SUPPLEMENTARY MATERIALS

A system dynamic modelling and analytical framework for imported dengue outbreak surveillance in Spain

Javier Del-Águila-Mejía[1,2], Fernando Morilla[3] and Juan de Mata Donado-Campos[1,4,5,6]

1. Departamento de Medicina Preventiva y Salud Pública y Microbiología, Facultad de Medicina. Universidad Autónoma de Madrid. C. Arzobispo Morcillo, 4, 28029 Madrid, Spain.
2. Servicio de Medicina Preventiva, Hospital Universitario de Móstoles. C. Dr. Luis Montes, s/n, 28935 Móstoles, Madrid, Spain.
3. Departamento de Informática y Automática, Universidad Nacional de Educación a Distancia, Juan del Rosal 16, 28040 Madrid, Spain.
4. Consorcio de Investigación Biomédica en Red de Epidemiología y Salud Pública (CIBERESP). Instituto de Salud Carlos III. Calle Monforte de Lemos 3-5. 28029. Madrid, Spain.
5. Departamento de Medicina. Universidad Europea de Madrid. C/ Tajo, s/n. Urb. El Bosque 28670 Villaviciosa de Odón. Madrid, Spain.
6. Instituto de Investigación Sanitaria del Hospital Universitario La Paz (IdiPAZ), Universidad Autónoma de Madrid. C. Arzobispo Morcillo, 4, 28029, Madrid, Spain

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1. METHODS

1.1 Vector population model

Vector population dynamics are intimately linked with climatic and environmental conditions, especially with temperature. Mosquitoes vital cycle has two different phases. The first one is the aquatic – immature phase, were egg hatch and mosquitoes goes through the larvae and pupae stages before the second, aerial – adult, phase. Only female adult mosquitoes participate in the disease transmission cycle, but to fully capture climate and environmental impact on adult population, the immature phase also needs to be taken into account (1).

One of the most complete models investigating vector life cycle dependency on climate is the work of Tran et al. (2), based itself on the work of Caily et al. (3). They build an ecologically complex model of vector population based on field investigations in Nice, France, considering factors such as climate conditions and parameters, environment carrying capacity and diapause periods. To capture all these aspects along the vector full life cycle, the model consists of 10 states: 3 aquatic immature states and 7 female adult ones.

The work of Tran et al. with *A. Albopictus* is of great relevance for it is among the few characterizing vector population dynamics in temperate European Mediterranean climate. Since parametrization and temperature-dependant functions are based on field work, they resemble climatic and environmental conditions that are expected to be found in the Mediterranean coast of Spain. The downside of such a complete model is the inherent complexity and risk of sensitivity to a multiplicity of parameters, which makes it difficult to include underlying uncertainty into consideration. This was also noted by others who simplified the model beginning from the same assumptions, like (4).

For the sake of simplicity, we chose to adapt Li's model (5). His approach merges all aquatic and adult stages in only two called, respectively, larvae and female adult with population dynamics which are explained by the ordinary differential equations (ODE) system:

$$\frac{dJ_v}{dt} = z * b_v S_v - \frac{\alpha J_v}{1 + J_v} - (d_0 + d_1 J_v) J_v$$

$$\frac{dS_v}{dt} = \frac{\alpha J_v}{1 + J_v} - \mu_v S_v \qquad \textit{[Eq. 1]}$$

Where J_v denotes immature aquatic mosquitoes and S_v, the female adult population. The birth rate is the oviposition rate of adult population denoted by b_v, and z represents the diapause

period, the period of the year in which mosquitoes egg hibernate during winter (z = 0) to hatch again in spring when temperatures rise (z = 1). α is the maturation rate of larvae turning adult as a function of total population considering intraspecific competition or ecological carrying capacity. Mortality is differentiated between larvae and adults, with the latter represented by μ_v and larvae subdivided in two terms, namely d_0 and d_1, the density independent and dependant coefficient, respectively.

Li's work also had in consideration the temperature dependency of some of these parameters. Larvae's birth rate $b_v(T)$ and constant mortality term $d_0(T)$, and adult mortality rate $\mu_v(T)$ are of interest. Li doesn't provide any parametrization and therefore we include it by referring to other author's proposals. $b_v(T)$ and $d_0(T)$, along with its parameters, are taken as expressed in the model of Tran et al. (2) by the following equations:

$$b_v(T) = \begin{cases} \dfrac{T(t) - T_E}{TDD_E}, & T(t) > T_E \\ 0, & otherwise \end{cases} \qquad [Eq.\ 2]$$

