Supplementary Material

Critical transitions in malaria transmission models are consistently generated by superinfection.

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1 The $SE_nCIR - LXV_nW$ model

The full model is represented by a system of ODE's [3]. Two coupled submodels describe malaria transmission within the human and mosquito populations, respectively [1]. As we show here, this formulation builds upon the classical model of Ross and MacDonald[13–15].

1.1 The human population model

This submodel subdivides the human population into different classes. Infected individuals are themselves subdivided into those who receive clinical treatment (C) and those who do not (I). Once individuals recover naturally from malaria, they enter a refractory period during which they are immune. They can not re-acquire the infection until they return to the susceptible class. This immune class does not contribute to transmission, unlike in the Chitnis *etal*'s model [5]. To implement superinfection, the infectious period depends on exposure to infectious bites by the mosquito (the intensity of transmission) following [4, 6].

The ODE system can be written as:

$$\frac{dS}{dt} = B - \beta\ S + \sigma R - \delta_H\, S + \rho\ C \tag{S1}$$

$$\frac{dE}{dt} = \beta\, S - \delta_H\, E - \gamma_H\, E \tag{S2}$$

$$\frac{dI}{dt} = (1-\chi)\,\gamma_H\, E - \eta\,\beta\ I + \nu\ C - r\ I - \delta_H\, I \tag{S3}$$

$$\frac{dR}{dt} = -\sigma R + r\ I - \delta_H\, R \tag{S4}$$

$$\frac{dC}{dt} = \chi\,\gamma_H\, E + \eta\,\beta\ I - \nu\ C - \rho\ C - \delta_H\, C \tag{S5}$$

In this formulation, the average time in the exposed class is given by $1/\gamma_H$ and is assumed to be exponentially distributed. A more general and realistic distribution for the duration of this

class has also been implemented [7, 12] (see section 3 and Appendix A1). The replenishment of susceptibles through immigration or births (B) and individual losses due to mortality (δ_H is a per capita human mortality rate[1]) are considered to balance each other so that the total population N is maintained at a constant size. Susceptible individuals become infected at a per capita rate, β, the "force of infection". In principle, $1/\beta$ can be estimated from the average age at which children first acquire malaria (assuming constant mosquito exposure). Only a fraction of infections, χ, is detected and receive clinical treatment (C). The complementary fraction $(1-\chi)$ represent infections that are not detected but are still infectious[2]. Individuals in the I class can still get re-infected and be detected upon reinfection but the per capita rate β of this process is decreased by a factor η. Finally, clearance rates for treated infected (C) and non-treated infected individuals (I) are given by ρ and r, respectively. See Table S1 for a full description of model parameters.

In endemic areas, longer recovery periods from infection correlate with higher levels of mosquito exposure (or transmission intensity) [6]. If the level of disease transmission is high, the recovery rate r tends to slow down. This rate can be described by a decreasing function of the rate at which humans receive infectious bites, Λ:

$$\Lambda = a\frac{W}{N} \tag{S6}$$

where W is the total number of infectious mosquitoes, N is total human population, and a is the number of bites per individual mosquito and unit time.

Although other decaying functions are possible, the form we use here was derived in [6] under the assumptions that infectious bites arrive at a constant (Poisson) rate, and that each infection lasts a constant period of time independent from any other concurrent infection. Under these assumptions, it can be shown that:

$$r(\Lambda) = \frac{\Lambda}{\exp(\Lambda/r_0) - 1} \tag{S7}$$

where $r(\Lambda)$ is the effective recovery rate at a given transmission intensity, Λ, and r_0 is a basal recovery rate when disease transmission is very low (e.g. in the absence of infectious mosquitoes).

In addition, the continuous exposure to the parasite can also boost immunity [10, 11], which translates also in slower rates of immunity loss. The same decaying function of transmission intensity was adopted for this dependence following [4]:

$$\sigma(\Lambda) = \frac{\Lambda}{\exp(\Lambda/\sigma_0) - 1} \tag{S8}$$

[1] When Eqs (S1)-(S5) are summed, a single equation for the evolution of human total population is found ($\frac{dN}{dt} = B - \delta_H N$). Throughout this work, we have considered that $B = \delta_H N$, which maintains human population constant. Then N can be regarded as another model parameter, which has been used to write the stationary solution (see Eqs. (S54)-(S59) in section 3 of this document).

[2] I individuals would tend to show milder symptoms that C, the reason why they would be less detectable. This assumption was a useful approximation to study the potential impact of increasing temperatures on highland malaria based on data from a Kenyan plantation with good access to treatment in a local hospital[1]. This is not the only possible interpretation of these two classes. More generally, as explained above, C and I correspond respectively to detected/treated and non-detected/non-treated, regardless of symptoms' severity

Model Parameter	Symbol	Min. Value	Max. Value	A	B
Human related parameters					
Rate of loss of immunity	σ_0	1e-06	0.1	0.00067	0.003
Recovery rate ($I \to R$)	r_0	1e-06	0.01	0.0063	0.009
Exposed number	n_H	1	50	1	5
Incubation rate	γ_H	0.048	0.14	0.05	0.05
External force of infection	β_e	0	0.0001	1e-05	1e-05
Detection probability	χ	0	0.5	0.2	0.2
Recovery rate ($C \to S$)	ρ	0	1	0.2	0.2
Case probability	η	0	1	0.01	0.01
Recovery rate ($C \to I$)	ν	0.2	1	0.1	0.2
Adult mosquito related parameters					
Biting rate	a	0.1	0.5	0.3	0.3
Per bite vector to host infectivity probability ($M \to H$)	b	0.01	1	0.5	0.8
Per bite host to vector infectivity probability ($H \to M$)	c	0	1	0.2	0.2
Death rate	δ_M	0.01	0.1	0.04	0.06
Larva related parameters					
No of larval recruits per oviposition event	N_L	0	1e+02	66	66
Carraying capacity	K_0	1e+02	1e+05	3e+04	4e+04
Development rate	d_L	0.01	0.2	0.067	0.067
Death rate	δ_L	0.01	0.5	0.5	0.5
Plasmodium related parameters					
Exposed number	n_P	1	50	1	10
Incubation rate	γ_P	0.05	0.1	0.05	0.083

Table S1: A and B are the two parameter combinations around which we have conducted the exploration of the parameter space. Minimum and maximum values define the subregion of the parameter space we have explored. In a previous study from an epidemic region [1], these ranges have provided a good fit to data. Two extra parameters do not appear in this table: the birth (death) rate of humans, δ_H, and the human population size, N. This is because, dynamically, the parameter space has only 19 dimensions. The extra rate δ_H can be used to define a dimensionless time which introduces dimensionless rates in all equations. In addition, human and mosquito populations can be all divided by total human population size, so that state variables become fractions of humans in each class and number of mosquitoes per human in each of mosquito classes. Throughout our paper, for the sake of clarity, state variables remain absolute numbers of humans and moquitoes, human mortality rate is $\delta_H = 5.4\,10^{-5}$, so time is expressed in days, and, accordingly, all rates are expressed in day^{-1}.

