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

Sebastian Funk[1,2,*], Adam J. Kucharski[1,2], Anton Camacho[1,2], Rosalind M. Eggo[1,2], Laith Yakob[1,3], W. John Edmunds[1,2]

1 Centre for the Mathematical Modelling of Infectious Diseases, London School of Hygiene & Tropical Medicine, London, United Kingdom
2 Department of Infectious Disease Epidemiology, London School of Hygiene & Tropical Medicine, London, United Kingdom
3 Department for Disease Control, London School of Hygiene & Tropical Medicine, London, United Kingdom

* sebastian.funk@lshtm.ac.uk

Abstract

The pacific islands of Micronesia have experienced several outbreaks of mosquito-borne diseases over the past decade. Since these outbreaks occurred in confined island populations, their analysis can improve our understanding of the transmission dynamics of the pathogens involved, and particularly so for yet understudied pathogens such as Zika virus. Here, we compare 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 are 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 estimate a mean reproduction number 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, whereas for the dengue outbreak on Fais our mean estimate is 10 (5.5–18). We further found that the ranges of most disease-specific parameters largely overlap between dengue and Zika, but that reporting rates of Zika cases are much smaller (3%, 1–7) than those of dengue (68%, 43–98). These results suggests 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. Field studies on differences in vector density and biting exposure, as well as comparative modelling studies in other settings, could yield important further insights into the relationship between the transmission dynamics of Zika and dengue, and the specific setting in which they occur.

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Introduction

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

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

In contrast to dengue, Zika virus has not been described in great detail, and its epidemiology in human populations remains poorly understood. Here, we characterise the epidemiology of dengue and Zika outbreaks in tropical island settings by comparing three outbreaks in Yap State, Micronesia: the outbreak of Zika virus on the Yap Main Islands in 2007, a dengue outbreak on the Yap Main Islands in 2011, and a dengue outbreak on the island of Fais which lies about 270km to the East of the Yap Main Islands and has a much smaller land mass (2.6 km^2 vs 100 km^2), with its population is concentrated in a single population centre (Fig. 1). Island outbreaks are a particularly useful vehicle for understanding transmission dynamics as cases usually occur in episodic outbreaks, limiting interaction between pathogens and reducing the chances of misclassification. Moreover, all three outbreaks share particular characteristics: the two dengue outbreaks share the infecting agent; the two outbreaks on the Yap Main Islands the setting; and 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

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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

Data

The dengue time series from the Yap Main Islands consists of suspect dengue cases as identified by the Yap Department of Health [22]. 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.

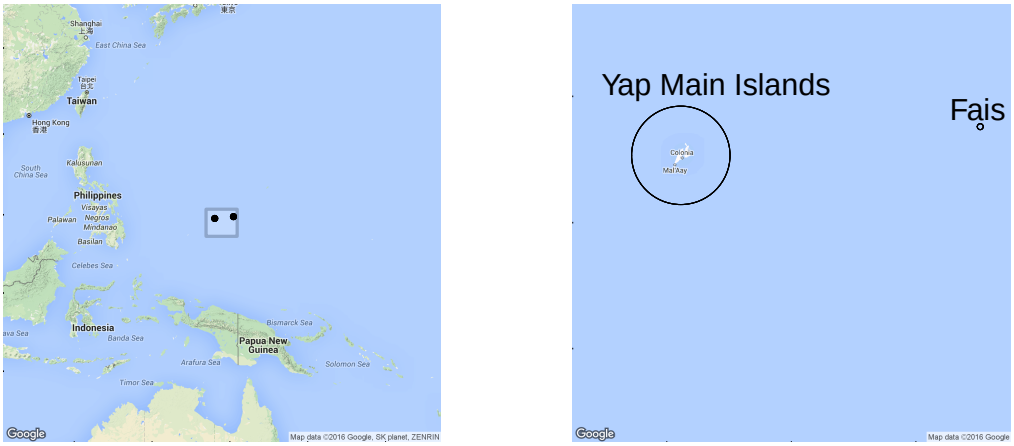

Figure 1. Geographical location of the Yap Main Islands and Fais. The two islands are marked in the left panel with black dots, and shown in more detail on the enlarged map in the right panel.