$$d_0(T) = \exp(-T(t)/2) + \mu_L \qquad [Eq.\ 3]$$

Where $T(t)$ is the variation in temperature along time, T_E is the minimal temperature needed for egg development (10.4 ℃)(2) and TDD_E is the total number of degree-days -quantity of accumulated heat- necessary for egg development (110 ℃)(2). For $d_0(T)$, μ_L is the minimum larvae mortality rate, which we set in 0.15 day^{-1} as the sum of all minimum mortality rates of all aquatic stages egg, larvae and pupae (2). The equation for adult mortality rate $\mu_v(T)$ is justified below. Egg hatching, here represented by $z * b_v(T)$, stops when the photoperiod length falls below a threshold and eggs enters diapause to start again in spring, when day length is long enough again (6). Field data from the French region of Alpes-Maritimes investigated diapause initiation, finding that 50% of egg stopped hatching under a photoperiod inferior to 12h40min (6). For Spain, we calculated the length of the day as a function of latitude and day of the year following (7). The diapause period was thus set to happen every year between Sep 15th and March 23rd next year, and during this period z = 0 in Eq. 1 and therefore egg hatching halts even if temperate conditions are met. Table S1 depicts all parameters included in the vector, epidemiological and transmission models.

The model can generate annual cycles of female vector adult population. It is not intended to infer an actual population in a given area from its ecological properties like (2). Instead, the model captures the qualitative properties of a theoretical population like the seasonality,

variation with temperature, peaks and other non-lineal potential effects. The final size is not important, for it can be latter escalated, as long as the core properties remain reflected.

1.2 Epidemiological interaction model

The epidemiological model is the main element of the working framework. Given a vector population (from another model, field data, or other) and a human population (SIR, SEIR, SIS, or other compartmental metapopulation model), the model simulates the arrival of an infectious traveller and the potential outbreak it may trigger during a whole season, defined by the natural year before vector population disappears until next spring.

The human population is a classical susceptible-infected-recovered (SIR) metapopulation model, with the following assumptions: (i) closed population (no births/deaths); (ii) no dengue deaths; (iii) *Recovered* population are immune permanently. Infected people can come from two sources: either from a susceptible becoming infected once the disease is being transmitted, or from an international traveller importing the infection, which becomes the outbreak trigger. Imported cases are injected (arrive) to the *Infected* container allowing to programme multiple scenarios in size, time, periodicity, etc.

Thus, the human population model can be described by the following ODE system:

$$\frac{d\,S}{dt} = -Incident\ cases - \ Imported\ cases$$

$$\frac{d\,I}{dt} = Incident\ cases + Imported\ cases - Recovered\ cases \qquad [Eq.\ 4]$$

$$\frac{d\,R}{dt} = Recovered\ cases$$

Infected vectors (Vi) are drawn from the selected vector population (V). Total vector population (V) is divided in two states: infected vectors (Vi), and susceptible vectors ($V - Vi$). Since Infected vectors remain infected until they die, Vi population is defined by:

$$\frac{dVi}{dt} = \lambda_v * \frac{I}{S + I + R} * (V - Vi) - \mu_v * Vi \qquad [Eq.\ 5]$$

Where the mortality rate μ_v is the same used in Eq. 1 calculated from the survivability function of Eq. 8 described in section 1.3.1, and λ_v is the vectorial force of infection.

Similarly, the *Infected* human population (*I*) equation 4 can be expanded following Eq. 5 to get:

$$\frac{dI}{dt} = \lambda_h * \frac{S}{S+I+R} * Vi + Imported\ cases - \gamma * I \qquad [Eq.\ 6]$$

Where λ_h is the force on infection in humans and the constant parameter *Gamma* is the recovery rate at which infected humans recover from the disease, the inverse of the mean duration in days of disease (5 days) (8).

1.2.1 Force of infection in vector and human populations

Equations 5 and 6 sustain the epidemiological model of disease. Under normal conditions, mosquitoes depend of host (either human or animal) to feed and sustain their life cycle and that would imply interaction between the two. However, since vector population model is independent, we will be focusing on the interaction that would sustain the transmission of Dengue disease only.

In the presence of either Infected humans (*I*) or infected vectors (*Vi*), the two populations interact with their susceptible counterpart: infected humans are bitten by susceptible vectors that have a chance to become infected, then transmitting the infection to susceptible humans after biting back. If the cycle is capable of self-sustaining, the transmission chain begins, and the evolution of infected humans and vector are captured by equations 5 and 6 with an interaction parameter, the force of infection *lambda* expressed by the rate at which mosquitoes bite (the inverse of the GCD, section 1.3.1) multiplied by the percentage of those bites that happen in humans (*anthropophilic index*, 88%) (9) and the probability of one bite transmitting/acquiring the infection (1.3.2):

$$\lambda_{v/h} = \frac{probability\ of\ transmission\ per\ bite_{v/h} * anthropophilic\ index}{Gonotrophic\ cycle\ duration} \qquad [Eq.\ 7]$$

Lambda is divided for the human and vector population depending of the $P_v(T)$ and $P_h(T)$ and their particularities described in section 1.3.2