The system of ODEs given above is completed by specifying next the force of infection, β, which introduces nonlinearity.

1.2 The transmission rate or "force of infection"

The transmission rate, β, is the per capita rate at which susceptibles acquire the infection per unit time as a result of infectious bites. This rate depends upon three factors: (1) the immune response of humans, which reduces the probability of actually developing malaria after receiving an infectious bite by a factor b, (2) the number of infectious mosquitoes, W, per human host, and (3) the biting rate, a:

$$\beta = b \frac{W}{N} a \tag{S9}$$

1.3 External sources of infection

Individuals can also acquire malaria by temporarily visiting endemic surrounding areas. We include this "immigration" of external malaria into the system by considering an additive external force of infection. In this way, the total force of infection has two additive components: the local force of infection caused by a focal mosquito population, and the external force of infection due to migratory movements between the focal and the surrounding area:

$$\beta = b \frac{W}{N} a + \beta_e \tag{S10}$$

In general, β_e depends on the intensity of human movement, as well as on malaria specific conditions and dynamics in the endemic surrounding region. In this work, for the sake of simplicity, we assume β_e to be a constant parameter.

1.4 The mosquito population model

We consider four different stages of the mosquito life cycle: egg, larva, pupa, and adults. Mosquito larvae emerge from the eggs within 24 hours, the larval stage is aquatic and lasts 1 to 2 weeks, the pupal stage is shorter, about 1 to 4 days. These developmental times depend upon characteristics of the mosquito species and temperature. Adult stages usually last longer and their survival curves are usually approximated by decaying exponentials. From an ecological and epidemiological point of view, the larval and adult stages are the most important. Thus, mosquito population dynamics can be simplified by considering only these two stages in the mosquito life cycle. The two-stage model is then given by:

$$\frac{dL}{dt} = f M \left(\frac{K_0 - L}{K_0} \right) - \delta_L L - d_L L \tag{S11}$$

$$\frac{dM}{dt} = d_L L - \delta_M M \tag{S12}$$

A per capita rate of fecundity determines the number of individuals recruited into the larval state per adult female mosquito. Since blood meals are required by females to produce eggs, fecundity depends on the biting rate. Here we assume a linear dependency, $f = N_L a$. The rate of emergence of adult mosquitoes from the larvae is presented as a per capita rate, d_L. This development rate is strongly influenced by temperature. Density-independent per capita death rates act both on larvae and adult mosquitoes. A carrying capacity, K_0, controls larval growth in a simple logistic way. This quantity is strongly coupled to water availability, because water pools of different sizes are the obligate habitats where mosquito breeds and larvae develop. In general, rainfall limits mosquito population and their abundance usually correlates strongly with seasonal rainfall variability. Essentially, the carrying capacity for mosquito larvae, K_0, fluctuates seasonally with rainfall.

This submodel can readily be coupled to the one representing disease dynamics within the human population. Typically, the adult mosquito population is divided into three classes: susceptible non-infected mosquitoes (X), infected non-infectious (V) and infectious mosquitoes (W) [5]. If y is the fraction of the human population transmitting the parasite to the mosquito vector, we can write:

$$\frac{dX}{dt} = -c\,a\,y\,X - \delta_M\,X + d_L\,L \tag{S13}$$

$$\frac{dV}{dt} = +c\,a\,y\,X - F(t) - \delta_M\,V \tag{S14}$$

$$\frac{dW}{dt} = F(t) - \delta_M\,W \tag{S15}$$

where $F(t)$ is the rate at which infected mosquitoes (V) turn into infectious mosquitoes (W) considering that the *Plasmodium* parasite requires some time to mature and reach the infecting stage within the mosquito body. This time is called the sporogonic phase or the extrinsic incubation period. The distribution of these times can be modeled by introducing a gamma distribution [12] (see appendix A1).

The sum of the last three equations adds up to Eq. (S12). Since there is no empirical evidence on a detrimental effect of *Plasmodium* infection on adult female mosquitoes, we consider that total mosquito dynamics is not affected by malaria transmission.

The full model described by the human subsystem of Eqs (S1)-(S5) and the mosquito subsystem of Eqs (S11), (S13)-(S15) can be simplified into the original Ross and MacDonald (RM) formulation:

$$\frac{dw}{dt} = c\,a\,y\,(m - w) - \delta_M\,w \tag{S16}$$

$$\frac{dy}{dt} = b\,a\,w\,(1 - y) - \delta_H\,y\,, \tag{S17}$$

where w and y are the number of infectious mosquitoes and human individuals per total human population, respectively, and m is the total number of mosquitoes per human. The following simplifications are required:

1. Mosquito and human populations are constant.

2. No external force of infection is considered.

3. No effect of mosquito exposure on the recovery rates.

4. No immunity.

5. Detected cases and non-detected human infections are lumped together into a single infectious class.

6. *Plasmodium's* incubation times in humans and vectors are neglected. Mosquitoes and humans become instantaneously infectious following an infectious bite.

Under these assumptions, and in the absence of E, C, and R classes, it is easy to see that our human submodel should give rise to Eq (S17) when human population size is constant. Notice, for instance, that the force of infection, $b\,a\,w$, coincides with Eq (S9). In addition, we show the equivalence of our mosquito submodel to Eq. (S16) of the RM model in Appendix A1.

2 The basic reproduction ratio

The basic reproduction ratio, R_0, is a dimensionless quantity defined as the number of secondary infections an infected individual will produce on average during the duration of its infectious phase in a totally disease-free but susceptible environment. In the absence of an external source of infection ($\beta_e = 0$ in Eq (S10)), R_0 provides a classical invasibility criterion. For our full model ($\beta_e \neq 0$), the parameter space can be divided into two regions: an externally maintained disease equilibrium, which corresponds to the area where $R_0 < 1$ in the model with $\beta_e = 0$, and typically will show very low levels of disease incidence, and a locally-driven endemic equilibrium, involving higher levels of disease, which corresponds to the area where $R_0 > 1$ in the model with $\beta_e = 0$ (see Fig 3 and 4 in the Main Text).

For comparison purposes, we calculate R_0 for the full model by using two different methods, the classical approach and the method based on the next generation matrix [**?**]. In order to estimate R_0 of the full model, it is necessary to assume that $\eta \ll 1$. This realistic assumption provides an analytical expression of R_0. We then check the goodness of this approximation for non-null values of η.

