Title: Detecting the impact of temperature on transmission of Zika, dengue and chikungunya using mechanistic models

Short title: Temperature predicts Zika, dengue, and chikungunya transmission

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39 *albopictus*

40

41

Abstract

Recent epidemics of Zika, dengue, and chikungunya have heightened the need to understand the seasonal and geographic range of transmission by *Aedes aegypti* and *Ae. albopictus* mosquitoes. We use mechanistic transmission models to derive predictions for how the probability and magnitude of transmission for Zika, chikungunya, and dengue change with mean temperature, and we show that these predictions are well matched by human case data. Across all three viruses, models and human case data both show that transmission occurs between 18-34°C with maximal transmission occurring in a range from 26-29°C. Controlling for population size and two socioeconomic factors, temperature-dependent transmission based on our mechanistic model is an important predictor of human transmission occurrence and incidence. Risk maps indicate that tropical and subtropical regions are suitable for extended seasonal or year-round transmission, but transmission in temperate areas is limited to at most three months per year even if vectors are present. Such brief transmission windows limit the likelihood of major epidemics following disease introduction in temperate zones.

Author Summary (150-200 words)

Understanding the drivers of recent Zika, dengue, and chikungunya epidemics is a major public health priority. Temperature may play an important role because it affects mosquito transmission, affecting mosquito development, survival, reproduction, and biting rates as well as the rate at which they acquire and transmit viruses. Here, we measure the impact of temperature on transmission by two of the most common mosquito vector species for these viruses, *Aedes aegypti* and *Ae. albopictus*. We integrate data from several laboratory experiments into a mathematical model of temperature-dependent transmission, and find that transmission peaks at

26-29°C and can occur between 18-34°C. Statistically comparing model predictions with recent observed human cases of dengue, chikungunya, and Zika across the Americas suggests an important role for temperature, and supports model predictions. Using the model, we predict that most of the tropics and subtropics are suitable for transmission in many or all months of the year, but that temperate areas like most of the United States are only suitable for transmission for a few months during the summer (even if the mosquito vector is present).

72 **Main Text**

73 Epidemics of dengue, chikungunya, and Zika are sweeping through the Americas, and are part of
74 a global public health crisis that places an estimated 3.9 billion people in 120 countries at risk
75 [1]. Dengue virus (DENV) distribution and intensity in the Americas has increased over the last
76 three decades, infecting an estimated 390 million people (96 million clinical) per year [2].
77 Chikungunya virus (CHIKV) emerged in the Americas in 2013, causing 1.8 million suspected
78 cases from 44 countries and territories (www.paho.org). In the last two years, Zika virus (ZIKV)
79 has spread throughout the Americas, causing 714,636 suspected and confirmed cases, with many
80 more unreported (http://ais.paho.org/phip/viz/ed_zika_cases.asp, as of January 5, 2017). The
81 growing burden of these diseases (including links between Zika infection and both microcephaly
82 and Guillain-Barré syndrome [3]) and potential for spread into new areas creates an urgent need
83 for predictive models that can inform risk assessment and guide interventions such as mosquito
84 control, community outreach, and education.

85 Predicting transmission of DENV, CHIKV, and ZIKV requires understanding the
86 ecology of the vector species. For these viruses the main vector is *Aedes aegypti*, a mosquito that
87 prefers and is closely affiliated with humans, while *Ae. albopictus*, a peri-urban mosquito, is an
88 important secondary vector [4,5]. We expect one of the main drivers of the vector ecology to be
89 the climate, particularly temperature. For that reason, mathematical and geostatistical models that
90 incorporate climate information have been valuable for predicting and responding to *Aedes* spp.
91 spread and DENV, CHIKV, and ZIKV outbreaks [5–10].

92 The effects of temperature in ectotherms are largely predictable from fundamental
93 metabolic and ecological processes. Survival, feeding, development, and reproductive rates
94 predictably respond to temperature across a variety of ectotherms, including mosquitoes [11,12].

95 Because these traits help to determine transmission rates, the effects of temperature on
96 transmission should also be broadly predictable from mechanistic models that incorporate
97 temperature-dependent traits. Here, we introduce a model based on this framework that
98 overcomes several major gaps that currently limit our understanding of climate suitability for
99 transmission. Specifically, we develop models of temperature-dependent transmission for *Ae.*
100 *aegypti* and *Ae. albopictus* that are (a) mechanistic, facilitating extrapolation beyond the current
101 disease distribution, (b) parameterized with biologically accurate unimodal thermal responses for
102 all mosquito and virus traits that drive transmission, and (c) validated against human dengue,
103 chikungunya, and Zika case data across the Americas.

104 We synthesize available data to characterize the temperature-dependent traits of the
105 mosquitoes and viruses that determine transmission intensity. With these thermal responses, we
106 develop mechanistic temperature-dependent virus transmission models for *Ae. aegypti* and *Ae.*
107 *albopictus*. We then ask whether the predicted effect of temperature on transmission is consistent
108 with patterns of actual human cases over space and time. To do this, we validate the models with
109 DENV, CHIKV, and ZIKV human incidence data at the country scale from the Americas from
110 2014-2016. To isolate temperature dependence, we also statistically controlled for population
111 size and two socioeconomic factors that may influence transmission. If temperature
112 fundamentally limits transmission potential, transmission should only occur at actual
113 environmental temperatures that are predicted to be suitable, and conversely, areas with low
114 predicted suitability should have low or zero transmission (i.e., false negative rates should be
115 low). By contrast, low transmission may occur even when temperature suitability is high because
116 other factors like vector control can limit transmission (i.e., the false positive rate should be
117 higher than the false negative rate). Finally, if the simple mechanistic model accurately predicts

118 climate suitability for transmission, then we can use it to map climate-based transmission risk of
119 DENV, CHIKV, ZIKV, and other emerging pathogens transmitted by *Ae. aegypti* and *Ae.*
120 *albopictus* seasonally and geographically.

121 **Results**

122 *Temperature-dependent transmission*

123 Data gathered from the literature [9,13–15,15–21,21–30] revealed that all mosquito traits
124 relevant to transmission—biting rate, egg-to-adult survival and development rate, adult lifespan,
125 and fecundity—respond strongly to temperature and peak between 23°C and 34°C for the two
126 mosquito species (*Ae. aegypti* in Fig. 1 and *Ae. albopictus* in Fig. S1). DENV extrinsic
127 incubation and vector competence peak at 35°C [31–37] and 31-32°C [31,32,34,38],
128 respectively, in both mosquitoes—temperatures at which mosquito survival is low, limiting
129 transmission potential (Figs. 1, S1). Appropriate thermal response data were not available for
130 CHIKV and ZIKV extrinsic incubation and vector competence.

131

132 **Fig. 1.** Thermal responses of *Ae. aegypti* and DENV traits that drive transmission (data sources
133 listed in Table S2). Informative priors based on data from additional *Aedes* spp. and flavivirus
134 studies helped to constrain uncertainty in the model fits (see Materials and Methods; Table S3).
135 Points and error bars indicate the data means and standard errors (for display only; models were
136 fit from the raw data). Black solid lines are the mean model fits; red dashed lines are the 95%
137 credible intervals. Thermal responses for *Ae. albopictus* are shown in Fig. S1.