1.3 Temperature dependant parameters models

1.3.1 Survivability and Gonotrophic cycle duration

Delatte et al. (10) performed laboratory experiments on temperature and *A. Albopictus* developmental parameters, including survivability and gonotrophic cycle duration (GCD) in La Réunion island. Their work has been widely used in the modelling literature, and a recent study replicated it to study vector adaptability to temperate climate in Italy (11). Temperate *A. Albopictus* now finds its fittest survivability at 25ºC in northern Italy rather than at 15ºC in La Réunion, while the shortest GCD happen at the same temperature of 30ºC that subtropical ones. However, temperate mosquitoes in Italy at 25ºC have a shorter GCD compared with subtropical ones (11). Note that GCD is the days that female vector spends laying eggs after feeding, for later going back to feeding for starting a new cycle. Therefore, a shorter GCD means more bites during the vector's life span. That is why the vector biting rate is the inverse of the GCD i.e., the average biting frequency in days.

This climatic adaptation does not change the relationship between temperature and both parameters, as the function grows linearly with temperature until a tipping point in which further increase becomes prejudicial for the outcome. We can capture that property with a gaussian bell function that considers the maximum value of the biological function (i.e., maximum survivability or shortest GCD), the temperature at which it happens and an auxiliary dispersion parameter to better fit input data. With the following equation we define the value of our parameter (F) at any given temperature (T) as follows:

$$F(T) = ae^{\frac{-((T-b)^2)}{2*c^2}} \qquad [Eq.\ 8]$$

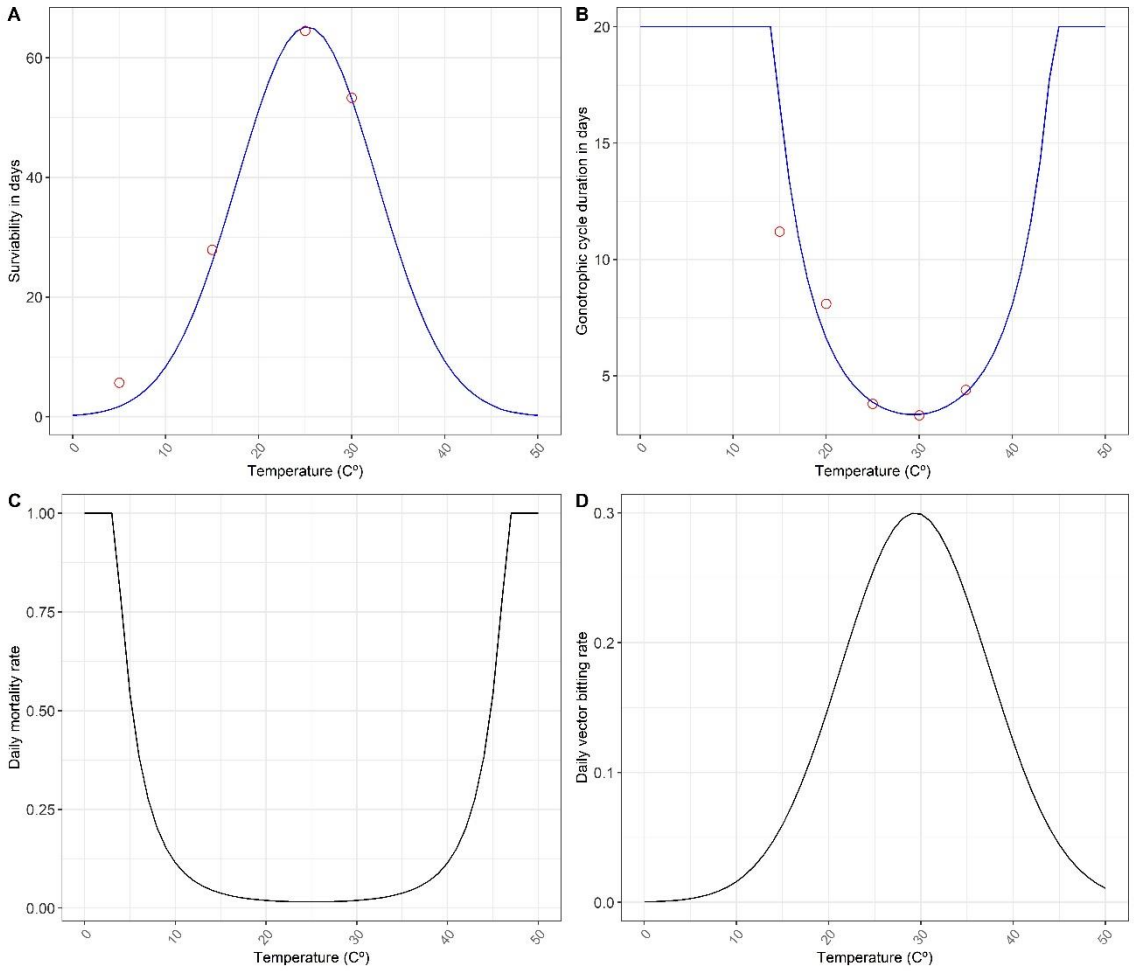
Where *a* is the optimal tipping value of the estimated parameter that happens at a temperature *b*, and *c* is a dispersion parameter which allows for curve fitting to data or assumptions.

