

# Epidemiological and ecological determinants of Zika virus transmission in an urban setting

## Supplementary Material

### Methods

The ordinary differential equations (ODE) model and the Markov-chain Monte Carlo (MCMC) fitting approach herein used are based on the framework previously proposed to study the introduction of dengue into the island of Madeira in 2012 [1]. We have changed this framework to relax major modelling assumptions on the mosquito sex ratio and success of egg hatching, have included humidity and rainfall as critical climate variables, and have also transformed the original least squares based MCMC into a Bayesian MCMC. The resulting framework is described in the following sections.

### Ento-Epidemiological Dynamic Model

The dynamics of infection within the human population are defined in equations 1-5. In summary, the human population is assumed to have constant size ( $N$ ) with mean life-expectancy of  $\mu^h$  years, and to be fully susceptible before introduction of the virus. Upon challenge with infectious mosquito bites ( $\lambda^{v \rightarrow h}$ ), individuals enter the incubation phase ( $E^h$ ) with mean duration of  $1/\gamma^h$  days, later becoming infectious ( $I^h$ ) for  $1/\sigma^h$  days and finally recovering ( $R^h$ ) with life-long immunity.

$$\frac{dS^h}{dt} = \mu^h N - \lambda^{v \rightarrow h} - \mu^h S^h \quad (1)$$

$$\frac{dE^h}{dt} = \lambda^{v \rightarrow h} - \gamma^h E^h - \mu^h E^h \quad (2)$$

$$\frac{dI^h}{dt} = \gamma^h E^h - \sigma^h I^h - \mu^h I^h \quad (3)$$

$$\frac{dR^h}{dt} = \sigma^h I^h - \mu^h R^h \quad (4)$$

$$N = S^h + E^h + I^h + R^h \quad (5)$$

For the dynamics of the mosquito population (equations 6-10), individuals are divided into two pertinent life-stages: aquatic (eggs, larvae and pupae,  $A$ ) and adult females ( $V$ ) as in [2]. The adults are further divided into the epidemiologically relevant stages for arboviral transmission: susceptible ( $S^v$ ), incubating ( $E^v$ ) for  $1/\dot{\gamma}^v$  days and infectious ( $I^v$ ) for life. The  $\dot{\cdot}$  (dot) notation is here adopted to distinguish climate-dependent entomological factors (further details in the following sections).

$$\frac{dA}{dt} = \dot{c}^v f \dot{\theta}^v \left( 1 - \frac{A}{K(R+1)} \right) V - (\dot{\epsilon}_A^v + \dot{\mu}_A^v) A \quad (6)$$

$$\frac{dS^v}{dt} = \dot{\epsilon}_A^v A - \lambda^{h \rightarrow v} - \dot{\mu}_V^v S^v \quad (7)$$

$$\frac{dE^v}{dt} = \lambda^{h \rightarrow v} - \dot{\gamma}^v E^v - \dot{\mu}_V^v E^v \quad (8)$$

$$\frac{dI^v}{dt} = \dot{\gamma}^v E^v - \dot{\mu}_V^v I^v \quad (9)$$

$$V = S^v + E^v + I^v \quad (10)$$

Here, the coefficient  $\dot{c}^v$  is the fraction of eggs hatching to larvae and  $f$  the resulting female proportion. For simplicity and lack of quantifications for local mosquito populations, it is assumed that the sex ratio remains at 1:1 (i.e.  $f = 0.5$ ). Moreover,  $\dot{\epsilon}_A^v$  denotes the rate of transition from aquatic to adult stages,  $\dot{\mu}_A^v$  the aquatic mortality,  $\dot{\mu}_V^v$  the adult mortality, and  $\dot{\theta}^v$  is the success rate of oviposition. The logistic term  $(1 - \frac{A}{K(R+1)})$  can be understood as the ecological capacity to receive aquatic individuals [3], scaled by a carrying capacity term  $K(R+1)$  in which  $K$  determines the maximum capacity and  $R$  is the local rainfall contribution (further details on following sections).