138

139 We estimated the posterior distribution of $R_0(T)$ and used it to calculate key temperature
140 values that indicate suitability for transmission: the mean and 95% credible intervals (95% CI)
141 on the critical thermal minimum, maximum, and optimum temperature for transmission by the
142 two mosquito species. At constant temperature, *Ae. aegypti* transmission peaked at 29.1°C (95%
143 CI: 28.4 – 29.8°C), and declined to zero below 17.8°C (95% CI: 14.6 – 21.2°C) and above
144 34.6°C (95% CI: 34.1 – 35.6°C) (Fig. 2). *Ae. albopictus* transmission peaked at 26.4°C (95% CI:
145 25.2 – 27.4°C) and declined to zero below 16.2°C (95% CI: 13.2 – 19.9°C) and above 31.6°C
146 (95% CI: 29.4 – 33.7°C) (Fig. 2). Overall, the thermal response curve for *Ae. albopictus* is
147 shifted towards lower temperatures than *Ae. aegypti,* so *Ae. albopictus* transmission is better
148 suited to colder environments. For a more realistic scenario in which daily temperature ranged
149 over 8°C, the transmission peak, minimum, and maximum were slightly lower for both *Ae.*
150 *aegypti* (28.5°C, 13.5°C, 34.2°C, respectively) and *Ae. albopictus* (26.1°C, 11.9°C, and 28.3°C,
151 respectively). The lower thermal maximum under fluctuating temperatures occurs because we
152 incorporated empirically supported irreversible lethal effects of temperatures that exceed thermal
153 maxima for survival (see Materials and Methods).

154

155 **Fig. 2**. Relative R_0 across constant temperatures (°C; top) for *Ae. albopictus* (light blue) and *Ae.*
156 *aegypti* (dark blue), and histograms of the posterior distributions of the critical thermal minimum
157 (bottom left), temperature at peak transmission (bottom middle), and critical thermal maximum
158 (bottom right; all in °C). Solid lines: mean posterior estimates; dashed lines: 95% credible
159 intervals. R_0 curves normalized to a 0-1 scale for ease of comparison and visualization.

160

161 The posterior distribution of $R_0(T)$ allows us to evaluate uncertainty in key temperature
162 values that define the transmission range, including critical thermal minimum, maximum, and
163 optimum. Uncertainty was higher for the critical thermal minimum for transmission than for the
164 maximum or optimum, and the two mosquito species overlapped most for this outcome (Fig. 2,
165 bottom panels). This occurred because several trait thermal responses increase gradually from
166 low to mid temperatures but decline more steeply at high temperatures (Fig. 1), so uncertainty is
167 greatest at low temperatures. *Ae. aegypti* has a substantially higher optimum and maximum
168 temperature than *Ae. albopictus* (Fig. 2) due to its greater rates of adult survival at high
169 temperatures (see Supplementary Materials for sensitivity analyses).

170

171 *Model validation*

172 We used generalized linear models (GLM) to ask whether the predicted relationship
173 between temperature and transmission, $R_0(T)$, was consistent with observed human cases of
174 DENV, CHIKV, and ZIKV. Specifically, we assessed whether $R_0(T)$ was an important predictor
175 of the probability of autochthonous transmission occurring and of the incidence given that
176 transmission occurred. We also controlled for human population size, virus species, and two
177 socioeconomic factors. (Note that we focused on testing the $R_0(T)$ model, rather than on
178 constructing the best possible statistical model of human case data.) To do this, we used the
179 version of the *Ae. aegypti* $R_0(T)$ model that includes 8°C daily temperature range, along with
180 country-scale weekly case reports of DENV, CHIKV, and ZIKV in the Americas and the
181 Caribbean between 2014-2016. We first addressed the fact that countries with larger populations
182 have greater opportunities for (large) epidemics by creating two predictors that incorporate
183 scaled $R_0(T)$ and population size. In the models of the probability of autochthonous transmission

184 occurring we used the product of the posterior probability that $R_0(T) > 0$ (which we notate as
185 GR_0) and the log of population size (p) to give $log(p)*GR_0$. In the models of incidence given that
186 transmission does occur we used the log of the product of the posterior mean of $R_0(T)$ and
187 population size, $log(p*R_0(T))$. To control for several socioeconomic factors that might obscure
188 the impact of temperature, we also included log of gross domestic product (GDP) and log percent
189 of GDP in tourism (using logs to improve normality). These are potential indicators of
190 investment in and/or success of vector control and infrastructure improvements that prevent
191 transmission. By comparing models that included the $R_0(T)$ metric alone, socioeconomic factors
192 alone, or both, we tested whether $R_0(T)$ was an important predictor of observed transmission
193 occurrence and incidence (see Table S4). Note that $R_0(T)$ is out of sample because it is derived
194 and calculated strictly from laboratory data on mosquitoes, and we perform a validation analyses
195 for $R_0(T)$ using independent case incidence reports. For this validation step we assessed model
196 adequacy for the transmission data in two ways. First we used the full dataset for case incidence
197 reports to select the best model (Table S4) and determine whether or not our predicted value of
198 relative $R_0(T)$ based on laboratory data was included in the model ("within sample" analysis).
199 Second we used a bootstrapping approach where models were fit on subsets of the case incidence
200 data that were randomly sampled and then predictive accuracy of the competing models (Table
201 S4) was assessed on left-out data ("out of sample" analysis).

202 For the probability of autochthonous transmission occurring, the model that included both
203 the $R_0(T)$ predictor and socioeconomic predictors had overwhelming support based on Bayesian
204 Information Criterion (BIC; model PA5 relative probability = 1, Table S4). Based on deviance
205 explained, the models that included $R_0(T)$, with or without the socioeconomic predictors out-
206 performed the model that did not include $R_0(T)$ (Table S4; Figs. 3A, S2). In analyses of out-of-

207 sample accuracy, models that included the $R_0(T)$ metric (with or without the socioeconomic
208 factors) were surprisingly accurate. They predicted the probability of transmission with 86-91%
209 out-of-sample accuracy for DENV (Table S4). For CHIKV and ZIKV, models that included the
210 $R_0(T)$ metric or population alone had 66-69% out-of-sample accuracy (Table S4). There were no
211 significant differences in out-of-sample accuracy between the top four models but for both
212 DENV and CHIKV/ZIKV the best model was significantly better than the worst model (see
213 Supplementary Code for full results). The lower out-of-sample accuracy for CHIKV and ZIKV
214 likely reflects the much lower frequency of positive values and the lower total sample size of this
215 dataset. All results were similar for a set of models that separated GR_0 from population size, so
216 for simplicity we show the model predictors that combines GR_0 and population size here (see
217 Table S4 and Supplementary Code for results of other models). Further, from a biological
218 perspective, the combined model better describes what we know about disease systems: if either
219 the probability of $R_0(T)$ being greater than zero is small or population size is very small,
220 transmission is unlikely to occur. Together, these analyses suggest that $R_0(T)$ is an important
221 predictor of transmission occurrence, but that CHIKV and ZIKV need further data to better
222 explain the probability of transmission occurrence (Figs. 3A, S2).