Transmission model

We implemented a variant of the Ross-McDonald model [23, 24], schematically depicted in Fig. 2. A 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. A 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

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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 [25]. 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 [26].

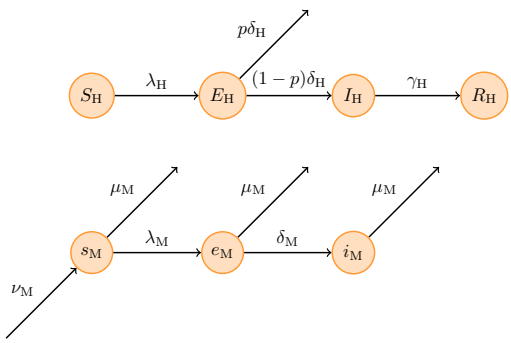

Figure 2. Model structure. Only compartments that are relevant to the observed case series are depicted. For details of the parameter values, see text.

We assumed that only a proportion p, upon exposure to the virus through a bite by an infectious mosquito, became infectious. Whilst it has recently been shown that those asymptomatically infected with dengue can transmit the virus to mosquitoes [6], these would be indistinguishable from symptomatic but unreported individuals in time series of cases. In other words, a proportion $1-p$ of exposures result in no onward transmission (which could be because of genetic, behavioural, or other factors), whilst asymptomatic and transmitting individuals are part of the proportion p of exposed individuals that become infectious (I_H), and their lack of symptomatic disease is reflected as part of the reporting rate, as defined in the likelihood function below. The system of ordinary differential equations (ODEs) governing the outbreaks are then:

$$\begin{aligned}
\frac{dS_H}{dt} &= -\lambda_H S_H \\
\frac{dE_H}{dt} &= +\lambda_H S_H - \delta_H E_H \\
\frac{dI_H}{dt} &= +p\delta_H E_H - \gamma_H I_H \\
\frac{dI_R}{dt} &= +\gamma_H I_H \\
\frac{ds_M}{dt} &= +\nu_M - \lambda_M s_M - \mu_M s_M \\
\frac{de_M}{dt} &= +\lambda_M s_M - (\delta_M + \mu_M) e_M \\
\frac{di_M}{dt} &= \delta_M e_M - \mu_M i_M
\end{aligned} \tag{1}$$

Here, λ_H and λ_M are the forces of infection acting on humans and mosquitoes, respectively, $\delta_H = 1/D_{\text{inc,H}}$ and $\delta_M = 1/D_{\text{inc,M}}$ are the incubation rates, defined as the

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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, and $\mu_{\mathrm{M}} = 1/D_{\mathrm{life,V}}$ is the mosquito death rate, defined as the inverse of the average mosquito life span.

The forces of infection can be written as

$$\begin{aligned} \lambda_H &= \tau b_{\mathrm{H}} m i_{\mathrm{M}} \\ \lambda_M &= \tau b_{\mathrm{M}} \frac{I_{\mathrm{H}}}{N_{\mathrm{H}}} \end{aligned} \tag{2}$$

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 basic reproduction of this model can be derived from the next-generation matrix [27].

$$R_0 = \tau \sqrt{\frac{p b_{\mathrm{H}}}{\gamma_{\mathrm{H}}} \frac{b_{\mathrm{M}}}{\delta_{\mathrm{M}}} \frac{\delta_{\mathrm{M}}}{\mu_{\mathrm{M}} + \delta_{\mathrm{M}}}} \tag{3}$$