The expression of R_0^2 can always be factored into:

$$R_0^2 = V_0\, R \tag{S18}$$

where V_0 is the vectorial capacity and R is a factor that only depends on human-related disease parameters. The full expression of R in terms of model parameters is given in Eq (S43). With the next-generation-matrix method, V_0 can be written as:

$$V_0 = \frac{M}{N} a^2\, b\, c\, \frac{1}{\delta_M} \left(\frac{n_V\, \gamma_P}{n_V\, \gamma_P + \delta_M} \right)^{n_V} \tag{S19}$$

where M is the total mosquito population size at equilibrium and is given by:

$$M = K_0 \frac{d_L}{\delta_M} \frac{f - \delta_M \left(1 + \frac{\delta_L}{d_L}\right)}{f} \tag{S20}$$

where N is a constant human population size. Since mosquito life-history parameters are very sensitive to the environment, the condition $\frac{f}{\delta_M} \geq 1 + \frac{\delta_L}{d_L}$ establishes when a mosquito population can be self-maintained in a given area, as explained in the Main Text.

Another illustrative factorization is the one that writes R_0 as the product of $R_0^{(b)}$ in the absence of medical treatment and a correction factor (always lower than 1) that reduces R_0 when drug treatment is considered:

$$R_0 = R_0^{(b)} F \tag{S21}$$

where $R_0(\chi = 0, \rho = 0) = R_0^{(b)}$.

2.1 The classical approach

R_0 establishes a threshold over which disease invasion takes place. Classically, this threshold is determined by analyzing the dynamics of the system when the whole population is susceptible. If we take as initial condition a situation where $S \approx N$, $E = C = R = 0$. and I is small, we can lump all human infected classes to obtain a single equation:

$$\frac{d(C + I + E)}{dt} = \beta\, S - \delta_H \left(E + C + I\right) - \alpha\, C - r I - \rho\, C \tag{S22}$$

There will be disease invasion when:

$$\frac{d(C + I + E)}{dt} > 0 \tag{S23}$$

This condition will be fulfilled at the initial condition under consideration if:

$$\beta\, N > \delta_H\, I + r\, I \tag{S24}$$

If we define R_0 as:

$$R_0 \equiv \frac{\beta}{(\delta_H + r)\, y} \tag{S25}$$

the threshold condition given by (S24) can be simply written as $R_0 > 1$. By using the value of the transmission rate, β, in terms of the number of infectious mosquitoes, Eq. (S9), and assuming that these and total adult mosquito population are at steady-state, M^* (see Eq. (3), Main Text), we can write:

$$R_0 = \frac{M^*}{N}\, b\, a^2\, c\, \frac{1}{(\delta_H + r)\, \delta_M} \left(\frac{n_P\, \gamma_P}{n_P\, \gamma_P + \delta_M}\right)^{n_P} \tag{S26}$$

where we have also assumed that $\delta_M \gg c\,a\,y$, which is always true as long as the fraction of infectious humans, y, is small enough.

This expression is known in the literature [4] in the limit when $n_P \to \infty$, which means that the duration of the sporogonic phase is assumed to be exactly $T_S = 1/\gamma_P$ without any associated variance. In this case, we have:

$$R_0 = \frac{M^*}{N}\, b\, a^2\, c\, \frac{1}{(\delta_H + r)\,\delta_M}\, \exp(-T_S\,\delta_M) \tag{S27}$$

As mentioned, M^* links this R_0 expression to the life-history parameters of mosquitoes, since a feasible stationary mosquito population, M^*, will be achieved (or not) through the natural dynamics of mosquitoes. Here we have extended a previous expression [4] to consider the effect of the variability on the duration of the sporogonic phase. As a result, we can write a new expression for R_0:

$$R_0 = \frac{K_0}{N}\frac{d_L}{\delta_M}\,\frac{f - \delta_M\,(1 + \frac{\delta_L}{d_L})}{f}\, b\, a^2\, c\, \frac{1}{(\delta_H + r)\,\delta_M}\, \left(\frac{n_P\,\gamma_P}{n_P\,\gamma_P\, +\, \delta_M}\right)^{n_P} \tag{S28}$$

Notice that the R_0 calculated in this way does not depend on model parameters η or σ because these do not influence the initial phases of disease expansion, but rather the dynamics of the disease once it is established in the population. In addition, this expression does not depend on clinical treatment. This is because we have assumed that the number of cases (C) is always low in comparison to the number of infections (I). A more general expression that includes treatment is possible and will be derived elsewhere. It requires the more general approach of the next generation matrix presented next.

2.2 The next generation matrix

The next generation matrix can be defined for a vector-borne disease such as malaria as:

$$K(S, X) = \begin{pmatrix} 0 & S\,a_{12} \\ X\,a_{21} & 0 \end{pmatrix} \tag{S29}$$

where S is the number of susceptible individuals and X is the density of susceptible mosquitoes per human. The matrix entries a_{ij} denote the average infectivity of species j on species i, i. e., the probability that an individual of species j infects and individual of species i during its infectious period. Given this matrix definition, and an initial condition (S, X), the disease increases (or decreases) from one generation to the other, on average, according to the only eigenvalue of this matrix:

$$\lambda(S, X) = \sqrt{S\,a_{12}\,X\,a_{21}} \tag{S30}$$

Naturally, this eigenvalue gives us a threshold for disease invasion if we take as initial condition a totally naive population, $(S, X) = (N, m)$. Therefore,

$$R_0 = \lambda(N, m) \tag{S31}$$

where m is the number of mosquitoes per human and N is the total human population in a disease-free initial situation.

2.2.1 Mosquito average infectivity, a_{12}

If a mosquito has just bitten an infectious human and happens to acquire the infection, we can calculate the total probability that this mosquito infects a human during blood meals later in her life. Let us write mosquito average infectivity as $a_{HM}^{(0)}$. The probability that a human is infected by a singly mosquito due to an infectious bite per unit time is (see Eqs. (S9)-(S10) for $W = 1$):

$$\beta(1) = b\,\frac{a}{N} \tag{S32}$$

In order to calculate $a_{HM}^{(0)}$, we need to weight the probability rate given by Eq. (S32) by the probability that the mosquito is already infectious and alive at time t. In fact, we can write:

$$a_{HM}^{(0)} = b\,\frac{a}{N}\int_0^\infty p_M(t)\,\exp(-\delta_M\,t)\,dt \tag{S33}$$

where $p_M(t)$ is the probability of the mosquito being already infectious at t:

$$p_M(t) = \mathbf{Pr}\,\{T_D < t\} = \int_0^t f_M(\tau)\,d\tau \tag{S34}$$

and the exponential gives the probability that the mosquito has survived until time t. Since we assume that developmental times are gamma distributed, $f_M(\tau)$ is the gamma probability density function:

$$f_M(\tau) = \frac{(n_P\,\gamma_P)^{n_P}}{\Gamma(n_P)}\exp(-n_P\,\gamma_P\,\tau)\,\tau^{n_P-1} \tag{S35}$$

where $1/\gamma_P$ is the average developmental time, T_D, of the *Plasmodium*.