223

224 **Fig. 3**. *Ae. aegypti* $R_0(T)$ and population size predict the probability and magnitude of
225 transmission of DENV, CHIKV, and ZIKV across the Americas. A, $log(p)*GR_0$ (the posterior
226 probability that $R_0(T) > 0$ times the log of population size) versus the probability of local
227 transmission in the data. B, $log(p*R_0(T))$ (log of $R_0(T)$ times the population size) versus the log
228 of incidence, given that it exceeds the threshold for local transmission. Tick-marks and points:
229 human transmission occurrence and incidence data, respectively, by country-week in the

230 Americas and Caribbean. Lines and shaded areas: mean and 95% CI from GLM fits for DENV
231 (blue) and CHIKV and ZIKV (red). For simplicity, we show the models that only include the
232 covariates $log(p)*GR_0$ or $log(p*R_0(T))$, respectively, and do not include the socioeconomic
233 covariates (models PA6 and IM4 in Table S4). For each case report data point, $log(p)*GR_0$ and
234 $log(p*R_0(T))$ were calculated at the mean temperature 10 weeks prior to the reporting week [39].

235

236 $R_0(T)$ was also an important predictor of incidence, given that autochthonous
237 transmission did occur. Within-sample, incidence was best predicted by the model that included
238 both $R_0(T)$ and the socioeconomic predictors (model IM5 in Table S4) based on BIC (relative
239 probability = 1). The models that included $R_0(T)$ out-performed those that did not based on
240 deviance explained (Table S4). In out-of-sample validation, the models that included $R_0(T)$
241 explained the magnitude of incidence based on mean absolute percentage error (85-86%
242 accuracy versus 83% accuracy for models that did not include $R_0(T)$; Table S4), but this
243 difference was not statistically significant. For illustration, we show the simpler model that only
244 contains the $R_0(T)$ predictor in the main text (Fig. 3B; model IM1 in Table S4). Notably, the
245 models that contained $R_0(T)$ predicted incidence well for all three viruses, despite the lower
246 incidence of CHIKV and ZIKV.

247 Although predicted $R_0(T)$ correlated with the observed occurrence and magnitude of
248 human incidence for all three viruses, these observed incidence metrics were higher for DENV
249 than for CHIKV and ZIKV. While the reason for this difference is unclear, the most likely
250 explanation is that DENV is much more established in the region, so it is more likely to be
251 detected, diagnosed, and reported. Because ZIKV and CHIKV are newly emerging, they may not
252 have fully saturated the region at this early stage.

253 The ability of the model to explain the probability and magnitude of transmission is
254 notable given the coarse scale of the human incidence versus mean temperature data (i.e.,
255 country-scale means), the lack of CHIKV- and ZIKV-specific trait thermal response data to
256 inform the model, the nonlinear relationship between transmission and incidence, and all the
257 well-documented factors other than temperature that influence transmission. Together, these
258 analyses show simple mechanistic models parameterized with laboratory data on mosquitoes and
259 dengue virus are consistent with observed temperature suitability for transmission. Moreover, the
260 similar responses of human incidence of ZIKV, CHIKV, and DENV to temperature suggest that
261 the thermal ecology of their shared mosquito vectors is a key determinant of outbreak location,
262 timing, and intensity.

263

264 *Mapping climate suitability for transmission*

265 The validated model can be used to predict where transmission is not excluded (posterior
266 probability that $R_0(T) > 0$, a conservative estimate of transmission risk). Considering the number
267 of months per year at which mean temperatures do not prevent transmission, large areas of
268 tropical and subtropical regions, including Puerto Rico and parts of Florida and Texas, are
269 currently suitable year-round or seasonally (Fig. 4). These regions are fundamentally at risk for
270 DENV, CHIKV, ZIKV, and other *Aedes* arbovirus transmission during a substantial part of the
271 year (Fig. 4). Indeed, DENV, CHIKV, and/or ZIKV local transmission has occurred in Texas,
272 Florida, Hawaii, and Puerto Rico (www.cdc.gov). On the other hand, many temperate regions
273 experience temperatures suitable for transmission three months or less per year (Fig. 4), and the
274 virus incubation periods in humans and mosquitoes restrict the transmission window even
275 further. Temperature thus limits the potential for the viruses to generate extensive epidemics in

temperate areas even where the vectors are present. Moreover, many temperate regions with seasonally suitable temperatures currently lack *Ae. aegypti* and *Ae. albopictus* mosquitoes, making vector transmission impossible (Fig. 4, black line). The posterior distribution of $R_0(T)$ also allows us to map months of risk with different degrees of uncertainty (e.g., 97.5%, 50%, and 2.5% posterior probability that that $R_0 > 0$), ranging from the most to least conservative (Fig. S4).

Fig. 4. Map of predicted temperature suitability for virus transmission by *Ae. albopictus* and *Ae. aegypti*. Color indicates the consecutive months in which temperature is permissive for transmission (predicted $R_0 > 0$) for *Aedes* spp. transmission based on the minimum likely range (> 97.5% posterior probability that $R_0 > 0$). Black lines indicate the CDC estimated range for the two *Aedes* spp. in the United States. Model suitability predictions combine temperature mean and 8°C daily variation and are informed by laboratory data (Figs. 1, S1) and validated against field data (Fig. 3).

Discussion

Temperature is an important driver of—and limitation on—vector transmission, so accurately describing the temperature range and optimum for transmission of DENV, CHIKV, and ZIKV is critical for predicting their geographic and seasonal patterns of spread [12,40]. We directly estimated the temperature – transmission relationship using mechanistic transmission models for each mosquito species (Fig. 2). These models are built using empirical estimates of the (unimodal) effects of temperature on mosquito and pathogen traits that drive transmission, including survival, development, reproduction, and biting rates (Figs. 1, S1). Because these trait

thermal responses are unimodal across the majority of ectotherm taxa and traits, and because the traits combine nonlinearly to drive transmission, the emergent relationship between temperature and transmission is difficult to infer directly from field data or from individual trait responses. Here, we present a model of temperature-dependent DENV, CHIKV, and ZIKV transmission that advances on previous models because it is mechanistic, fitted from experimental trait data, and validated against independent human case data at a broad geographic scale (Fig. 3).

Mechanistic understanding is valuable for extrapolating beyond the current spatial and temporal range of transmission (Fig. 4), as compared to environmental niche models, for example [5,41,42]. Of the six previous mechanistic temperature-dependent models of DENV, CHIKV, or ZIKV transmission by *Ae. aegypti* and *Ae. albopictus* that we were able to reproduce, three had similar thermal optima [7,43,44] while the other three had dramatically higher optima (3-6°C) [9,45] (Fig. S5). Two models predicted much greater suitability for transmission at low temperatures [45], four predicted greater suitability at high temperatures [7,9,45], and two were very similar to ours [43,44] (Fig. S5). Only one of these previous models was (like ours) statistically validated against independent data not used to estimate model parameters, and its predictions were very similar to those of our model [43]. Other mechanistic and environmental niche models could not be directly compared with ours [5,10,40–42], either because fully reproducible equations, parameters, and/or code were not provided or because their predicted marginal effects of temperature were not displayed. Visually, our maps are similar to maps based on a previous model of *Ae. aegypti* and *Ae. albopictus* persistence suitability indices [40]. Recent environmental niche models of Zika distribution have shown similar but more constrained predicted distributions of environmental suitability, in part because these models include not just

321 temperature suitability but also further environmental, socioeconomic, and demographic
322 constraints [5,41,42,46].