From equations 6-10, the mean number of viable female offspring produced by one female adult during

its life-time, i.e. the basic offspring number  $Q$ , was derived (equation 11). Most parameters defining  $Q$  are climate-dependent, and for fixed mean values of the climate variables (ex. mean rainfall  $\bar{R}$ ), expressions were derived for the expected population sizes of each mosquito life-stage modelled ( $A_0, V_0$ ) which are used to initialize the vector population (equations 12-13).

$$Q = \frac{\dot{\epsilon}_A^v}{\dot{\epsilon}_A^v + \dot{\mu}_A^v} \frac{\dot{c}f\dot{\theta}^v}{\dot{\mu}_V^v} \quad (11)$$

$$A_0 = K (\bar{R} + 1) \left(1 - \frac{1}{Q}\right) \quad (12)$$

$$V_0 = K (\bar{R} + 1) \left(1 - \frac{1}{Q}\right) \frac{\dot{\epsilon}_A^v}{\dot{\mu}_V^v} \quad (13)$$

## Viral Transmission

In respect to the *infected host-type* being considered, the vector-to-human ( $\lambda^{v \rightarrow h}$ ) and human-to-vector ( $\lambda^{h \rightarrow v}$ ) incidence rates are assumed to be, respectively, density-dependent and frequency-dependent (equations 14-15). Here,  $\dot{a}^v$  is the biting rate and  $\dot{\phi}^{v \rightarrow h}$  and  $\phi^{h \rightarrow v}$  are the vector-to-human and human-to-vector transmission probabilities per bite. Conceptually, this implies that (i) an increase in the density of infectious vectors should directly raise the risk of infection to a single human, while (ii) an increase in the frequency of infected humans raises the risk of infection to a mosquito biting at a fixed rate. The basic reproductive number ( $R_0$ ) is defined similarly to previous modelling approaches (equation 16) [4, 5]. We further derived an expression for the effective reproductive ratio ( $R_e$ , equation 17), taking into account the susceptible proportion of the population in real-time.

$$\lambda^{v \rightarrow h} = \left(\dot{a}^v \dot{\phi}^{v \rightarrow h} I^v S^h / N\right) \propto I^v \quad (14)$$

$$\lambda^{h \rightarrow v} = \left(\dot{a}^v \phi^{h \rightarrow v} I^h S^v / N\right) \propto I^h / N \quad (15)$$

$$R_0 = \frac{(V/N) \dot{a}^v \dot{\phi}^{v \rightarrow h} \phi^{h \rightarrow v} \dot{\gamma}^v \gamma^h}{\dot{\mu}_V^v (\sigma^h + \mu^h) (\gamma^h + \mu^h) (\dot{\gamma}^v + \dot{\mu}_V^v)} \quad (16)$$

$$R_e = (S^h / N) \times (S^v / N) \times R_0 / (V/N) \quad (17)$$

## Markov Chain Monte Carlo Fitting Approach

For the fitting process, the MCMC algorithm by Lourenco et al. is here altered to a Bayesian approach by formalising a likelihood and parameter priors [1]. For this, the jumping distributions of each parameter were kept as Gaussian (symmetric), effectively retaining a random walk Metropolis kernel. We define our acceptance probability  $\alpha$  of a parameter set  $\Theta$ , given model ODE output  $y$  as:

$$\alpha = \min\left\{1, \frac{\pi(y|\Theta^*)\pi(\Theta^*)}{\pi(y|\Theta^o)\pi(\Theta^o)}\right\} \quad (18)$$

where  $\Theta^*$  and  $\Theta^o$  are the proposed and current (accepted) parameter sets (respectively), and  $\pi(y|\Theta^*)$  and  $\pi(y|\Theta^o)$  are the likelihoods of the ODE output representing the epidemic data, given each parameter set. We assume uniform priors to all estimated parameters, and the likelihoods to be the product of the conditional Poisson probabilities of each epidemic data and ODE point:

$$\pi(y|\Theta) = \prod_{i=1}^N [Pr\{y_i = d_i\}] \quad (19)$$

To address MCMC convergence, we quantified  $\sqrt{\hat{R}}$ , the Gelman-Rubin statistic (which compares the variance between and within M independent MCMC chains) [6]. This statistic is expected to approximate 1 when M independent chains have converged to the same stationary distributions. Values significantly larger than 1, for instance, indicate that the between-chain variance is greater than the within-chain variance, highlighting that the MCMC may need more time to converge or tuning of jump parameters is required [6]. For calculation details please refer to [1].