Parameter estimation

To fit the model to the data sets, we used a Bayesian framework with dengue-like prior distributions, and samples from the posterior distribution generated using Markov-chain Monte Carlo (MCMC). The observation likelihood at each data point was assumed to be distributed approximately according to a negative binomial distribution [28], estimated using a normal approximation with mean rZ_{H} and variance $rZ_{\mathrm{H}} + r^2 Z_{\mathrm{H}}^2 \phi_{\mathrm{m}}^2 + \phi_{\mathrm{a}}$, where r is the proportion of infectious cases reported, Z_{H} is incidence of symptomatic cases in the human population at each time point, ϕ_{m} represents overdispersion in reporting and ϕ_{a} an additive overdispersion term to avoid numerical instabilities caused by zeroes. 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 estimated the parameters of the model by fitting to all three time series simultaneously, with the following constraints: the mosquito lifespan was to be the same for all three time series, as the same vector species were likely to be involved; probabilities of infection from a potentially infectious bite, the proportion asymptomatic and transmitting, the proportion symptomatic and reported and overdispersion in reporting, as well as intrinsic and extrinsic incubation periods and human infectious periods were all to be disease-specific but the same across settings; and mosquito densities and biting frequencies 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. We assumed no preexisting immunity in the population, except for the Yap Main Islands, where only a proportion q of the population was assumed to be susceptible to dengue infection. In other words, our Zika

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model is the assumed equivalent of a single-serotype dengue model not incorporating cross-reactivity between heterologous viruses or serotypes. All outbreaks were started with a single infectious case, and date at which that case became infectious fitted as a separate parameter for all three outbreaks.

The MCMC procedure for parameter estimation was implemented using the *libbi* software package [29], run from the statistical package *R* [30] using the *RBi* [31] and *RBi.helpers* [32] packages. The algorithm was run for 10 million iterations, with the first 25% discarded as burn-in, and convergence was confirmed visually.

Results

All three time series of cases are shown in Figure 3. 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 7391 (2000 census data), and 73% (95% CI: 68–77) were later found with evidence of recent Zika infection [9]. The outbreak of dengue on the Yap Main (and Outer) Islands began on 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 November, 2011, with 142 cases reported with onset during that week. The last cases were reported with onset on 16 February, 2012. 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.

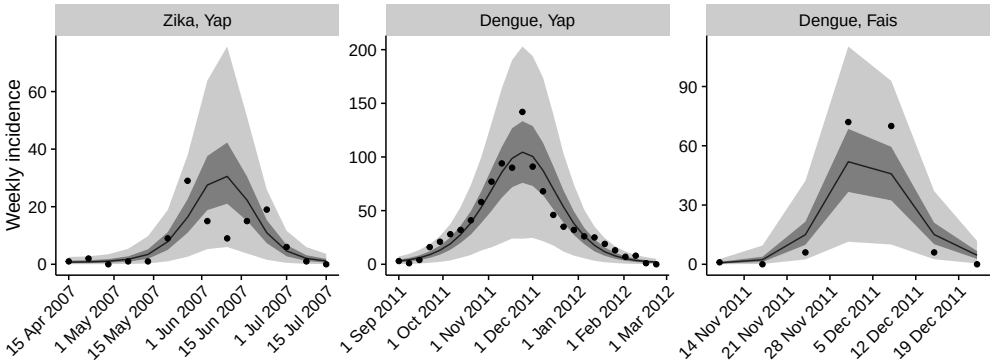

Figure 3. Time-line of the outbreaks. Left to right: Zika virus on the Yap Main Islands, 2007; dengue outbreak on the Yap Main (and Outer) Islands, 2011 and Fais, 2011. Shown are the data (weekly incidence) as dots, and model fits (mean, line; interquartile range, dark grey; 95% credible interval, light grey).