323 Even though the thermal response data are imperfect—for example, CHIKV and ZIKV
324 thermal response data are missing—and the human case data are reported at a coarse spatial
325 scale, the validation analyses suggest that $R_0(T)$ is an important predictor of both the probability
326 of transmission occurring and the magnitude of incidence for DENV, CHIKV, and ZIKV. This
327 has several key implications. First, temperature-dependent transmission is pervasive enough to
328 be detected at a coarse spatial scale. Second, dynamics of the mosquito predict transmission for a
329 suite of *Ae. aegypti*-transmitted viruses, without additional virus-specific information. Third,
330 climate and socio-economic factors combine to shape variation in incidence across countries.
331 Finally, these simple predictors explain a substantial proportion of the variance in both the
332 probability and intensity of transmission.

333 Predicting arbovirus transmission at a higher spatial resolution and precision will require
334 more detailed information on factors like the exposure and susceptibility of human populations,
335 environmental variation (e.g., oviposition habitat availability, seasonal and daily temperature
336 variation), and socioeconomic factors. However, as a first step our mechanistic model provides
337 valuable insight because it makes broad predictions about suitable environmental conditions for
338 transmission, it is mechanistic and grounded in experimental trait data, it is validated against
339 independent human case data, and its predictions are applicable across three different viruses.
340 Using these thermal response models as a scaffold, additional drivers could be incorporated to
341 obtain more precise and specific predictions about transmission dynamics, which could in turn be
342 used for public health and vector control applications. For this purpose, all code and data used in
343 the models are available as Supplementary Files.

The socio-ecological conditions that enabled CHIKV, ZIKV, and DENV to become the three most important emerging vector-borne diseases in the Americas make the emergence of additional *Aedes*-transmitted viruses likely (potentially including Mayaro, Rift Valley fever, yellow fever, Uganda S, or Ross River viruses). Efforts to extrapolate and to map temperature suitability (Fig. 4) will be critical for improving management of both ongoing and future emerging epidemics. Mechanistic models like the one presented here are useful for extrapolating the potential geographic range of transmission beyond the current envelope of environmental conditions in which transmission occurs (e.g., under climate change and for newly invading pathogens). Accurately estimating temperature-driven transmission risk in both highly suitable and marginal regions is critical for predicting and responding to future outbreaks of these and other *Aedes*-transmitted viruses.

Materials and Methods

Temperature-sensitive R_0 models

We constructed temperature-dependent models of transmission using a previously developed R_0 framework. We modeled transmission rate as the basic reproduction rate, R_0—the number of secondary infections that would originate from a single infected individual introduced to a fully susceptible population. In previous work on malaria, we adapted a commonly used expression for R_0 for vector transmission to include the temperature-sensitive traits that drive mosquito population density :

$$R_0(T) = \left(\frac{a(T)^2\, b(T)\, c(T)\, e^{-\mu(T)/PDR(T)}\, EFD(T)\, p_{EA}(T)\, MDR(T)}{N\, r\, \mu(T)^3}\right)^{1/2} \qquad (1)$$

Here, (T) indicates that the trait is a function of temperature, T; a is the per-mosquito biting rate, b is the proportion of infectious bites that infect susceptible humans, c is the proportion of bites

366 on infected humans that infect previously uninfected mosquitoes (i.e., $b*c$ = vector competence),
367 μ is the adult mosquito mortality rate (lifespan, $lf = 1/\mu$), PDR is the parasite development rate
368 (i.e., the inverse of the extrinsic incubation period, the time required between a mosquito biting
369 an infected host and becoming infectious), EFD is the number of eggs produced per female
370 mosquito per day, p_{EA} is the mosquito egg-to-adult survival probability, MDR is the mosquito
371 immature development rate (i.e., the inverse of the egg-to-adult development time), N is the
372 density of humans, and r is the human recovery rate. For each temperature-sensitive trait in each
373 mosquito species, we fit either symmetric (Quadratic, $-c(T - T_0)(T - T_m)$) or asymmetric (Brière,
374 $cT(T - T_0)(T_m - T)^{1/2}$) unimodal thermal response models to the available empirical data [47]. In
375 both functions, T_0 and T_m are respectively the minimum and maximum temperature for
376 transmission, and c is a positive rate constant.

377 We consider a normalized version of the R_0 equation such that it is rescaled to range from
378 zero to one with the value of one occurring at the unimodal peak. Although absolute values of R_0
379 that are used to determine when transmission is stable depend on additional factors not captured
380 in our model, the minimum and maximum temperatures for which $R_0 > 0$ map exactly onto our
381 normalized equations, allowing us to accurately calculate whether or not transmission should be
382 possible at all. Empirical estimates of absolute values of R_0 are difficult to obtain in any case, but
383 it is much easier to determine whether transmission is occurring and for how long. While
384 different model formulations for predicting R_0 versus temperature can produce results with
385 different magnitudes and potentially different overall shapes [48], the temperatures for which R_0
386 is above or below zero (or one) are mostly model independent. For instance, two competing
387 models differ only by whether or not the formula in equation (1) is squared, but the square of a
388 number (e.g., an absolute R_0 value) greater than one is always greater than one, and the square of

389 a number less than one is always less than one. Therefore, the threshold temperatures at which
390 absolute $R_0 > 0$ or absolute $R_0 > 1$ will be exactly the same for either choice of formula (Fig. S6).
391 Similarly, because different expressions for R_0, including the square of equation (1), map
392 monotonically onto our function, they will produce identical estimates for the temperatures at
393 which transmission declines to zero and peaks (Fig. S6). Consequently, our use of relative R_0
394 adequately describes the nonlinear relationship between mosquito and virus traits and
395 transmission.

396 We fit the trait thermal responses in equation (1) based on an exhaustive search of
397 published laboratory studies that fulfilled the criterion of measuring a trait at three or more
398 constant temperatures, ideally capturing both the rise and the fall of each unimodal curve (Tables
399 S1-S2). Constant-temperature laboratory conditions are required to isolate the direct effect of
400 temperature from confounding factors in the field and to provide a baseline for estimating the
401 effects of temperature variation through rate summation [49]. We attempted to obtain raw data
402 from each study, but if they were not available we collected data by hand from tables or digitized
403 data from figures using WebPlotDigitizer [50]. We obtained raw data from Delatte [19] and Alto
404 [21] for the *Ae. albopictus* egg-to-adult survival probability (*pEA*), mosquito development rate
405 (MDR), gonotrophic cycle duration (GCD, which we assumed was equal to the inverse of the
406 biting rate) and total fecundity (TFD) (Table S2). Data did not meet the inclusion criterion for
407 CHIKV or ZIKV vector competence (*b, c*) or extrinsic incubation period (*EIP*) in either *Ae.*
408 *albopictus* or *Ae. aegypti*. Instead, we used DENV EIP and vector competence data, combined
409 with sensitivity analyses.

