in the outbreaks. All uncertainty in our model is in the   314
likelihood which encodes the reporting process. The beginning of what could be seen as   315
a second wave coincided with the arrival of the US Centres for disease Control and   316
Prevention (CDC) teams in Yap, which may have changed reporting rates [9]. With this   317
in mind, our estimate of the proportion of cases reported should be interpreted as an   318
average over the whole outbreak.   319

 Our estimates of human-to-human reproduction numbers for dengue in the Yap   320
Main Islands are consistent with those previously reported in the literature [50], and   321
overlap with the range of 2.8–12.5 estimated from the exponential growth rate   322
alone [51]. The estimate of the human-to-human reproduction number for dengue in   323
Fais, on the other hand, is one of the largest ever observed in the literature, and larger 324
than previous estimates of dengue on small islands [52]. It is conceivable that in this   325
outbreak, everybody was infected within a generation or two. The outbreak hit a   326
population that occupies a small island and is not believed to ever have been exposed to   327
dengue previously, which would explain the rapid spread.   328

 More generally, the estimates for R_0 are similar between dengue and Zika where they 329
have been observed in the same setting on the Yap Main Islands, but differ strongly   330
between the dengue outbreaks on the Yap Main Islands and Fais. This suggests that   331

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outbreak setting and human population and mosquito densities are more important in governing transmission dynamics than differences between the pathogens. In other words, while our results suggest that insights from studying dengue transmission in one location can be used to predict the spread of Zika, care must be taken when extrapolating from insights on either of the pathogens in one location to another. Our results suggest that measuring mosquito densities and biting exposure in different settings could provide important information for estimating expected attack rates. In our case, Fais is a much smaller island, and one in which the assumption of random mixing is much more justified than on the Yap Main Islands, where spatial transmission dynamics may dilute the potential for rapid spread, leading to a smaller effective biting rate.

Our estimates of the reproduction number should be interpreted with caution as they could be influenced by heterogeneity. It has been shown if mixing is proportionate but heterogeneous (which is to be expected for dengue or Zika), the reproduction number increases the stronger the heterogeneity [53]. This can cause difficulties in the interpretation of reproduction numbers based on homogeneous models applied to outbreak data [54]. This and other structural limitations of the modelling approach could be contributing in an unknown way to differences or similarities in the estimated values of the reproduction number, and experiments and observational studies will be required to corroborate our findings.

In summary, we have studied three island outbreaks of vector-borne disease and elucidated on similarities and differences. We found that Zika transmission dynamics are similar to dengue when observed in the same setting, and that differences in human population structure and vector density are more important in determining transmission dynamics than difference between the two pathogens. For a new and yet understudied virus such as Zika, comparative studies like this one, especially when conducted on outbreaks in closed populations, can yield important insights into analogies that could be explored for interpreting observed transmission patterns and predicting future dynamics. Field studies on differences in vector density and biting exposure, as well as comparative modelling studies in other settings, would yield important further insights into the relationship between the transmission dynamics of Zika and dengue, and the specific setting in which they occur.

Acknowledgments

Supporting Information

S1 Text

Modelling results. R code to reproduce the modelling results, including additional models considered as sensitivity analysis.

S2 Data

Time series of cases. Incidence is given as the number of new cases reported in the week beginning at *onset_week*.

References

1. Stanaway JD, Shepard DS, Undurraga EA, Halasa YA, Coffeng LE, Brady OJ, et al. The global burden of dengue: an analysis from the Global Burden of Disease Study 2013. Lancet Infect Dis. 2016 Feb;Available from: http://dx.doi.org/10.1016/S1473-3099(16)00026-8.

2. Furuya-Kanamori L, Liang S, Milinovich G, Soares Magalhaes RJ, Clements ACA, Hu W, et al. Co-distribution and co-infection of chikungunya and dengue viruses. BMC Infect Dis. 2016;16(1):84. Available from: http://dx.doi.org/10.1186/s12879-016-1417-2.

3. Burke DS, Nisalak A, Johnson DE, Scott RM. A prospective study of dengue infections in Bangkok. Am J Trop Med Hyg. 1988 Jan;38(1):172–180.

4. Endy TP, Chunsuttiwat S, Nisalak A, Libraty DH, Green S, Rothman AL, et al. Epidemiology of inapparent and symptomatic acute dengue virus infection: a prospective study of primary school children in Kamphaeng Phet, Thailand. Am J Epidemiol. 2002 Jul;156(1):40–51.

5. Carrington LB, Simmons CP. Human to mosquito transmission of dengue viruses. Front Immunol. 2014;5:290. Available from: http://dx.doi.org/10.3389/fimmu.2014.00290.