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The estimated disease-specific parameters span overlapping ranges (Table 1). Durations of infection and incubation largely correspond to the given prior distributions, indicating that these were not strongly identifiable from the available data. Whilst the data did not allow us to estimate the proportion of infections asymptomatic and not transmitting to great precision, there was a strong difference in the proportion of infectious people reported, between a mean of 68% (95% credible interval 43–98) for dengue and a mean of 3% (2–7) for Zika.

Location-specific parameters indicated a considerable difference in the number of female mosquitoes per person, with a mean estimate of 3.1 (0.7–8.7) on the Yap Main Islands and 7.7 (4.1–9.9) on Fais. The proportion of the population initially susceptible to dengue on the Yap Main Islands was estimated to be 29% (19–41). Average mosquito lifespan was estimated to be 13 days (5–28).

Table 1. 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. CI: credible interval.

Disease-specific parameters						
	Dengue		Zika			
	Mean	95% CI	Mean	95% CI	Prior	Reference
$D_{\mathrm{inf,H}}$	4.6	(1.9, 7.9)	5.8	(2.9, 8.8)	Normal(4.5, 0.75)	[33]
$D_{\mathrm{inc,H}}$	5.6	(4.9, 6.4)	5.8	(5.1, 6.7)	Log-normal(5.9, 0.07)	[25]
$D_{\mathrm{inc,M}}$	8.6	(4.3, 15)	9.1	(4.4, 17)	Log-normal(9.8, 0.36)	[25]
b_{H}	0.75	(0.34, 0.99)	0.79	(0.40, 0.99)	Uniform(0,1)	n/a
b_{M}	0.79	(0.51, 0.99)	0.71	(0.27, 0.99)	Uniform(0,1)	n/a
p	0.73	(0.43, 0.98)	0.69	(0.26, 0.99)	Uniform(0,1)	n/a
r	0.68	(0.43, 0.98)	0.03	(0.01, 0.07)	Uniform(0,1)	n/a
Location-specific parameter						
	Yap		Fais			
	Mean	95% CI	Mean	95% CI	Prior	Reference
m	3.1	(0.7, 8.7)	7.7	(4.1, 9.9)	Log-uniform(0.1, 10)	n/a
τ	0.71	(0.35, 0.99)	0.87	(0.63, 1.00)	Uniform(0.3, 1)	[34]
q	0.29	(0.19, 0.41)			Uniform(0, 1)	n/a
Common parameter						
	Mean	95% CI			Prior	Reference
$D_{\mathrm{life,M}}$	13	(5, 28)			Uniform(4, 30)	[34]

The mean estimates of the basic reproduction number, R_0 were 4.3 (3.1–6.1) for dengue on the Yap Main Islands, 4.8 (2.9–8.1) for Zika on the Yap Main Islands, and 10 (5.5 – 18) for dengue on Fais (Fig. 4). By combining the estimated parameters between settings and disease, we estimated R_0 for Zika on Fais to 11 (5.2 – 21). The differences in R_0 between Zika and Fais are due to estimated differences in the number of female mosquitoes per person and the biting frequency. Pooling these together into an effective biting rate, $e = m\tau$, or the number of bites experienced per person, per day, we estimated this to be 1.9 (0.6–4.4) for the Yap Main Islands and 6.6 (3.6 – 9.4) for Fais.