For example, using data from Marini et al. (11), *a* is the longest longevity registered (65 days) that happens at a temperature *b* of 25ºC. Using MATLAB, we fitted the model to adjust the value of *c* in 7.5 to account for median longevity rates at 10, 15, 25 and 30ºC (Figure S1). Thus, a discrete experiment performed at constant temperatures can be converted on a continuous function that fulfil biological properties of survivability and gonotrophic cycle duration.

The same function can be adapted to GCD. We used data from Marini and Delatte to cover a wider range of input values since Marini only reports data for 25 and 30ºC. So GCD at 15, 20 and

35ºC are taken from Delatte's work, assuming the limitation of merging data from different experiment and vector strains.

Figure S1. Survivability and Gonotrophic cycle durations functions adjustment, and daily mortality and vector biting rate



(A) Survivability distribution function. (B) Gonotrophic cycle duration function. Red points represent the adjustment points from discrete experiments *performed by Marini et al.* (11). (C) Daily mortality rate derived from "A" with the upper limit set to 1. (D) Daily vector biting rate derived from "B".

1.3.2 Probability of dengue transmission

Every time an infected human gets bitten by a susceptible vector there is a chance that the infection will be passed and vice versa. This probability is also temperature-dependant and it has been well studied in *A. Aegypti* vector but not so well in *A. Albopictus* so most studies on the latter have the limitation of assuming the former's parameters values without confirmation (12). Probability of transmission have been modelled as a function of temperature in *A. Aegypti* by (13) with the following equations:

Probability of infection from humans to vector per bite (P_v):

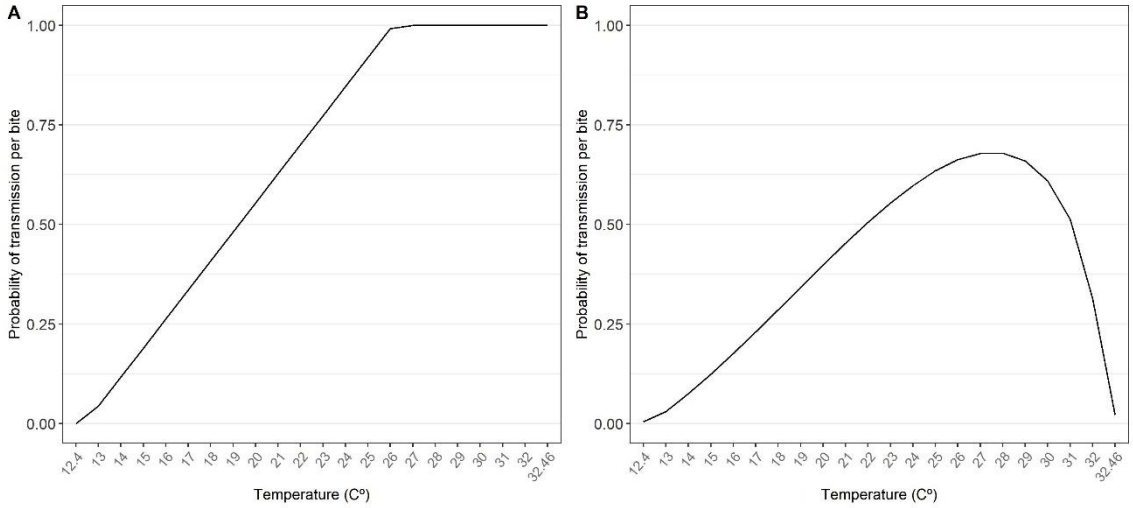
$$P_v(T) = \begin{cases} 0.0729T - 0.9037 & (12.4ºC \leq T \leq 26.1ºC) \\ 1 & (26.1ºC \leq T \leq 32.5ºC) \end{cases} \quad [Eq.\ 9]$$

Probability of transmission from vector to human per bite (P_h):

$$P_h(T) = 0.7 * [0.001044T(T - 12.286)\sqrt{32.461 - T}] \ (12.386ºC \leq T < 32.461ºC) \quad [Eq.\ 10]$$

Both equations show a linear increase of transmission probabilities from 12.4ºC. However, P_v becomes 1 above 26.1ºC while P_h decreases when T>28ºC and sharply reaches zero when T > 32.5ºC. That means that between 12.4ºC and 30ºC both probabilities grow linearly but above 32ºC no transmission in any way was recorded (Fig S2). These functions have been employed in *A. Albopictus* dengue modelling by with the particularity that P_h is considered to by only 70% that the value for *A. Aegypti* based on a literature review (12).

Figure S2. Probability of transmission per bite from human to vector (A) and from vector to human (B)



These functions are limited to the temperature range from 12.4 to 32.46 degrees Celsius

Table S1. Parameters employed in the models.