410 Following Johnson *et al.* [51], we fit a thermal response for each trait using Bayesian
411 models. We first fit Bayesian models for each trait thermal response using uninformative priors

412 (T_0 ~ Uniform (0, 24), T_m ~ Uniform (25, 45), c ~ Gamma (1, 10) for Brière and c ~ Gamma (1,
413 1) for Quadratic fits) chosen to restrict each parameter to its biologically realistic range (i.e., T_0 <
414 T_m and we assumed that temperatures below 0°C and above 45°C were lethal). Any negative
415 values for all thermal response functions were truncated at zero, and thermal responses for
416 probabilities (p_{EA}, b, and c) were also truncated at one. We modeled the observed data as arising
417 from a normal distribution with the mean predicted by the thermal response function calculated
418 at the observed temperature, and the precision τ, ($\tau = 1/\sigma$), distributed as τ ~ Gamma (0.0001,
419 00001). We fit the models using Markov Chain Monte Carlo (MCMC) sampling in JAGS, using
420 the R [52] package *rjags* [53]. For each thermal response, we ran five MCMC chains with a
421 5000-step burn-in and saved the subsequent 5000 steps. We thinned the posterior samples by
422 saving every fifth sample and used the samples to calculate R_0 from 15-40°C, producing a
423 posterior distribution of R_0 versus temperature. We summarized the relationship between
424 temperature and each trait or overall R_0 by calculating the mean and 95% highest posterior
425 density interval (HPD interval; a type of credible interval that includes the smallest continuous
426 range containing 95% of the probability, as implemented in the *coda* package [54]) for each
427 curve across temperatures.

428 We fit a second set of models for each mosquito species that used informative priors to
429 reduce uncertainty in R_0 versus temperature and in the trait thermal responses. In these models,
430 we used Gamma-distributed priors for each parameter T_0, T_m, c, and τ fit from an additional
431 'prior' dataset of *Aedes* spp. trait data that did not meet the inclusion criteria for the primary
432 dataset (Table S3). We found that these initial informative priors could have an overly strong
433 influence on the posteriors, in some cases drawing the posterior distributions well away from the
434 primary dataset, which was better controlled and met the inclusion criteria. We accounted for our

435 lower confidence in this data set by increasing the variance in the informative priors, by
436 multiplying all hyperparameters (i.e., the parameters of the Gamma distributions of priors for T_0,
437 T_m, and c) by a constant k to produce a distribution with the same mean but $1/k$ times larger
438 variance. We chose the value of k based on our relative confidence in the prior versus main data.
439 Thus we chose $k = 0.5$ for *b, c,* and *PDR* and $k = 0.01$ for *lf*. This is the main model presented in
440 the text (Fig. 2). It is comparable to some but not all previous mechanistic models for *Ae. aegypti*
441 and *Ae. albopictus* transmission (Fig. S5). Results of our main model, fit with informative priors,
442 did not vary substantially from the model fit with uninformative priors (Figs. S7-S8).

443 Incorporating daily temperature variation in transmission models

444 Because organisms do not typically experience constant temperature environments in
445 nature, we incorporated the effects of temperature variation on transmission by calculating a
446 daily average R_0 assuming a daily temperature range of 8°C, across a range of mean
447 temperatures. This range is consistent with daily temperature variation in tropical and subtropical
448 environments but lower than in most temperate environments. At each mean temperature, we
449 used a Parton-Logan model to generate hourly temperatures and calculate each temperature-
450 sensitive trait on an hourly basis [55]. We assumed an irreversible high-temperature threshold
451 above which mosquitoes die and transmission is impossible [56,57]. We set this threshold based
452 on hourly temperatures exceeding the critical thermal maximum (T_m in Tables S1-S2) for egg-to-
453 adult survival or adult longevity by any amount for five hours or by 3°C for one hour. We
454 averaged each trait over 24 hours to obtain a daily average trait value, which we used to calculate
455 relative R_0 across a range of mean temperatures. We used this model in the validation against
456 human cases (Fig. 3) and the risk map (Fig. 4).

457 Model validation with DENV, CHIKV, and ZIKV incidence data

458 To validate the model, we used data on human cases of DENV, CHIKV, and ZIKV at the
459 country scale and mean temperature during the transmission window. Using statistical models
460 (as described below), we estimated the effects of predicted $R_0(T)$ on the probability of local
461 transmission and the magnitude of incidence, controlling for population size and several
462 socioeconomic factors. We downloaded and manually entered Pan American Health
463 Organization (PAHO) weekly case reports for DENV and CHIKV for all countries in the
464 Americas (North, Central, and South America and the Caribbean Islands) from week 1 of 2014
465 to week 8 of 2015 for CHIKV and from week 52 of 2013 to week 47 of 2015 for DENV
466 (www.paho.org). ZIKV weekly case reports for reporting districts (e.g., provinces) within
467 Colombia, Mexico, El Salvador, and the US Virgin Islands were available from the CDC
468 Epidemic Prediction Initiative (https://github.com/cdcepi/) from November 28, 2015 to April 2,
469 2016. We aggregated the ZIKV data into country-level weekly case reports to match the spatial
470 resolution of the DENV, CHIKV, and covariate data.

471

472 Temperature data collection

473 We matched the DENV, CHIKV, and ZIKV incidence data with temperature using daily
474 temperature data from METAR stations in each country, averaged at the country level by
475 epidemic week. A previous study found a six-week lagged relationship between temperature and
476 oviposition for *Aedes aegypti* in Ecuador [39]. Assuming that the subsequent transmission,
477 disease development, medical care-seeking, and case reporting in humans takes an additional
478 four weeks, we assumed *a priori* a ten-week lag between temperature and incidence (i.e., mean
479 temperature for the week that is ten weeks prior to each case report). METAR stations are
480 internationally standardized weather reporting stations that report hourly temperature and

481 precipitation measures. Outlier weather stations were excluded if they reported a daily maximum
482 temperature below 5°C or a daily minimum temperature above 40°C during the study period,
483 extremes that would certainly eliminate the potential for transmission in a local area. Because
484 case data are reported at the country level, we needed a collection of weather stations in each
485 country that accurately represent weather conditions in the areas where transmission occurs,
486 excluding extreme areas where transmission is unlikely. For the study period of October 1, 2013
487 through April 30, 2016, we downloaded daily temperature data for each station from Weather
488 Underground using the *weatherData* package in R [58]. We removed all data from Chile because
489 it spans so much latitude and the terrain is so diverse that its country-level mean is unlikely to be
490 very representative of the temperature where an outbreak occurred.