## Fitted Parameters

With the MCMC approach described above, all combinations of the *open* parameters in the ODE system that most likely represent the outbreak are explored (Table 3). In summary, the MCMC estimates distributions for: (1) the carrying capacity  $K$ , used to indirectly estimate the number of adult mosquitoes per human; (2) time point of the first case  $t_0$ , assumed to be in a human; (3) a linear coefficient  $\eta$  that scales the effect of temperature on aquatic and adult mortality rates; (4) a linear coefficient  $\alpha$  that scales the effect of temperature on the extrinsic incubation period; (5) a non-linear coefficient  $\rho$  that scales the effects of humidity and rainfall on entomological parameters; (6) the human infectious period  $1/\sigma^h$ ; and

(7) the human incubation period  $1/\gamma^h$ .

By introducing the linear coefficients  $\eta$  and  $\alpha$ , the relative effect of temperature variation on mortality and incubation is not changed *per se*, but instead the baselines are allowed to be different from the laboratory ideal conditions used by Yang et al. in laboratory experiments [2]. For MCMC solutions in which  $\eta, \alpha \rightarrow 1$  the laboratory-based relationships are kept. For a discussion on possible biological factors that may justify  $\eta$  and  $\alpha$  please refer to the original description of the method [1] and [7]. Finally, the introduction of  $\rho$  allows the MCMC to vary the strength with which entomological parameters react to significant deviations from local humidity and rainfall means. In practice, the effect of rainfall and humidity can be switched off by the MCMC when  $\rho \rightarrow 0$  and made stronger when  $\rho \rightarrow +\infty$  (details below).

## Constant Parameters

The framework described above has only 4 fixed parameters that are neither climate-dependent nor estimated in the MCMC approach (Table 2). Amongst these,  $\phi^{h \rightarrow v}$  is the per bite probability of transmission from human-to-mosquito, which we assume to be 0.5 [8,9]; the sex ratio of the adult mosquito population  $f$  is assumed to be 1:1 [8,9]; the life-expectancy of the human population is assumed to be an average of 75 years [10]; and the biting rate is taken to be on average 0.25 although with the potential to vary dependent on humidity levels (details below) [11,12].

## Climate-Dependent Parameters

For each of the temperature-dependent entomological parameters, polynomial expressions are found *de novo* or taken from previous studies fitting laboratory entomological data with temperature (T) values used in Celsius. For rainfall (R) and humidity (U), positive or negative relationships to entomological parameters are introduced using simple expressions, with values used after normalization to  $[0, 1]$ . We assume that some parameters are affected by a combination of temperature with either rainfall or humidity, but take their effects to be independent. A list of climate-dependent parameters and references is found in Table 1.

Polynomials of 4th degree for the mortality ( $\mu_A^v, \mu_V^v$ ) and success oviposition ( $\theta^v$ ) rates are taken from the study by Yang and colleagues under temperature-controlled experiments on populations of *Aedes aegypti* (equations 19-21) [2]. We simplify the 7th degree polynomial for aquatic to adult ( $\epsilon_A^v$ ) rate of the

same study into a 3rd degree one (equation 20). For the relationship between the extrinsic incubation period ( $1/\gamma^v$ ) and temperature we apply a similar simplification to the formulation by Focks et al. which assumes that replication is determined by a single rate-controlling enzyme [13–15] (equation 24). The probability of transmission per mosquito bite ( $\phi^{v \rightarrow h}$ ) is here modelled (equation 25) as estimated by Lambrechts and colleagues [16]. Finally, the relationship between temperature and the fraction of eggs that successfully hatch ( $c^v$ ) is estimated *de novo* (equation 26) by fitting a 3rd degree polynomial to *Aedes aegypti* and *albopictus* empirical data described by Dickerson et al. (see Figure S1) [9, 17].

$$\epsilon_A^v(T) = 0.2506 - 0.0488T + 0.0029T^2 - 0.00004T^3 \quad (20)$$

$$\mu_A^v(T) = 2.13 - 0.3797T + 0.02457T^2 - 0.0006778T^3 + 0.000006794T^4 \quad (21)$$

$$\mu_V^v(T) = 0.8692 - 0.1599T + 0.01116T^2 - 0.0003408T^3 + 0.000003809T^4 \quad (22)$$

$$\theta^v(T) = -5.4 + 1.8T - 0.2124T^2 + 0.01015T^3 - 0.0001515T^4 \quad (23)$$

$$\gamma^v(T) = 1.0/((1245.0 - 49.6T + 0.49T^2)/24.0) \quad (24)$$

$$\phi^{v \rightarrow h}(T) = 0.001044T \times (T - 12.286) \times (32.461 - T)^{1/2} \quad (25)$$

$$c^v(T) = (-184.8 + 27.94T - 0.9254T^2 + 0.009226T^3)/100.0 \quad (26)$$

We normalise the time series of rainfall (R) and humidity (U), further using the mean normalised values ( $\bar{R}, \bar{U}$ ) as reference for extreme deviations from the expected local tendencies [3, 18]. Rainfall is assumed to affect positively the fraction of eggs that successfully hatch ( $c^v$ ) [3, 19–21]. A similar positive relationship is taken for the vector biting rate ( $a^v$ ) and humidity levels [12], in contrast to a negative effect on the adult mosquito mortality rate ( $\mu_V^v$ ) [19].