Parameter	Description	Value	Source
Vector population model			
b_v	Larvae birth rate (day^{-1})	Eq. 2	(2)
α	Emergence rate of larvae to adult	40	-
d_0	Larvae constant mortality rate (day^{-1})	Eq. 3	(2)
d_1	Larvae density-dependant mortality rate (day^{-1})	0.004	-
T_E	Minimal temperature needed for egg development (℃)	10.4	(2,10)
TDD_E	Number of degree-days needed for egg development (℃)	110	(2)
μ_L	Minimum larvae mortality rate (day^{-1})	0.15	(2)
μ_v	Adult mosquito mortality rate (day^{-1}) as a function of survivability	Eq. 8	-
Epidemiological interaction model			
Gamma	Recovery rate from disease	0.2	(8)
$antropophilic\ index$	Percentage of blood meals that female vectors take from human sources	0.88	(9)
Lambda	Force of infection	Eq. 7	
Gonotrophic cycle duration	Time in days that a female vector spends laying eggs after taking a blood meal. Once completed, it will seek a blood meal again. Its inverse becomes the average daily biting rate.	Eq. 8	-
Temperature dependant parameters			
a_s	Highest mean longevity recorded ($days$)	64.2	(11)
b_s	Temperature under which a_s happens (℃)	25.2	(11)
c_s	Dispersion parameter for adjustment of the bell function	7.5	calculated
a_{gc}	Lowest mean gonotrophic cycle duration recorded ($days$)	3.3	(11)
b_{gc}	Temperature under which a_{gc} happens (℃)	30	(11)
c_{gc}	Dispersion parameter for adjustment of the bell function	8	calculated
$P_v(T)$	Probability of infection from humans to vector per bite	Eq. 9	(13)
$P_h(T)$	Probability of infection from vectors to humans per bite	Eq. 10	(13)

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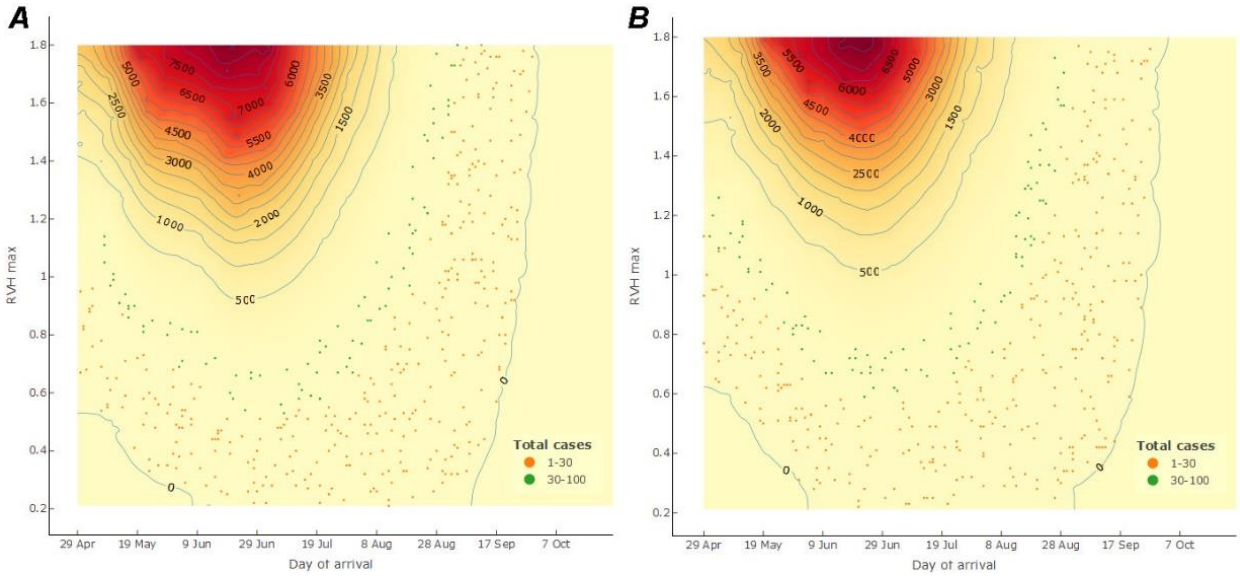
3. SUPPLEMENTARY RESULTS