491 Socioeconomic covariate data

492 We accessed available data on projected 2016 gross domestic product (GDP) for
493 countries of interest via the International Monetary Fund's World Economic Outlook Database
494 (http://www.imf.org/external/ns/cs.aspx?id=28). The direct and total contributions of tourism to
495 GDP in 2016 were compiled from World Travel and Tourism Council economic impact reports
496 (http://www.wttc.org/research/economic-research/economic-impact-analysis/country-
497 reports/#undefined). We retrieved population size data for 2013-2015 from the United Nations
498 Population Division (https://esa.un.org/unpd/wpp/Download/Standard/Population/) and averaged
499 them across the three years for each country. Throughout the analyses below, unless otherwise
500 specified, we used the natural log of the population size and of GDP as our predictors. We have
501 two reasons for this choice. The first is that, intuitively, the relative order of magnitude of the
502 population/GDP is more important in determining observed outbreak sizes or probabilities than
503 their absolute sizes. Second, population sizes and GDPs across countries tend to exhibit clumped

504 patterns with a few outliers that are much larger than the others. From a statistical perspective,
505 using the un-transformed populations (or GDPs) results in those few large/rich countries having
506 very high leverage in the analysis, and thus potentially skewing the results. Taking a log of the
507 population better balances these predictors and is the standard accepted approach when using
508 these kinds of predictors in regression models.

509 Validation analyses with human incidence versus temperature datasets

510 To validate the $R_0(T)$ model while controlling for population and socio-economic factors,
511 we used generalized linear regression on the weekly case count data. Importantly, we focused on
512 testing whether the case counts were consistent with the transmission – temperature relationship
513 predicted from our model, rather than on maximizing the variation explained in the statistical
514 model. We are more specifically interested in understanding autochthonous transmission (i.e.,
515 locally acquired, not just imported cases). We set country-level thresholds for the number of
516 cases defining autochthonous transmission for our three diseases separately, based on current
517 transmission understanding: seven cases of CHIKV, 70 cases of DENV, and three cases of
518 ZIKV. We derived these thresholds in the following way. First, we looked for data on outbreaks
519 of travel related cases in countries that are not expected to experience any local transmission. For
520 instance, in 2014 Canada experienced 320 confirmed, travel-related cases of chikungunya
521 (http://www.phac-aspc.gc.ca/publicat/ccdr-rmtc/15vol41/dr-rm41-01/rapid-eng.php), equivalent
522 to an average of more than six cases per week. Thus, to be conservative in our estimates, we set
523 the threshold of transmission as seven cases/week for CHIKV. The reported weekly cases of
524 DENV transmission in our study sample are considerably higher than for CHIKV (mean DENV
525 incidence was nearly 100 times higher mean CHIKV incidence). We chose a moderately high
526 threshold of 70 cases in a week (i.e., 10 times higher than the CHIKV threshold based on

527 Canadian cases) to reflect higher overall incidence and increased potential for travel related
528 cases. We examined the sensitivity of the results to choice of threshold by varying it from 25 to
529 100, and we found qualitatively similar results for all thresholds that we tested. As ZIKV is not
530 as well established as either CHIKV or DENV at this time, smaller numbers of cases may
531 indicate autochthonous transmission. Consequently, we chose a threshold of three cases for
532 ZIKV (approximately half the CHIKV threshold). Further, the results were fairly sensitive to the
533 ZIKV threshold as many locations have small numbers of cases. Since higher thresholds exclude
534 a very large proportion of available case data making analysis impossible, we used the slightly
535 less conservative threshold of three cases for autochthonous transmission of ZIKV. The resulting
536 data consisted of zeros for no transmission and positive case counts when transmission is
537 presumed to be occurring. To model these data, we used a hurdle model that first uses logistic
538 regression on the presence/absence of local transmission data to understand the factors correlated
539 with local transmission occurring or not (PA analysis). Then we modeled the log of incidence
540 (number of new cases per reporting week) for positive values with a gamma generalized linear
541 models (GLM; i.e., incidence analysis).

542 We were interested in understanding whether $R_0(T)$ was an important predictor of human
543 transmission occurrence and incidence, after controlling for potentially confounding factors like
544 population size and socioeconomic conditions. To do this, we fit a series of models with different
545 subsets of predictors that included $R_0(T)$, the socioeconomic variables with population, or both
546 (see Table S4 for full models). To control for human population size, we created new metrics
547 based on $R_0(T)$ and population size to use for validation against the PAHO incidence data. We
548 define GR_0, which is the posterior probability that $R_0(T) > 0$. We use $log(p)*GR_0$, where p is the
549 population size, as the relevant R_0-based predictor for the PA analysis. For the incidence

550 analysis, we instead use $log(p*R_0(T))$ as the predictor. In all cases log refers to the natural
551 logarithm. For simplicity, we refer to these as the $R_0(T)$ metrics hereafter and in the Results.

552 In both the PA and incidence analyses, we first used the full data sets to examine which
553 of the candidate models best described the data. Randomized quantile residuals indicated that the
554 logistic and gamma GLM models were performing adequately. We compared the approximate
555 model probabilities, calculated from the BIC scores, as well as the proportion of deviance
556 explained (D^2) from each model. Next we examined the performance of the models in predicting
557 out of sample, for both PA and incidence analyses. To do this we created 1000 random
558 partitions, where 90% of the data were used to train the model and 10% were used for testing. In
559 the PA analyses we classified each partition based on presence/absence, with separate
560 classification thresholds for DENV versus CHIKV/ZIKV as these grouping had much different
561 probabilities of occurrence. We assessed the performance of the model for the PA analysis based
562 on the mean misclassification rate. In the incidence analyses we assessed the model performance
563 based on the predictive mean absolute percentage error (MAPE). Since differences in prediction
564 success between the models in both the PA and incidence analyses were not statistically
565 significant, we present the simpler models that only include the $R_0(T)$ metrics in the main text
566 (Fig. 3) and the models that additionally include socioeconomic covariates in the Supplementary
567 Information (Figs. S2-S3). We plotted the model predictions as a function of the $R_0(T)$ metrics
568 together with the observed data for the PA and incidence analyses using the R package *visreg*
569 [59].

570 The residuals of the incidence model exhibit "inverse trumpeting," in which residual
571 variation is larger at low than high predicted incidence (Fig. S9). This occurs in part because we
572 forced the model to go through the origin, i.e., no transmission when $R_0(T)$ or the population size

573 is equal to zero. However, the data did sometimes show transmission where we did not expect it,
574 potentially because of imported cases, errors in reporting, or small pockets of transmission
575 suitability in countries or times that are otherwise unsuitable on average. More local-scale case
576 reporting that separates autochthonous from travel-associated cases would be needed to tease
577 apart the source of this error.

578

579 Mapping temperature suitability for transmission

580 Using our validated model, we were interested in where the temperature was suitable for
581 *Ae. aegypti* and/or *Ae. albopictus* transmission for some or all of the year to predict the potential
582 geographic range of outbreaks in the Americas. We visualized the minimum, median, and
583 maximum extent of transmission based on probability of occurrence thresholds from the R_0
584 models for both mosquitoes. We calculated the number of consecutive months in which the
585 posterior probability of $R_0 > 0$ exceeds a threshold of 0.025, 0.5, or 0.975 for both mosquito
586 species, representing the maximum, median, and minimum likely ranges, respectively. The
587 minimum range is shown in Fig. 4 and all three ranges are overlaid in Fig. S4. This analysis
588 indicates the predicted seasonality of temperature suitability for transmission geographically, but
589 does not indicate its magnitude. To generate the maps, we cropped monthly mean temperature
590 rasters from 1950-2000 for all twelve months (Worldclim; www.worldclim.org/) to the Americas
591 (*R*, *raster* package, *crop* function) and assigned cells values of one or zero depending on whether
592 the probability that $R_0 > 0$ exceeded the threshold at the temperatures in those cells. We then
593 synthesized the monthly grids into a single raster that reflected the maximum number of
594 consecutive months where cell values equaled one. The resulting rasters were plotted in ArcGIS
595 10.3, overlaying the three cutoffs (Fig. S4). We repeated this process for both mosquito species.