2.2.2 Human average infectivity, a_{21}

Human average infectivity depends on the course of the disease once an infectious bite starts a malaria infective cycle in a human body. First, we calculate this by simply assuming a latency phase after which humans become infectious. Then, we will also calculate human infectivity for a more complicated situation when clinical malaria is introduced.

In the first case, if a human has just been bitten by an infectious mosquito and has become infected, the total probability that this person infects a non-infected mosquito during the whole life cycle of malaria within the human body can be calculated as:

$$a_{MH}^{(0)} = c\,a\int_0^\infty p_E(\tau)\,\exp\left(-\left[\delta_H + r_0\right]\right)\,d\tau \tag{S36}$$

where a is the mosquito biting rate, c is the probability of infection for a mosquito that happens to bite an infectious human, and the exponential factor is the probability of being

alive and still not recovered at time τ for humans. Notice that r_0 is the recovery rate from malaria infection of humans in a disease-free situation (see Eq. (S7)). Furthermore, as before:

$$p_E(t) = \mathbf{Pr}\left\{T_E < t\right\} = \int_0^t f_H(\tau)\, d\tau \tag{S37}$$

where $f_H(\tau)$ is the gamma probability density function for the duration of the latency phase, T_E, in humans.

In fact, the two integrals in Eqs. (S33) and (S36) are of the same type:

$$\int_0^\infty p(\tau)\, \exp(-\chi\, \tau)\, d\tau \tag{S38}$$

where $p(t)$ is a probability distribution function:

$$p(t) = \mathbf{Pr}\left\{T < t\right\} = \int_0^t f(\tau)\, d\tau \tag{S39}$$

and $f(\tau)$ is the probability density function associated to the random variable, T. If we assume that T behaves according to a gamma distribution, then the initial integral is easily calculated by parts:

$$\int_0^\infty p(\tau)\, \exp(-\chi\, \tau)\, d\tau = \frac{1}{\chi}\left(\frac{n\,\gamma}{n\,\gamma\, +\, \chi}\right)^n \tag{S40}$$

This analytical expression is used to solve these integrals (Eq. (S36) and (S33)), which yields:

$$a_{MH}^{(0)} = c\, a\, \frac{1}{\delta_H\, +\, r_0}\left(\frac{n_H\, \gamma_H}{n_H\, \gamma_H\, +\, \delta_H\, +\, r_0}\right)^{n_H} \tag{S41}$$

$$a_{HM}^{(0)} = b\, \frac{a}{N}\frac{1}{\delta_M}\left(\frac{n_P\, \gamma_P}{n_P\, \gamma_P\, +\, \delta_M}\right)^{n_P} \tag{S42}$$

which allows us to write $R_0 = \lambda(N, m)$, where $m = M^*/N$ (Eq. (S31)), and M^* is the total mosquito population at equilibrium (Eq. (3) in Main Text), as:

$$R_0 = a\,\sqrt{b\,c}\,\sqrt{\frac{K}{N}\frac{d_L}{\delta_M}\,\frac{f - \delta_M\,(1 + \frac{\delta_L}{d_L})}{f}}\,\sqrt{\frac{1}{(\delta_H + r_0)\,\delta_M}}\left(\frac{n_P\,\gamma_P}{n_P\,\gamma_P\, +\, \delta_M}\right)^{\frac{n_P}{2}}\left(\frac{n_H\,\gamma_H}{n_H\,\gamma_H + r_0 + \delta_H}\right)^{\frac{n_H}{2}} \tag{S43}$$

As far as we know, unlike previous expressions given for R_0 [4, 15] (compare also to Eq. (S28)), our calculation takes into account both the distributed delay introduced by the development of *Plasmodium* in the mosquito and the incubation phase of malaria in the human body.

3 Stationary Points

Here we provide a detailed description of the semi-analytical procedure to calculate the fixed points of the coupled mosquito-human model. This allows the evaluation of the Jacobian matrix at these points to study their stability properties. First, we extend the model to incorporate general distributions of incubation times in both the mosquito and human submodels. Then, we calculate the stationary states.

Distributed time-delay dynamics can be represented by a regular system of ODE's with a chain of latency stages, from E_1 to E_n, of appropriate length [12]:

$$\begin{aligned}
\frac{dS}{dt} &= B - \beta\ S + \sigma R - \delta_H\, S + \rho\ C \\
\frac{dE_1}{dt} &= \beta\, S - \delta_H\, E_1 - n_H \gamma_H\, E_1 \\
\frac{dE_2}{dt} &= n_H \gamma_H\, E_1 - n_H \gamma_H\, E_2 - \delta_H\, E_2 \\
\cdots &= \cdots \\
\frac{dE_n}{dt} &= n_H \gamma_H\, E_{n-1} - n_H \gamma_H\, E_n - \delta_H\, E_n \\
\frac{dI}{dt} &= (1-\chi)\, n_H \gamma_H\, E_n - \eta\, \beta\ I + \nu\ C - r\ I - \delta\, I \\
\frac{dR}{dt} &= -\sigma R + r\ I - \delta_H\, R \\
\frac{dC}{dt} &= \chi\, n_H \gamma_H\, E_n + \eta\, \beta\ I - \nu\ C - \rho\ C - \delta_H\, C
\end{aligned} \tag{S44}$$

Since the sum of identically exponentially distributed incubation times (between successive latency classes) will produce a gamma distribution for the total incubation time, the only extra assumption here is that the distribution of latency times T_E is well described by a gamma probability density function:

$$f_H(\tau) = \frac{(n_H\, \gamma_H)^{n_H}}{\Gamma(n_H)} \exp(-n_H\, \gamma_H\, \tau)\, \tau^{n_P - 1} \tag{S45}$$

of average $1/\gamma_H$ and variance $1/(n_H\, \gamma_H^2)$.

Note also that by adding up all Eqs above, the dynamics of the human population is still simply:

$$\frac{dN}{dt} = B - \delta_H\, N \tag{S46}$$

The model analyzed in the Main Text considers $B = b\, N$, with $b = \delta_H$, and therefore assumes constant human population size. The exploration of model behavior reported in the main text was carried out for values of the turnover rate δ_H of 5.4 10^{-5} day^{-1} (1.35 10^{-4} day^{-1} in reference [1]) and $N = 50000$, although, as explained in the caption of Table S1, these two parameters do not influence the stationary properties of the model.