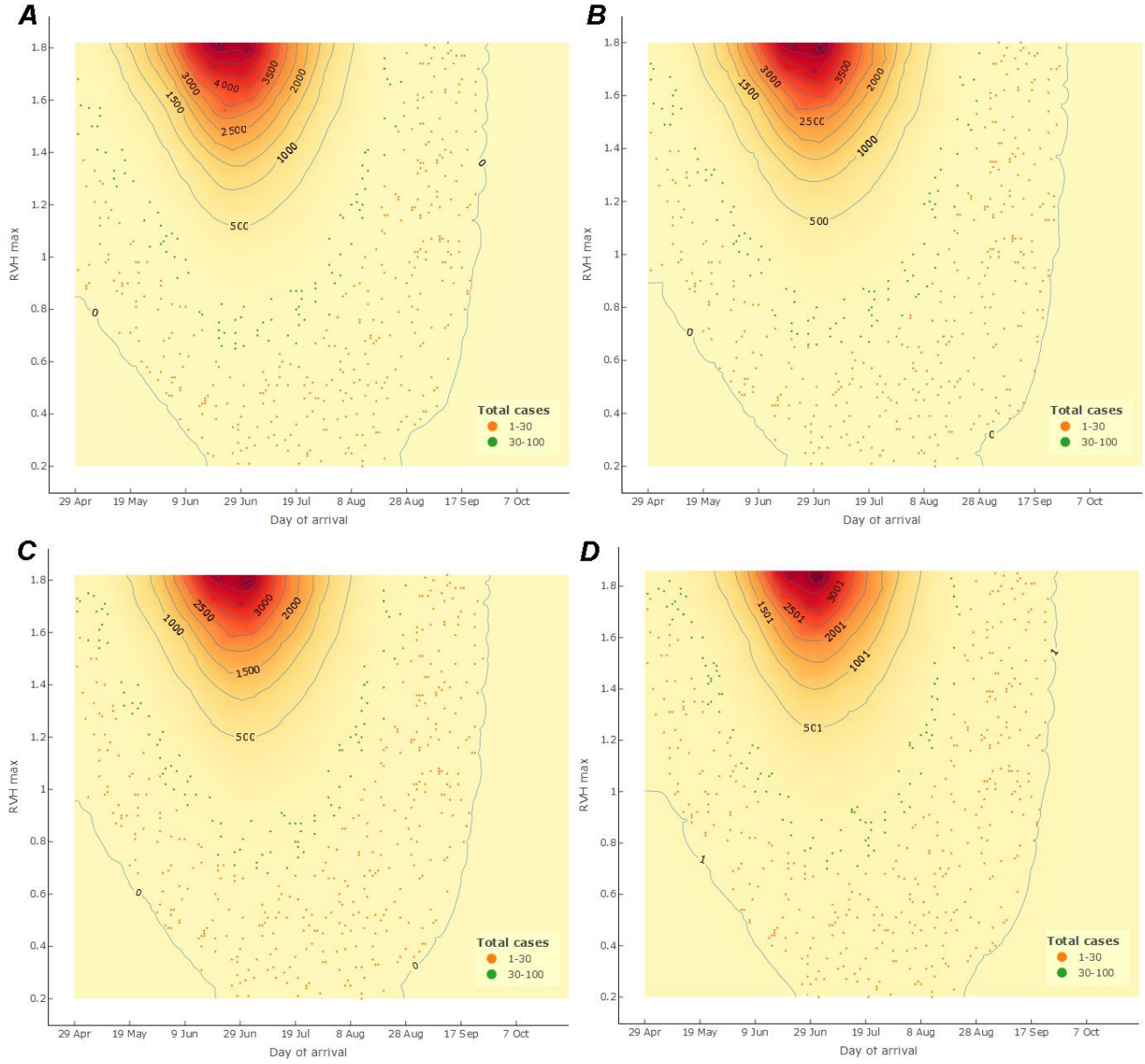
3.1 Level plots by province

Figure S3. Level plots of Dengue epidemic risk with varying VHRm and Day of arrival for Almería (A) and Málaga (B)



Each line (contour) defines a space containing all the results above the value of its label. Dots are represented for adding clarity when the distance between the first and second line is too wide. Due to algorithmic reasons, the first isoline corresponds to 0 rather than 1, without affecting the interpretation.

Figure S4. Level plots of Dengue epidemic risk with varying VHRm and Day of arrival for Castellón/Castelló (A), Alicante/Alacant (B), Murcia (C) and Valencia/València (D)



Each line (contour) defines a space containing all the results above the value of its label. Dots are represented for adding clarity when the distance between the first and second line is too wide. Due to algorithmic reasons, the first isoline corresponds to 0 rather than 1, without affecting the interpretation.

Figure S5. Level plots of Dengue epidemic risk with varying VHRm and Day of arrival for Sevilla (A), Badajoz (B), and Cádiz (C)