$$c^v(R) = (R - \bar{R})/\sqrt{1 + (R - \bar{R})^2} \quad (27)$$

$$a^v(U) = (U - \bar{U})/\sqrt{1 + (U - \bar{U})^2} \quad (28)$$

$$\mu_V^v(U) = \bar{U} - (U - \bar{U})/\sqrt{1 + (U - \bar{U})^2} \quad (29)$$

Below is the complete formulation for each entomological parameter in time (t), depending on the

climatic variables for which relationships are assumed to exist, including the MCMC fitter linear  $(\alpha, \eta)$  and non-linear  $(\rho)$  factors described above.

$$\epsilon_A^v(t) = \epsilon_A^v(T) \quad (30)$$

$$\mu_A^v(t) = \eta \mu_A^v(T) \quad (31)$$

$$\mu_V^v(t) = \eta \mu_V^v(T) [1 + \mu_V^v(U)]^\rho \quad (32)$$

$$\theta^v(t) = \theta^v(T) \quad (33)$$

$$\gamma^v(t) = \alpha \gamma^v(T) \quad (34)$$

$$\phi^{v \rightarrow h}(t) = \phi^{v \rightarrow h}(T) \quad (35)$$

$$c^v(t) = c^v(T) [1 + c^v(R)]^\rho \quad (36)$$

$$a^v(t) = a^v [1 + a^v(U)]^\rho \quad (37)$$

## References

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## Tables

**Table 1. Climate-dependent parameters.**

notation	description
$\epsilon_A^v(t)$	transition rate from aquatic to adult mosquito life-stages
$\mu_A^v(t)$	mortality rate of aquatic mosquito life-stage
$\mu_V^v(t)$	mortality rate of adult mosquito life-stage
$\theta^v(t)$	(human) intrinsic oviposition rate of adult mosquito life-stage
$\gamma^v(t)$	(vector) extrinsic incubation period of adult mosquito life-stage
$\phi^{v \rightarrow h}(t)$	vector-to-human probability of transmission per infectious bite
$c^v(t)$	egg hatching success
$a^v(t)$	adult vector biting rate

**Table 2. Constant parameters.**

notation	value	description	references
$a^v$	0.25 per day	mosquito biting rate	[11, 12]
$f$	0.5	proportion of females (sex ratio)	[8, 9]
$\phi^{h \rightarrow v}$	0.5	human-to-vector probability of transmission per infectious bite	–
$1/\mu^h$	75 years	human mean lifespan	[10]

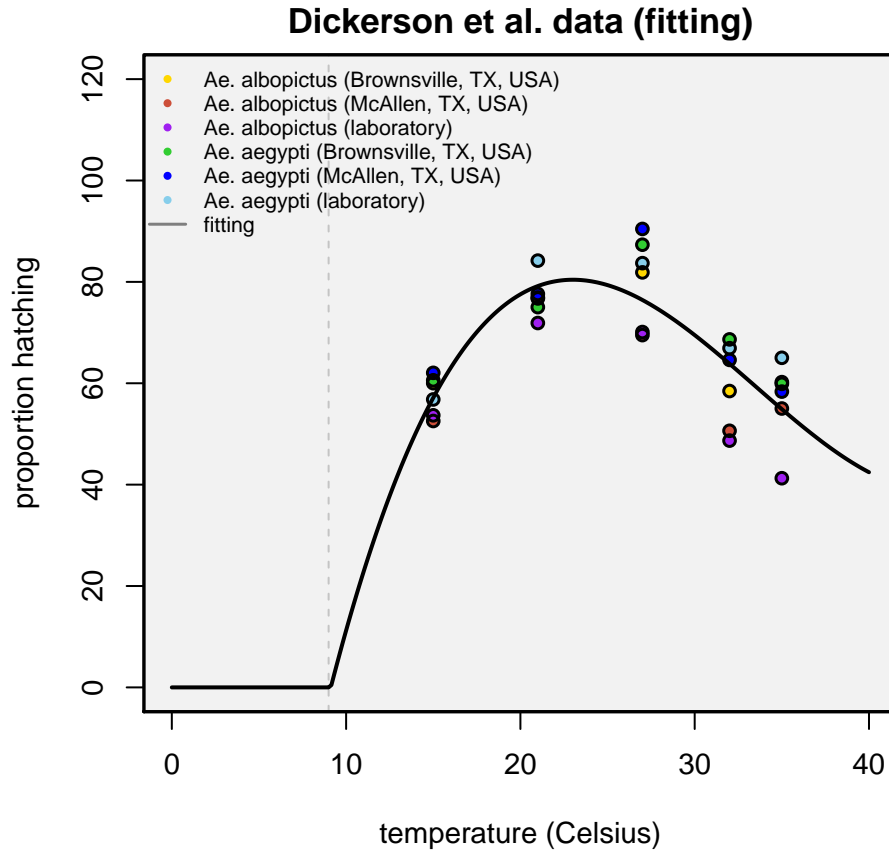
Parameters that are fixed in the ODE system.