If we apply these considerations also to the development of the *Plasmodium* parasite within infected mosquitoes, we can rewrite the mosquito submodel as follows:

$$\begin{aligned}
\frac{dL}{dt} &= f\,M\left(\frac{K-L}{K}\right) - \delta_L\,L - d_L\,L \\
\frac{dX}{dt} &= -c\,a\,y\,X - \delta_M\,X + d_L\,L \\
\frac{dV_1}{dt} &= +c\,a\,y\,X - n_P\,\gamma_P\,V_1 - \delta_M\,V_1 \\
\frac{dV_2}{dt} &= n_P\,\gamma_P\,V_1 - n_P\,\gamma_P\,V_2 - \delta_M\,V_2 \\
\cdots &= \cdots \\
\frac{dV_n}{dt} &= n_P\,\gamma_P\,V_{n-1} - n_P\,\gamma_P\,V_n - \delta_M\,V_n \\
\frac{dW}{dt} &= n_P\,\gamma_P\,V_n - \delta_M\,W
\end{aligned} \tag{S47}$$

Calculations and results presented in the Main Text are conducted with the coupled system defined by Eqs (S44)-(S47) with $n_P = n_H = 1$.

In order to calculate fixed points, we would typically make the above rate equations equal to zero, but this yields a high-dimensional system ($n_P + 3 + n_H + 4$). Here we propose a simpler algorithm to calculate the fixed points of this system of equations semi-analytically.

Given a fraction y of infectious humans, we have already seen that the infectious mosquito population reaches an equilibrium value (see Eq. (6) from main text), which is found by making Eqs (S47) equal to zero. We rewrite this expression below:

$$W^\star = \frac{a\,c\,y^\star}{\delta_M\,+\,a\,c\,y^\star}\left[\frac{n_P\,\gamma_P}{n_P\,\gamma_P + \delta_M}\right]^{n_P} M^\star \tag{S48}$$

In fact, all variables at the stable point point can be written in terms of $M^\star$, given by Eq. (3) in the Main Text, and, thus, in terms of the parameters of the system:

$$L^\star = \frac{\delta_M}{d_L}\,M^\star \tag{S49}$$

$$X^\star = \frac{\delta_M}{c\,a\,y + \delta_M}\,M^\star \tag{S50}$$

$$V_1^\star = \frac{c\,a\,y}{n_P\,\gamma_P\,+\,\delta_M}\,\frac{\delta_M}{c\,a\,y + \delta_M}\,M^\star \tag{S51}$$

$$V_k^\star = [\theta_P]^{k-1}\,V_1^\star \qquad k = 2, \cdots n_P \tag{S52}$$

where

$$\theta_P = \frac{n_P\,\gamma_P}{n_P\,\gamma_P + \delta_M} \tag{S53}$$

Alternatively, we can calculate the stable point of the human population given a total number of infectious mosquitoes, W, which determines, in turn, β (see Eqs (S9)-(S10)).

By assuming constant population size N, and by making Eqs (S44) equal to zero, after some algebra, we observe that the "endemic" fixed point can be written as:

$$S^\star = \frac{1}{1+z} N \tag{S54}$$

$$E_1^\star = \frac{\beta}{\delta_H + n_H \gamma_H} \frac{1}{1+z} N \tag{S55}$$

$$E_k^\star = [\theta_H]^{k-1} E_1^\star \tag{S56}$$

$$k = 2, \cdots n_H$$

$$I^\star = \beta \frac{\nu + (1-\chi)(\rho+\delta_H)}{q(1+z)} [\theta_H]^{n_H} N \tag{S57}$$

$$R^\star = \beta \frac{r\nu + (1-\chi) r (\rho+\delta_H)}{(\sigma+\delta_H) q (1+z)} [\theta_H]^{n_H} N \tag{S58}$$

$$C^\star = \beta \frac{\eta\beta + \chi(r+\delta_H)}{q(1+z)} [\theta_H]^{n_H} N \tag{S59}$$

where the constants θ_H, z, q, are defined as:

$$\theta_H = \frac{n_H \gamma_H}{n_P \gamma_H + \delta_H} \tag{S60}$$

$$q = \eta\beta(\rho + \delta_H) + (r + \delta_H)(\nu + \rho + \delta_H) \tag{S61}$$

$$z = \frac{\beta}{\delta_H} + \beta \left[\frac{\nu + (1-\chi)(\rho+\delta_H)}{q} \left\{ 1 + \frac{r}{\sigma + \delta_H} \right\} + \frac{\eta\beta + \chi(r+\delta_H)}{q} - \frac{1}{\delta_H} \right] [\theta_H]^{n_H} \tag{S62}$$

Notice that in all these expressions r and σ depend on Δ through Eqs (S7) and (S8), respectively, and ultimately on W. Therefore, we can write the fraction of infectious individuals as a complicated function of W:

$$y \equiv \frac{I+C}{N} = \beta \frac{\nu + (1-\chi)(\rho+\delta_H) + \eta\beta + \chi(r+\delta_H)}{q(1+z)} [\theta_H]^{n_H} \tag{S63}$$

Therefore, by using Eqs (S63) and (S48), it is possible to write a non-linear system of two equations and two unknowns y and W:

$$y = \mathcal{F}(W) \tag{S64}$$

$$W = \mathcal{G}(y) \tag{S65}$$

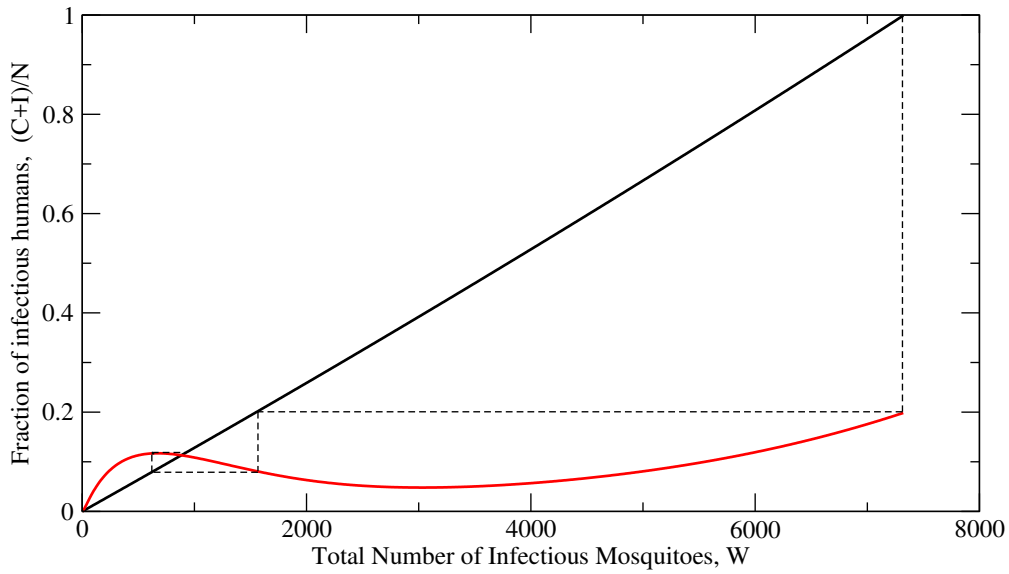

Figure S1: **Fraction of infectious humans *versus* total number of infectious mosquitoes.** The intersection of these two curves determines the stationary state. Population size $N = 50000$, the number of latent classes for the parasite $n_P = 5$, with the rest of the parameters taken from Table 1.