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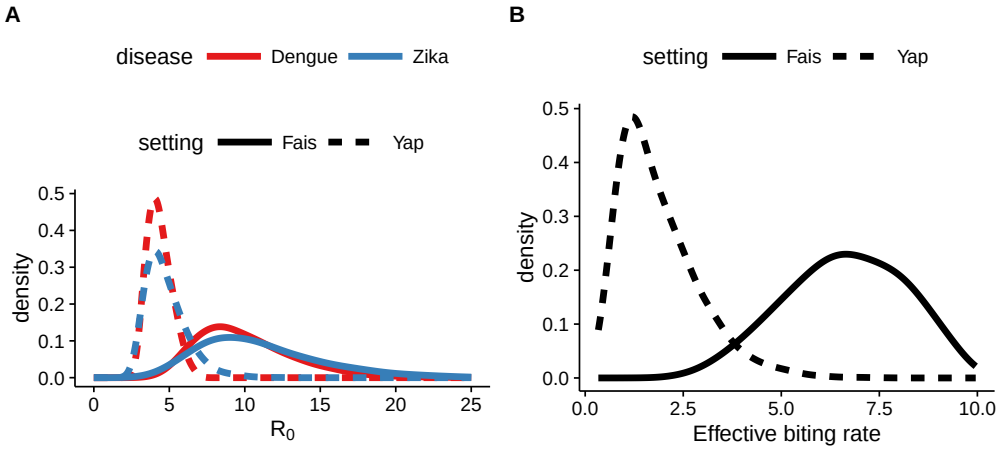

Figure 4. Posterior distributions of R_0 and e for the two settings and diseases. Solid lines: Fais; dashed lines: Yap Main Islands; red lines: dengue; blue lines: Zika. A) Basic reproduction number R_0. Note that the hypothetical R_0 for Zika in Fais is shown here as all parameters needed to calculate it have been estimated. B) Effective biting rate $e = m\tau$, or the number of bites experienced per person

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. Our estimates of basic reproduction numbers for dengue are consistent with those previously reported in the literature [35]. The estimates of the incubation and infectious periods of Zika are consistent with those of a recent systematic review [36]. They do not differ much from the dengue-based prior distributions, suggesting that either they are similar, or the data are not informative on this matter. Moreover, the R_0 estimates for Zika and dengue on the Yap Main Islands spans a very similar range. All these results give support to recent suggestions that dengue models could be readily adapted to study Zika outbreaks [13, 37].

Two findings are worth noting: one is the much lower proportion of those infectious with Zika virus that turn into reported clinical cases. Our mean estimate for this proportion is 3%, compared to 68% for dengue. From the available data, it is not possible to disentangle asymptomatic individuals from symptomatic individuals that did not present to health-care workers. In a serological household study on the Yap Main Islands, it was estimated that 73% (68–77) of the population had been infected in the outbreak, consistent with our estimate of 69% (26–99) of the population to have become infectious. The serological study further found that 18% (10–27) of those infected had developed clinical symptoms. Combined with our estimate that only 3% (1–7) of infectious Zika cases were reported as confirmed or probable cases, this would suggest that approximately 17% (4–70) of those with symptoms reported to a health provider. Understanding these proportions is of particular importance when trying to project overall attack rates and expected rates of complications from infection from time series

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of observed cases.

The second important finding is that the estimates for R_0 are remarkably similar between dengue and Zika where they have been observed in the same setting, but differ strongly between the Yap Main Islands and Fais. This, and the fact that all our estimates of biological parameters overlap strongly between the two infections, suggests that the 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 model has a number of limitations. We have assumed that the outbreaks were limited by the number of susceptibles and ignored any effects of varying seasonal or other environmental factors that may have curtailed transmission, and none of the sites reported another outbreak immediately following the decline. We have further assumed that there is no immunological interaction between dengue and Zika, and that therefore the whole population was fully susceptible to Zika infection on the Yap Main Islands. More generally, individual variation in exposure to infectious bites and the probability of developing disease due to genetic or other individual factors might change expected case numbers. Further, our model is deterministic and ignores any underlying stochasticity that may have played a role especially early and late in the outbreaks. Because of these assumptions, what could be interpreted as two peaks in the Zika outbreak on the Yap Main Islands is combined into a single outbreak in our model fit. We did not have any further information to distinguish whether this two-peaked structure is a stochastic effect in the presence of low reporting levels, one of geographical transmission, or one of delays associated with the incubation periods involved in Zika transmission.

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 such as this one, especially when conducted on outbreaks in closed populations, yields important insights into analogies that can be explored in interpreting observed transmission patterns and predicting future dynamics.

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