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Supporting Information Legends

S1 Appendix. Supplementary Results, References, Figures S1-S15, and Tables S1-S3.

S2 Appendix. Table S4. Model validation results.

S3 Appendix. Online code, data, and analyses. Available as a ZIP file on Figshare: https://figshare.com/s/b79bc7537201e7b5603f, DOI: https://dx.doi.org/10.6084/m9.figshare.4563928.

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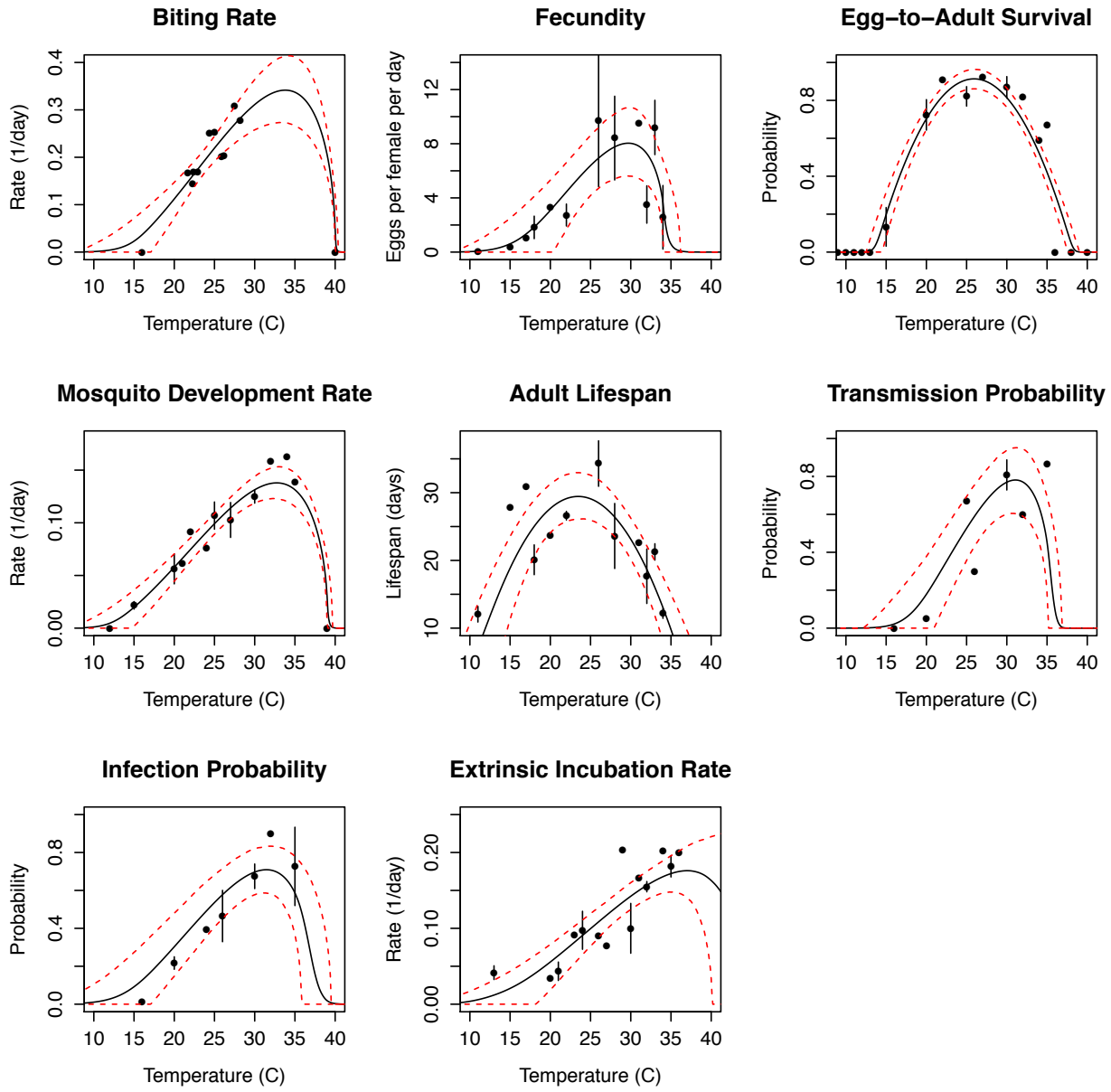
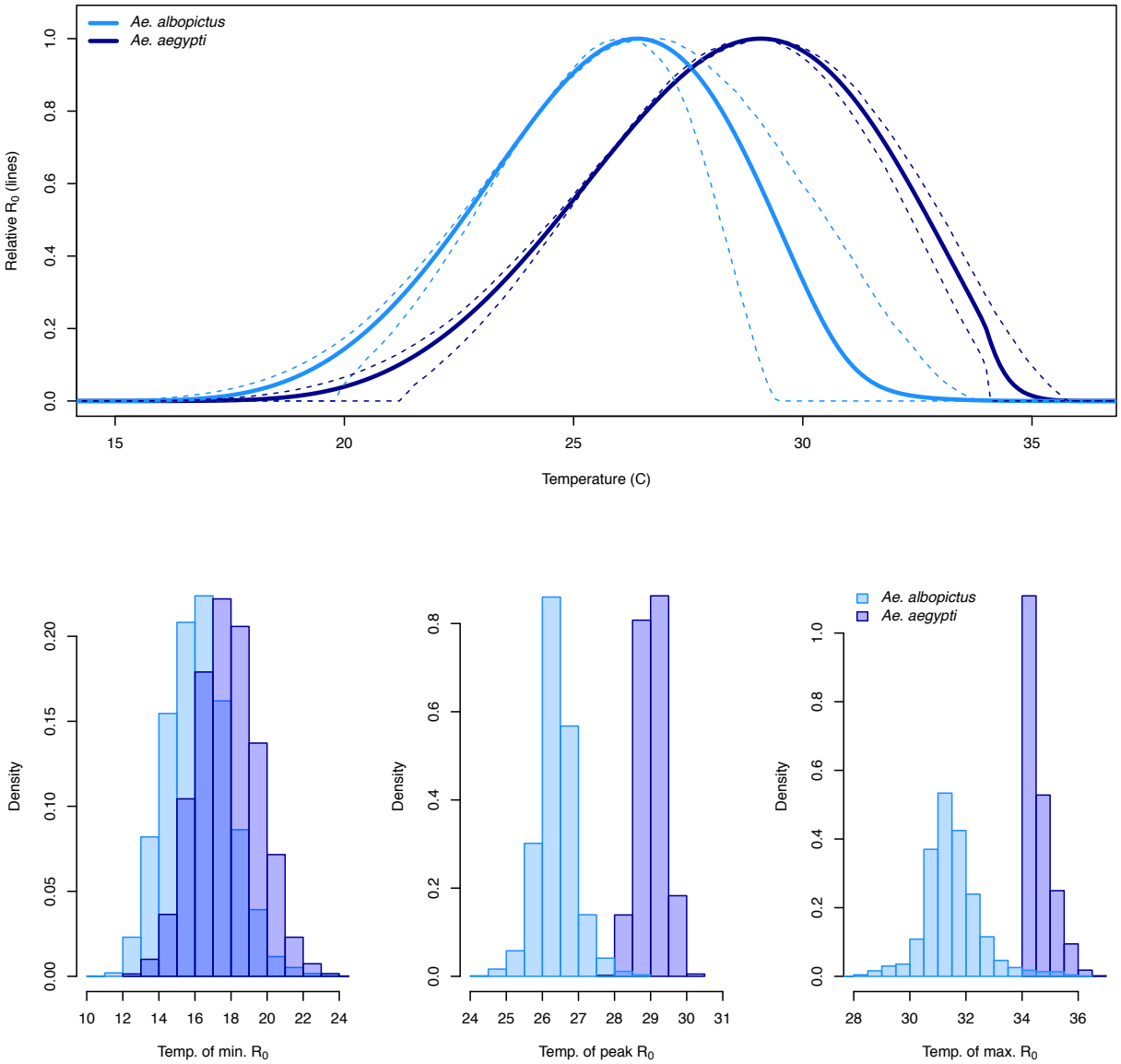
Figure 1