6. Duong V, Lambrechts L, Paul RE, Ly S, Lay RS, Long KC, et al. Asymptomatic humans transmit dengue virus to mosquitoes. Proc Natl Acad Sci U S A. 2015 Nov;112(47):14688–14693. Available from: http://dx.doi.org/10.1073/pnas.1508114112.

7. Murphy BR, Whitehead SS. Immune Response to Dengue Virus and Prospects for a Vaccine. Annual Review of Immunology. 2011 apr;29(1):587–619. Available from: http://dx.doi.org/10.1146/annurev-immunol-031210-101315.

8. Kindhauser MK, Allen T, Frank V, Santhana RS, Dye C. Zika: the origin and spread of a mosquito-borne virus. Bull World Health Organ. 2016;E-pub: 9 Feb 2016. Available from: http://dx.doi.org/10.2471/BLT.16.171082.

9. 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 Jun;360(24):2536–2543. Available from: http://dx.doi.org/10.1056/NEJMoa0805715.

10. Hayes EB. Zika virus outside Africa. Emerg Infect Dis. 2009 Sep;15(9):1347–1350. Available from: http://dx.doi.org/10.3201/eid1509.090442.

11. Musso D, Nilles EJ, Cao-Lormeau VM. Rapid spread of emerging Zika virus in the Pacific area. Clin Microbiol Infect. 2014 Oct;20(10):O595–O596. Available from: http://dx.doi.org/10.1111/1469-0691.12707.

12. Cao-Lormeau VM, Roche C, Teissier A, Robin E, Berry AL, Mallet HP, et al. Zika virus, French polynesia, South pacific, 2013. Emerg Infect Dis. 2014 Jun;20(6):1085–1086. Available from: http://dx.doi.org/10.3201/eid2006.140138.

13. Kucharski AJ, Funk S, Eggo RMM, Mallet HP, John Edmunds J, Nilles EJ. Transmission dynamics of Zika virus in island populations: a modelling analysis of the 2013-14 French Polynesia outbreak. ArXiv e-prints. 2016 Feb;Available from: http://dx.doi.org/10.1101/038588.

14. Zanluca C, Melo VCAd, Mosimann ALP, Santos GIVd, Santos CNDd, Luz K. First report of autochthonous transmission of Zika virus in Brazil. Mem Inst Instituto Oswaldo Cruz. 2015 06;110:569 – 572. Available from: http://www.scielo.br/scielo.php?script=sci_arttext&pid= S0074-02762015000400569&nrm=iso.

15. Campos GS, Bandeira AC, Sardi SI. Zika Virus Outbreak, Bahia, Brazil. Emerg Infect Dis. 2015 Oct;21(10):1885–1886. Available from: http://dx.doi.org/10.3201/eid2110.150847.

16. Mlakar J, Korva M, Tul N, Popović M, Poljšak-Prijatelj M, Mraz J, et al. Zika Virus Associated with Microcephaly. N Engl J Med. 2016 Feb;Available from: http://dx.doi.org/10.1056/NEJMoa1600651.

17. Oehler E, Watrin L, Larre P, Leparc-Goffart I, Lastère S, Valour F, et al. Zika virus infection complicated by Guillain-Barr''e syndrome – case report, French Polynesia, December 2013. Euro Surveill. 2014;19(9):pii=20720. Available from: http://dx.doi.org/10.2807/1560-7917.ES2014.19.9.20720.

18. Cao-Lormeau VM, Blake A, Mons S, Lastère S, Roche C, Vanhomwegen J, et al. Guillain-Barré Syndrome outbreak associated with Zika virus infection in French Polynesia: a case-control study. The Lancet. 2016 mar;Available from: http://dx.doi.org/10.1016/S0140-6736(16)00562-6.

19. World Health Organization. WHO statement on the first meeting of the International Health Regulations (2005) (IHR 2005) Emergency Committee on Zika virus and obsestatementrved increase in neurological disorders and neonatal malformations; 2016. URL: http://www.who.int/mediacentre/news/statements/2016/1st-emergency-committee-zika/en/, Archived at http://www.webcitation.org/6fKDu7nbN on Feb 15, 2016. Available from: http://www.webcitation.org/6fKDu7nbN.

20. Savage HM, Fritz CL, Rutstein D, Yolwa A, Vorndam V, Gubler DJ. Epidemic of dengue-4 virus in Yap State, Federated States of Micronesia, and implication of Aedes hensilli as an epidemic vector. Am J Trop Med Hyg. 1998 Apr;58(4):519–524. Available from: http://www.ajtmh.org/content/58/4/519.abstract.