In fact, it is useful to invert Eq. (S65) (see Eq (S48)) and write:

$$y = \frac{\delta_M}{c\,a}\,\frac{[\theta_P]^{-n_P}\ w}{1\ -\ [\theta_P]^{-n_P}\ w} \tag{S66}$$

where $w \equiv W/M^\star$ and θ_P is defined in Eq. (S53).

Thus, since we have $y = \mathcal{G}^{-1}(W)$, all we need is to solve for the value of W that satisfies the equation $\mathcal{G}^{-1}(W) - \mathcal{F}(W) = 0$. This can be done numerically (see Fig S1). Thus, the solution of the system defined by Eqs (S64)-(S65) provides the equilibrium values $W^\star$ and $y^\star$, which are then used to generate the steady state of the whole system through Eqs (S48)-(S52) and (S54)-(S59).

4 The Dominant Period

Once stationary points are calculated, the Jacobian matrix J^* of the coupled ODE system (see Eqs (S44)-(S47)) can be evaluated at the corresponding fixed points. This matrix encodes information about the fate of small perturbations away from the fixed point. The temporal dynamics of these small perturbations can be written in terms of a linear combination of exponentials where the rates are obtained as eigenvalues, this is, as the roots, λ, of the characteristic polynomial (see Eq. (7) from the main text). Because this polynomial can have as many roots as the dimension of the dynamical system, there will be as many eigenvalues as the number of equations in the initial ODE system. If and only if all the associated eigenvalues have all strictly negative real parts, the fixed point is asymptotically

locally stable. In this case, we can always define the dominant eigenvalue, λ_0, as the one with the largest real part (the least negative one). It controls the long-lasting mode in the decay towards the fixed point. When this dominant eigenvalue is a complex number, the decay towards the fixed point occurs through damped oscillations. Whereas the speed of the decay is controlled by the real part of the eigenvalue, the frequency of the oscillations is given by its imaginary part. In this case, it is possible to define a characteristic period or *dominant period* as follows:

$$T_0 = 2\,\pi\,\frac{1}{Im(\lambda_0)} \tag{S67}$$

where $Im(\lambda_0)$ stands for the imaginary part of the dominant eigenvalue. Since damped oscillations in disease dynamics can be sustained by stochasticity [2], T_0 can be regarded as the typical, endogeneous oscillation period of the disease. Its value depends only on model parameters. Fig 3 (Main text) maps this value in the parameter subspace defined by mosquito carrying capacity, K, and biting rate, a.

5 Hysteresis in $SE_nCIR - LXV_nW$ model

As a complement to Fig 4 in the Main Text, here we also represent the response of the system to variable biting rates, a in terms of the entomological infection rate (EIR), measured as the number of infectious bites per year (see Fig S2).

6 Bistabilty in the Ross-MacDonald Model (RM)

To underscore the generality of the conclusion that superinfection always introduces the possibility of bistability, we derive here conditions for model parameters under which the simple RM model exhibits this behavior. The RM model assumes, first, that both mosquito and human populations are constant; second, that vectors and humans are either infectious or susceptible at any given time; and third, that once infected, humans clear malaria infection at a constant rate r. A susceptible human can acquire the infection from the bite of an infectious mosquito. A healthy mosquito can in turn acquire the parasite by biting an infectious human. The same biting rate (a) controls these two processes. Per-bite transmission probabilities differ however from vector to host (b) and from host to vector (c). Finally, constant per capita death rates act on both mosquitoes (δ_M) and humans (δ_H). Because populations are constant and can be divided in either infectious or susceptible classes, the state of the human-mosquito system can be described by only two variables: the fraction of infectious humans (y), and the number of infectious mosquitoes per human (w). Therefore, the temporal evolution of the state variables can be written as:

$$\frac{dw}{dt} = c\,a\,y\,(m-w) - \delta_M\,w \tag{S68}$$

$$\frac{dy}{dt} = (b\,a\,w\,+\beta_e)(1-y) - (\delta_H + r)\,y \tag{S69}$$

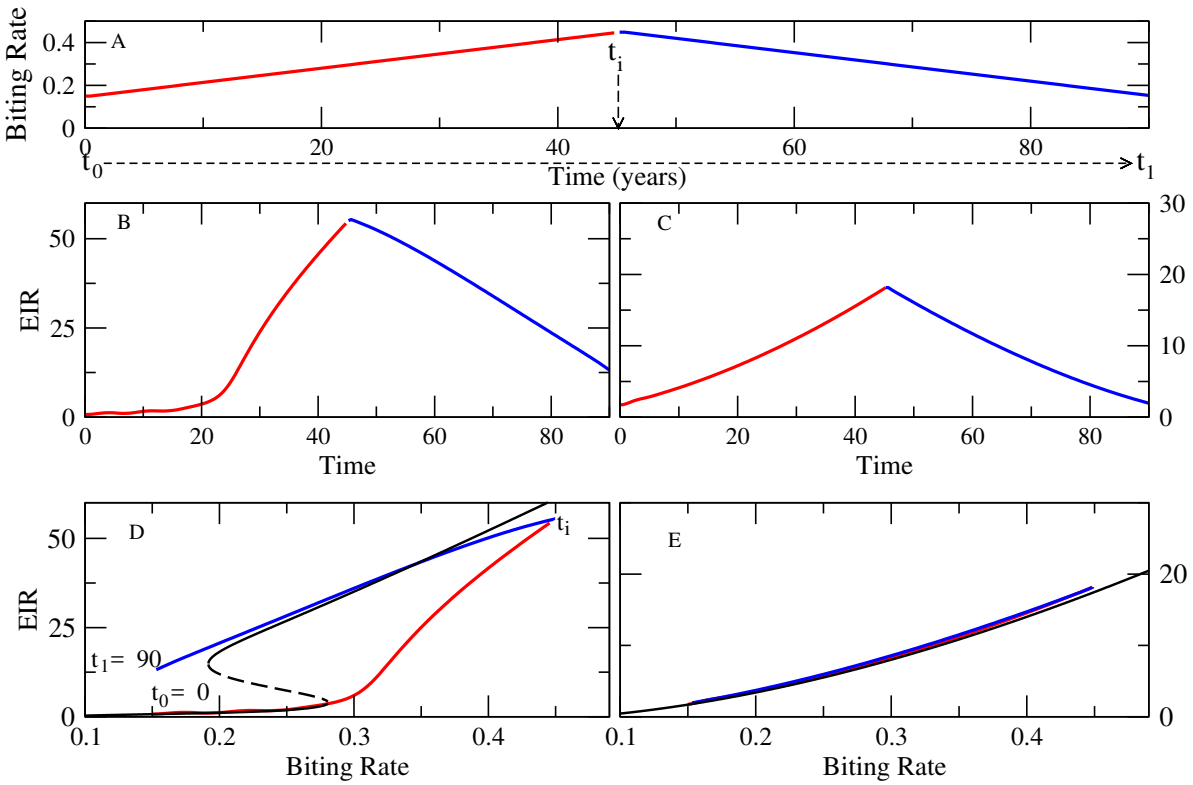

Figure S2: **Hysteresis Cycles**. Response of the EIR to a slowly increasing biting rate, a, from low to high values and back (Panel A). We plot the time evolution of the system in terms of this empirically measurable model output variable. For comparison purposes, we analyze the model both with (left panels) and without (right panels) the slowing down effect (the decrease in the rate of recovery and that of immunity loss due to repeated infectious bites). The color of the curves changes from blue to red when the biting rate changes from increasing to decreasing linearly with time. The diagrams correspond to the horizontal broken line of the upper left panel in Fig 2 (Main Text). In the presence of the slowing-down effect, as biting rates go from low to high and back in a linear way (panel A) with the rest of parameters constant, the EIR shows a highly non-linear response (panel B), which can be also represented as a hysteresis cycle on the bifurcation diagram (panel D).

where m is the total number of mosquitoes per human and β_e is an external transmission rate or the rate at which susceptible humans acquire the infection from outside the system.

The classical RM model considers no external infection inputs ($\beta_e = 0$), and no explicit human mortality rate ($\delta_H = 0$), although, implicitly within that framework, the latter can be considered as a small correction to the recovery rate, r. By dividing the first equation by m, and considering these two classical assumptions, the system above can be re-written as:

$$\frac{dx}{dt} = c\,a\,y\,(1-x) - \delta_M\,x \tag{S70}$$

$$\frac{dy}{dt} = b\,a\,m\,x\,(1-y) - r\,y \tag{S71}$$

where x is now the fraction of infectious mosquitoes.

This system is simple enough to calculate the stationary state by the intersection of the two corresponding isolines (see Fig S4):

$$0 = c\,a\,y\,(1-x) - \delta_M\,x \tag{S72}$$

$$0 = b\,a\,m\,x\,(1-y) - r\,y \tag{S73}$$

In fact, the non-linear system can be solved explicitly, first, for y, and then for x, or the other way around. We can write:

$$0 = c\,a\,y\left(1 - \frac{r\,y}{a\,b\,m\,(1-y)}\right) - \delta_M\frac{r\,y}{a\,b\,m\,(1-y)} \tag{S74}$$

$$0 = y\,(c\,a^2\,b\,m\,(1-y) - c\,a\,r\,y - \delta_M\,r) \tag{S75}$$

In sum, the RM model has only two stationary equilibrium points, the disease-free equilibrium ($x = 0$, $y = 0$) and the endemic equilibrium ($x = x^\star$, $y = y^\star$) which is given by:

$$x^\star = \frac{a^2\,b\,c\,m - \delta_M\,r}{a\,b\,m\,(a\,c + \delta_M)} \tag{S76}$$

$$y^\star = \frac{a^2\,b\,c\,m - \delta_M\,r}{a\,c\,(a\,b\,m + r)} \tag{S77}$$

By contrast, when we introduce superinfection as a slowing down effect on the recovery rate r due to the intensity of transmission [6], we next show the possibility of coexisting stable stationary points for some parameter combinations, as well as the presence of a saddle-node bifurcation as a key model parameter crosses a given threshold.

As mentioned, the influence of repeated infectious bites on the recovery rate is introduced by assuming the Dietz function [6] (see Eq (S7)), which we will write here in terms of the dimensionless fraction of infectious mosquitoes, x:

$$r(x;\,a,m,r_0) = \frac{a\,m\,x}{\exp\left(\frac{a\,m\,x}{r_0}\right) - 1} \tag{S78}$$

For a given parameter set, the recovery rate is no longer constant but slows down as the density of infectious mosquitoes per human, represented here on the x axis, increases (see Fig S3).

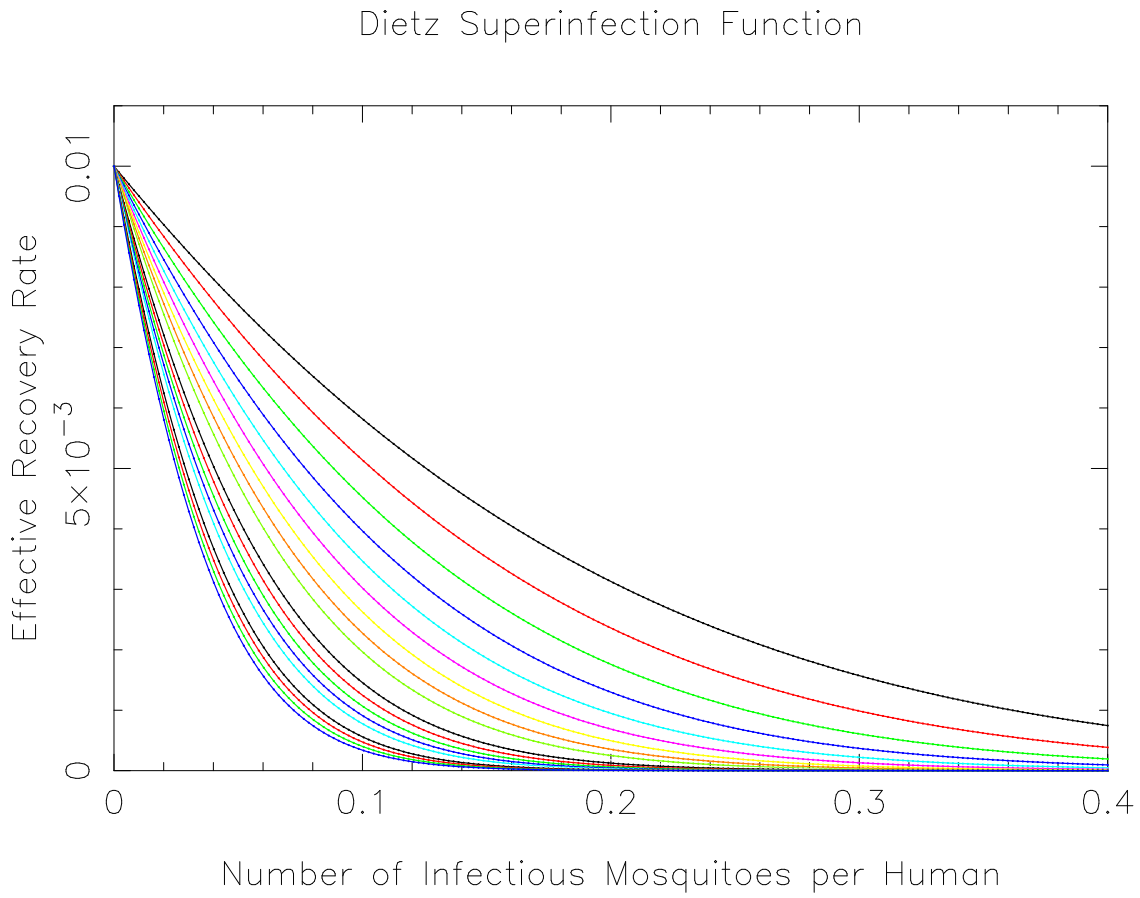

Figure S3: Dietz superinfection function for different values of the biting rate (from $a = 0.1$ to $a = 0.5$), $r_0 = 0.01$ and $m = 0.6$. The effective recovery rate decreases as the number of infectious mosquitoes per human increases. Higher biting rates make this decay sharper.