Biting Rate
Rate (1/day)
Temperature (C)
Fecundity
Eggs per female per day
Temperature (C)
Egg−to−Adult Survival
Probability
Temperature (C)
Mosquito Development Rate
Rate (1/day)
Temperature (C)
Adult Lifespan
Lifespan (days)
Temperature (C)
Transmission Probability
Probability
Temperature (C)
Infection Probability
Probability
Temperature (C)
Extrinsic Incubation Rate
Rate (1/day)
Temperature (C)

762 **Figure 2**



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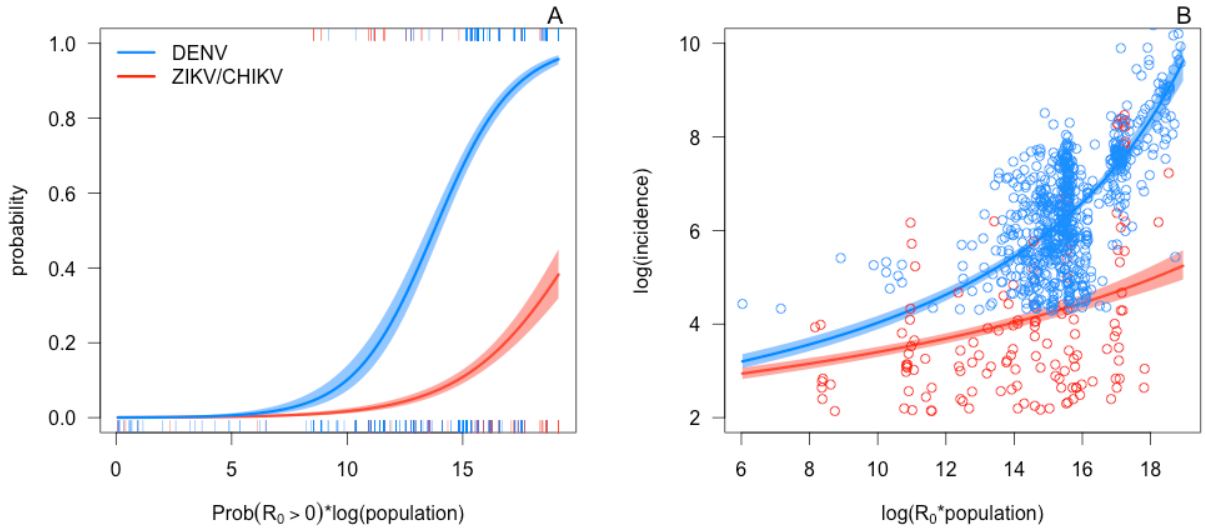
765 **Figure 3**



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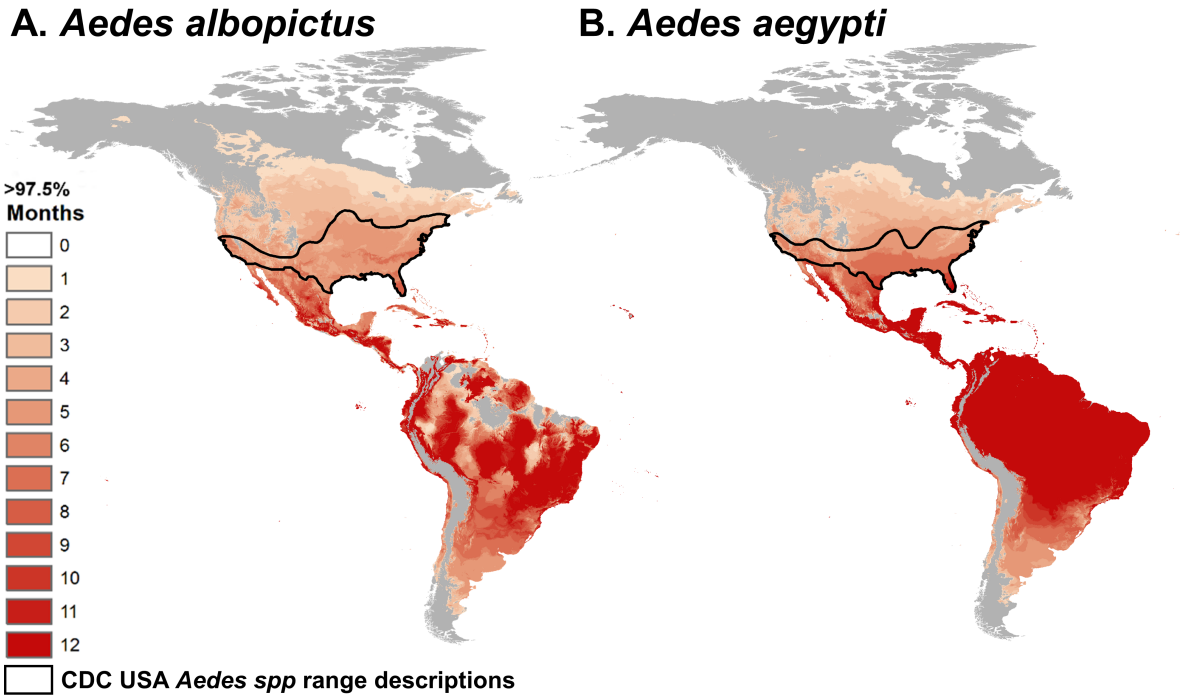
768 **Figure 4**



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