21. Ledermann JP, Guillaumot L, Yug L, Saweyog SC, Tided M, Machieng P, et al. Aedes hensilli as a potential vector of Chikungunya and Zika viruses. PLoS Negl Trop Dis. 2014 Oct;8(10):e3188. Available from: http://dx.doi.org/10.1371/journal.pntd.0003188.

22. Nukui Y, Tajima S, Kotaki A, Ito M, Takasaki T, Koike K, et al. Novel Dengue Virus Type 1 from Travelers to Yap State, Micronesia. Emerg Infect Dis. 2006 feb;12(2):343–346. Available from: http://dx.doi.org/10.3201/eid1202.050733.

23. Nilles E, Hancock W, Marfel M, Yolwa A, Aure F, Regan J, et al.. An explosive dengue outbreak on a small Micronesia atoll; 2012. Presented at the American Society of Tropical Medicine and Hygiene (ASMTH) 61st Annual Meeting. Poster.

24. Shinichi N. Mosquito Fauna in the Federated States of Micronesia: A Discussion of the Vector Species of the Dengue Virus. South Pac Stud. 2014;34(2).

25. Smith DL, Battle KE, Hay SI, Barker CM, Scott TW, McKenzie FE. Ross, Macdonald, and a Theory for the Dynamics and Control of Mosquito-Transmitted Pathogens. PLoS Pathog. 2012 04;8(4):e1002588. Available from: http://dx.doi.org/10.1371%2Fjournal.ppat.1002588.

26. Reiner RC, Perkins TA, Barker CM, Niu T, Chaves LF, Ellis AM, et al. A systematic review of mathematical models of mosquito-borne pathogen transmission: 1970-2010. Journal of The Royal Society Interface. 2013 feb;10(81):20120921–20120921. Available from: http://dx.doi.org/10.1098/rsif.2012.0921.

27. Chan M, Johansson MA. The incubation periods of Dengue viruses. PLoS One. 2012;7(11):e50972. Available from: http://dx.doi.org/10.1371/journal.pone.0050972.

28. Adams B, Boots M. How important is vertical transmission in mosquitoes for the persistence of dengue? Insights from a mathematical model. Epidemics. 2010 Mar;2(1):1–10. Available from: http://dx.doi.org/10.1016/j.epidem.2010.01.001.

29. Diekmann O, Heesterbeek JAP, Roberts MG. The construction of next-generation matrices for compartmental epidemic models. J R Soc Interface. 2010 Jun;7(47):873–885. Available from: http://dx.doi.org/10.1098/rsif.2009.0386.

30. Svensson Å. A note on generation times in epidemic models. Mathematical Biosciences. 2007 jul;208(1):300–311. Available from: http://dx.doi.org/10.1016/j.mbs.2006.10.010.

31. Nishiura H. Time variations in the generation time of an infectious disease: Implications for sampling to appropriately quantify transmission potential. MBE. 2010 oct;7(4):851–869. Available from: http://dx.doi.org/10.3934/mbe.2010.7.851.

32. Champredon D, Dushoff J. Intrinsic and realized generation intervals in infectious-disease transmission. Proceedings of the Royal Society B: Biological Sciences. 2015 dec;282(1821):20152026. Available from: http://dx.doi.org/10.1098/rspb.2015.2026.

33. Majumder MS, Cohn E, Fish D, Brownstein JS. Estimating a feasible serial interval range for Zika fever. Bulletin of the World Health Organization. 2016 feb;Available from: http://dx.doi.org/10.2471/BLT.16.171009.

34. European Centre for Disease Prevention and Control. Zika virus infection outbreak, Brazil and the Pacific region; 2015. ECDC: Stockholm.

35. Lessler J, Ott CT, Carcelen AC, Konikoff JM, Williamson J, Bi Q, et al. Times to Key Events in the Course of Zika Infection and their Implications for Surveillance: A Systematic Review and Pooled Analysis; 2016. Available from: http://dx.doi.org/10.1101/041913.

36. Ferguson NM, Cucunuba ZM, Dorigatti I, Nedjati-Gilani GL, Donnelly CA, Basanez MG, et al. Countering the Zika epidemic in Latin America. Science. 2016 jul;353(6297):353–354. Available from: http://dx.doi.org/10.1126/science.aag0219.

37. Andraud M, Hens N, Marais C, Beutels P. Dynamic epidemiological models for dengue transmission: a systematic review of structural approaches. PLoS One. 2012;7(11):e49085. Available from: http://dx.doi.org/10.1371/journal.pone.0049085.

38. National Environmental Agency, Singapore. Life Cycle of an Aedes Mosquito; 2016. URL: *http://www.dengue.gov.sg/subject.asp?id=12*, Archived at *http://www.webcitation.org/6k2u72BA2* on Feb 15, 2016. Available from: http://www.webcitation.org/6fKDu7nbN.