**Table 3. Estimated parameters.**

<b>notation</b>	<b>description</b>	<b>ranges / priors</b>
$t_0$	time point of first case (in a human)	$(\infty, \infty)$
$K$	aquatic carrying capacity	$(0, \infty)$
$\eta$	linear factor for mosquito mortality	$(0, \infty)$
$\alpha$	linear factor for extrinsic incubation period	$(0, \infty)$
$\rho$	non-linear factor for effects of humidity and rainfall	$(0, \infty)$
$\sigma^h$	human infectious period	$(0, 15)$
$\gamma^h$	human (intrinsic) incubation period	$(0, 15)$
$\zeta$	observation rate	$(0, 1)$

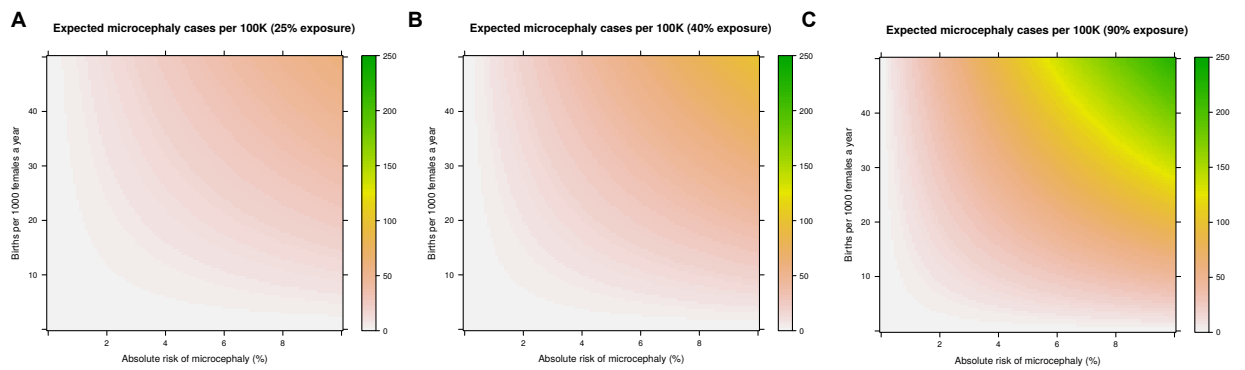
Free parameters used by the Bayesian MCMC approach to fit the data.

## Supporting Information Legends



**Supplementary Figure 1. Relationship between temperature and egg hatching success.**

Empirical data on *Aedes aegypti*'s and *albopictus*'s egg hatching success (in the model  $\hat{c}$ ) is taken from [17]. Data includes measurements of hatching for 5 different temperatures above 15 Celsius, including 2 wild and 1 laboratory populations for each of the vector-species. Fitting implemented with a third degree polynomial in R (which can be found in the Results section of the main text). When modelling, negative proportions below 10 Celsius are manually corrected to zero (left of shaded grey line).



**Supplementary Figure 2. Sensitivity to microcephaly risk.** Expected number of cases of microcephaly (MC) and other neurological complications (NC) for theoretical ranges of birth rate (per 1K females) and risk of complications assuming (A) 25%, (B) 40%, or (C) 90% exposure of all pregnancies. See Figure 5 of main text for details.