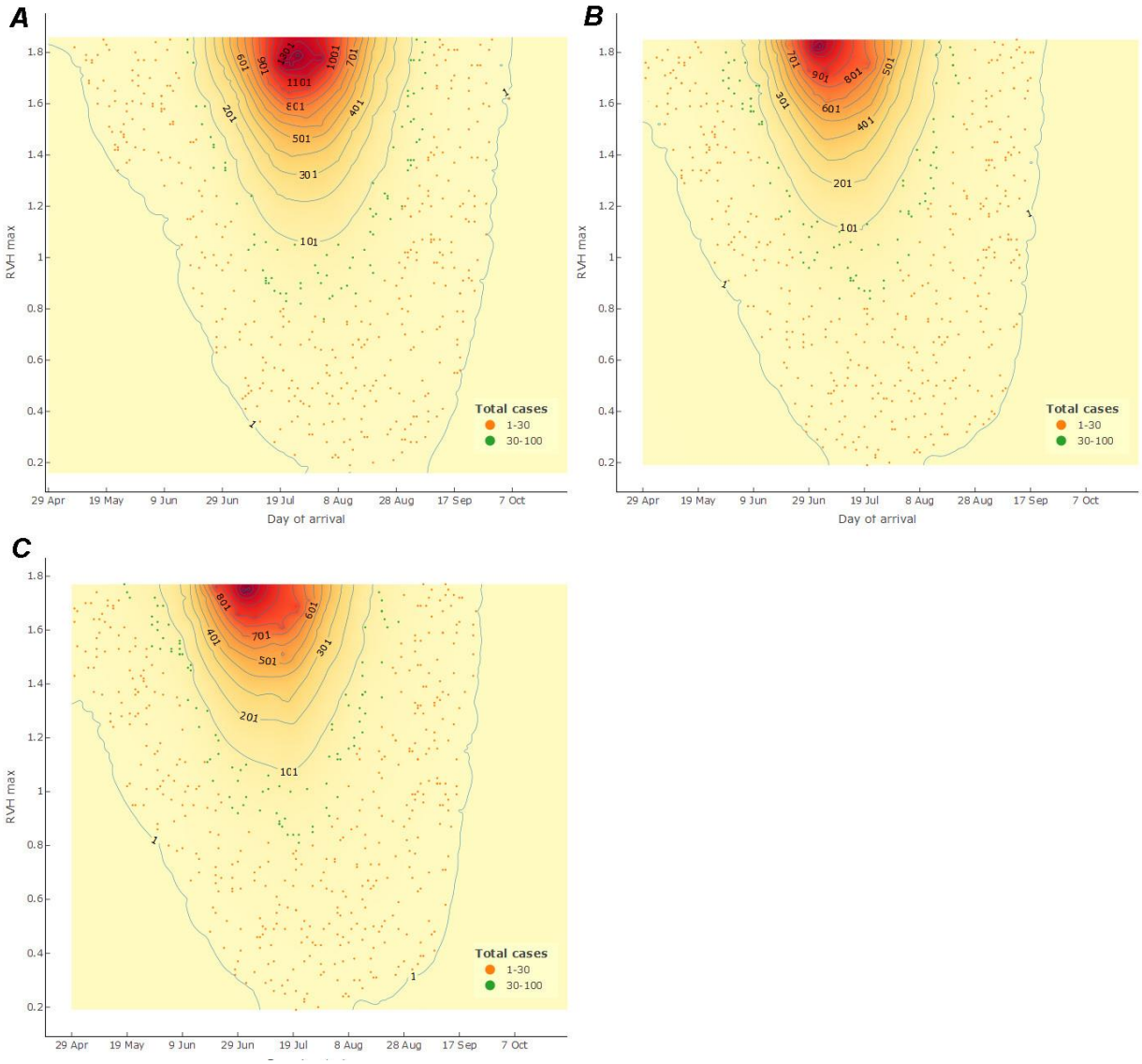


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Figure S6. Level plots of Dengue epidemic risk with varying VHRm and Day of arrival for Illes Balears (A) and Barcelona (B)