39. Spiegelhalter DJ, Best NG, Carlin BP, van der Linde A. Bayesian Measures of Model Complexity and Fit. Journal of the Royal Statistical Society: Series B (Statistical Methodology). 2002;64(4):583–639. Available from: http://dx.doi.org/10.1111/1467-9868.00353.

40. Nguyen NM, Kien DTH, Tuan TV, Quyen NTH, Tran CNB, Thi LV, et al. Host and viral features of human dengue cases shape the population of infected and infectious Aedes aegypti mosquitoes. Proceedings of the National Academy of Sciences. 2013 may;110(22):9072–9077. Available from: http://dx.doi.org/10.1073/pnas.1303395110.

41. Champagne C, Salthouse DG, Paul R, Cao-Lormeau VM, Roche B, Cazelles B. Structure in the variability of the basic reproductive number (R_0) for Zika epidemics in the Pacific islands. bioRxiv. 2016;Available from: http://dx.doi.org/10.1101/064949.

42. Murray LM. Bayesian State-Space Modelling on High-Performance Hardware Using LibBi. 2013 Jun;Available from: http://arxiv.org/abs/1306.3277.

43. R Core Team. R: A Language and Environment for Statistical Computing. Vienna, Austria; 2015. Available from: https://www.R-project.org/.

44. Jacob PE, Lee A, Funk S. RBi: R interface to LibBi; 2015. R package version 0.1-1. Available from: https://github.com/libbi/RBi.

45. Funk S. RBi.helpers: RBi helper functions; 2015. R package version 0.1. Available from: https://github.com/sbfnk/RBi.helpers.

46. Vaughn DW, Green S, Kalayanarooj S, Innis BL, Nimmannitya S, Suntayakorn S, et al. Dengue viremia titer, antibody response pattern, and virus serotype correlate with disease severity. J Infect Dis. 2000 Jan;181(1):2–9. Available from: http://dx.doi.org/10.1086/315215.

47. Cauchemez S, Besnard M, Bompard P, Dub T, Guillemette-Artur P, Eyrolle-Guignot D, et al. Association between Zika virus and microcephaly in French Polynesia, 2013–15: a retrospective study. The Lancet. 2016 may;387(10033):2125–2132. Available from: http://dx.doi.org/10.1016/S0140-6736(16)00651-6.

48. Paul LM, Carlin ER, Jenkins MM, Tan AL, Barcellona CM, Nicholson CO, et al. Dengue Virus Antibodies Enhance Zika Virus Infection; 2016. Available from: http://dx.doi.org/10.1101/050112.

49. Dejnirattisai W, Supasa P, Wongwiwat W, Rouvinski A, Barba-Spaeth G, Duangchinda T, et al. Dengue virus sero-cross-reactivity drives antibody-dependent enhancement of infection with zika virus. Nature Immunology. 2016 jun;17(9):1102–1108. Available from: http://dx.doi.org/10.1038/ni.3515.

50. Johansson MA, Hombach J, Cummings DAT. Models of the impact of dengue vaccines: A review of current research and potential approaches. Vaccine. 2011 aug;29(35):5860–5868. Available from: http://dx.doi.org/10.1016/j.vaccine.2011.06.042.

51. Nishiura H, Kinoshita R, Mizumoto K, Yasuda Y, Nah K. Transmission potential of Zika virus infection in the South Pacific. International Journal of Infectious Diseases. 2016 apr;45:95–97. Available from: http://dx.doi.org/10.1016/j.ijid.2016.02.017.

52. Hyman JM, Nesse H, Aguilera X, Olea A, Fuentes R, Chowell G. The basic reproduction number R_0 and effectiveness of reactive interventions during dengue epidemics: The 2002 dengue outbreak in Easter Island, Chile. MBE. 2013 aug;10(5/6):1455–1474. Available from: http://dx.doi.org/10.3934/mbe.2013.10.1455.

53. Dye C, Hasibeder G. Population dynamics of mosquito-borne disease: effects of flies which bite some people more frequently than others. Transactions of the Royal Society of Tropical Medicine and Hygiene. 1986 jan;80(1):69–77. Available from: http://dx.doi.org/10.1016/0035-9203(86)90199-9.

54. Perkins TA, Scott TW, Menach AL, Smith DL. Heterogeneity, Mixing, and the Spatial Scales of Mosquito-Borne Pathogen Transmission. PLoS Comput Biol. 2013 dec;9(12):e1003327. Available from: http://dx.doi.org/10.1371/journal.pcbi.1003327.