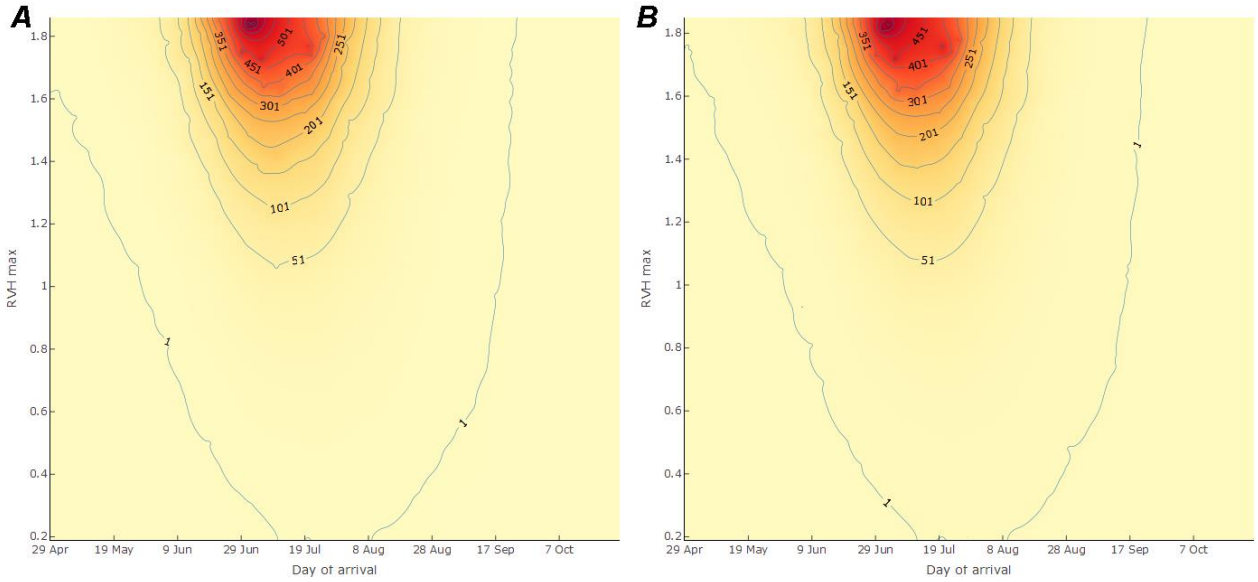

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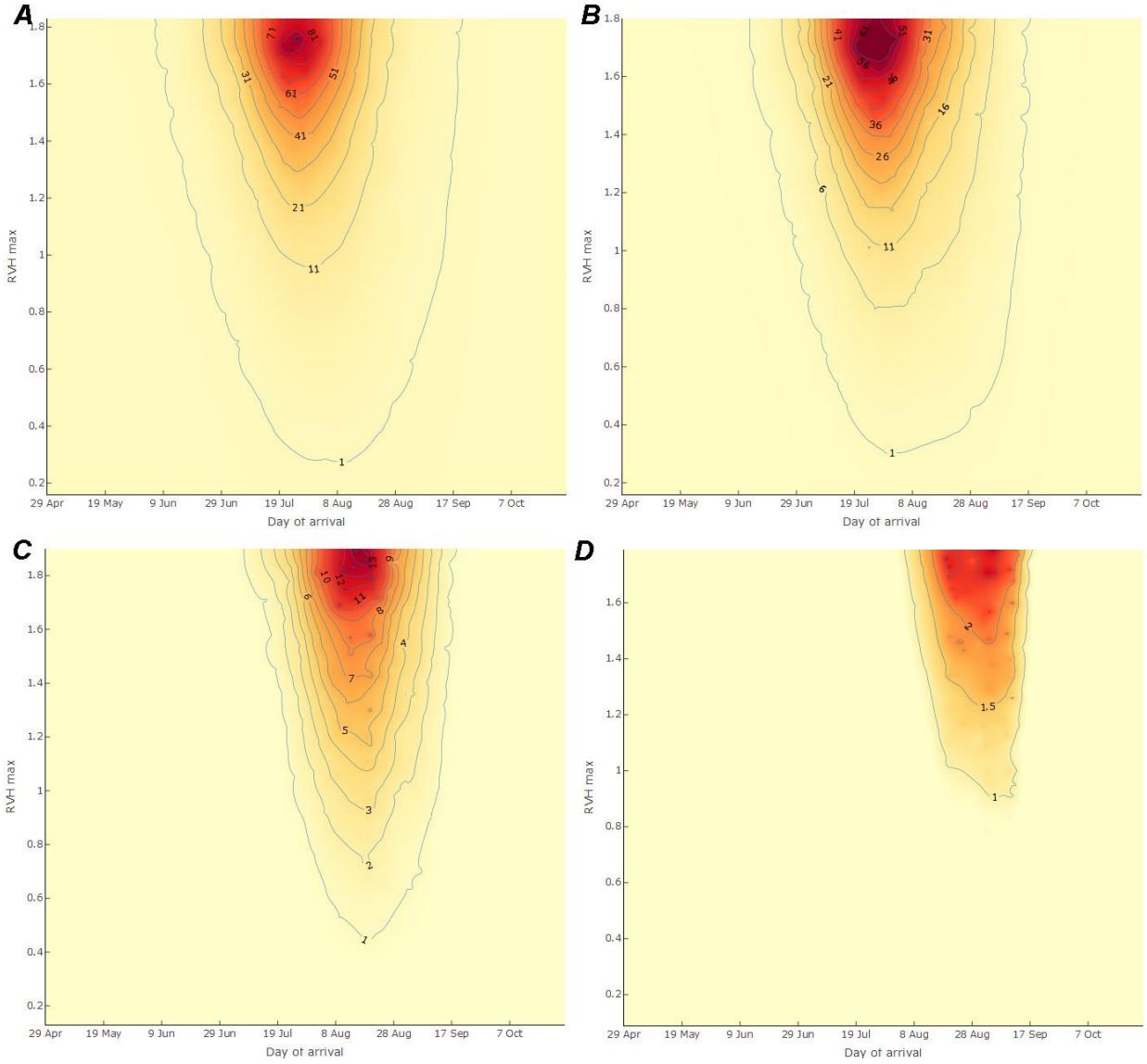
Figure S7. Level plots of Dengue epidemic risk with varying VHRm and Day of arrival for Tarragona (A), Cáceres (B), Granada (C) and Zaragoza (D)



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