6.1 Conditions for bistability

In order to find the conditions under which coexistence of endemic states is possible, we will first go back to the two isolines whose intersection define those states. From Eq (S73), the fraction of infectious humans for a given fraction of infectious mosquitoes can be written as:

$$y = \frac{a\,b\,m\,x}{a\,b\,m\,x\,+\,r(x)} \tag{S79}$$

where $r(x)$ is given by Eq. (S78). Let us call the last function $F_1(x)$. Likewise, from Eq (S72), the fraction of infectious mosquitoes for a given fraction of infectious humans can be written as:

$$x = \frac{a\,c\,y}{a\,c\,y\,+\,\delta_M} \tag{S80}$$

which can be easily inverted:

$$y = \frac{\delta_M x}{a\,c\,(1-x)} \tag{S81}$$

Let us call this 2nd function $F_2(x)$, this gives the corresponding fraction of infectious humans for a given fraction of infectious mosquitoes at equilibrium. Therefore, the two isolines can be represented by the functions $y = F_1(x)$ and $y = F_2(x)$ (see Fig S4).

The intersection of the functions $F_1(x)$ and $F_2(x)$ can be calculated numerically. Using this method, analytic conditions for model parameters indicating when there will be one, two, or more than two intersecting points are difficult to find. In order to approach this point analytically, we first analyze the curvature of the two isolines.

The first and second derivative of the 2nd isoline with respect to x are:

$$F_2'(x) = \frac{\delta_M}{a\,c\,(1-x)^2} \tag{S82}$$

$$F_2''(x) = 2\frac{\delta_M}{a\,c\,(1-x)^3}. \tag{S83}$$

Thus, they are both positive in the range $0 < x < 1$. In other words, $F_1(x)$ is an increasing function of x and never changes curvature, as x is a fraction. Now, let us look at the first and second derivative of the 1st isoline, in the case where the recovery rate is a constant parameter, $r(x) = r_0$

$$F_1'(x) = \frac{a\,b\,m\,r_0}{(a\,b\,m\,x\,+\,r_0)^2} \tag{S84}$$

$$F_1''(x) = -2\frac{a\,b\,m\,r_0}{(a\,b\,m\,x\,+\,r_0)^3}. \tag{S85}$$

Then, $F_1(x)$ is always an increasing function of x and, again, never changes curvature since $x > 0$.

Therefore, if the recovery is constant, $F_1(x)$ and $F_2(x)$ never change curvature but have opposite curvatures, and both are monotonically increasing. Since $F_1(x)$ has a horizontal

asymptote at 1, and $F_2(x)$ a vertical asymptote at 1, if the two curves cross defining an endemic stationary state, they can only do it once. This is always true more generally because either $F_1(0) = F_2(0)$ for $\beta_e = 0$, or $F_1(0) > F_2(0)$, for $\beta_e > 0$. As a consequence, necessarily, at least one change of curvature is required to find additional crossing points and therefore, more than a single endemic stationary state.

Since $F_2(x)$ does not depend on the recovery rate, only $F_1(x)$ can potentially exhibit a curvature change. Let us look at the second derivative of the 1st isoline when the recovery rate is no longer constant but given by Eq. (S78). Because this leads to complex expressions, it is useful to write them in terms of the new variable $A \equiv \exp\left(\frac{amx}{r_0}\right)$

$$F_1'(x) = \frac{b}{(b(A-1)+1)^2}\frac{am}{r_0}A \tag{S86}$$

$$F_1''(x) = \left(\frac{am}{r_0}\right)^2 A\, b\frac{1-b-bA}{(1+b(A-1))^3} \tag{S87}$$

Notice that the first derivative never changes its sign and it is always positive, meaning that the isoline is a monotonic increasing function of x. The second derivative has a denominator that is always positive. The sign of the 2nd derivative is entirely determined by the numerator $N(y) \equiv 1-b-bA$. All we need to establish is under which conditions this function changes sign. These conditions will be necessary for the coexistence of non-trivial stationary states.

By equating to zero the function $N(y)$, one can find the inflection point to be:

$$x_i = \frac{r_0}{am}\log\left(\frac{1-b}{b}\right) \tag{S88}$$

which is only positive as long as $1-b > b$, a condition only satisfied when $b < 0.5$. Interestingly enough, in order to have the possibility of coexistence of stationary states, we require $b < 0.5$. This is our first necessary condition. In sum, the fact that the x_i have to be positive forces b to be less than 0.5. Then, in that case, $F_1''(x) > 0 \;\forall\; x < x_i$ and $F_1''(x) < 0 \;\forall\; x > x_i$.

Moreover, to be biologically meaningful, the change of curvature x_i should happen for a value less than 1 in our context. Even more restrictively, it should be smaller than its possible largest value, which is the value of the infectious mosquito fraction that corresponds to a fraction of infectious humans equal to 1. This condition will be true when $b > b_c$, where the critical value is given by:

$$b_c = \frac{1}{1+\exp\left(\frac{am}{r_0}\frac{ac}{ac+\delta_M}\right)} \tag{S89}$$

To sum up, by calculating expressions for the two isolines of the system with superinfection, we have checked that one of them is a monotonic increasing function that never changes curvature, and that the other is a monotonic increasing function which can have an inflection point, x_i, for some parameter combinations. By requiring this point to be well defined, we

Model Parameter	Symbol	Min. Value	Max. Value	Value
M: Biting rate	a	0.1	0.4	0.35
M: Infectivity probability ($H \to M$)	c	0	1	0.05
M: Mosquito Mortality Rate	δ_M	0.01	0.1	0.05
M: No of Mosquitoes per Human	m	0.01	3.5	0.6
H: Infectivity probability ($M \to H$)	b	0.01	1	0.1
H: External Transmission Rate	β_e	0	0.0001	0
H: Human Mortality Rate	δ_H	$5.5\ 10^{-5}$	0.00014	0
H: Recovery rate ($I \to S$)	r_0	0.001	0.01	0.01

Table S2: **Minimum and maximum values define a realistic subregion of the parameter space.** H: Human- M: Mosquito-realated parameters

are able to identify two necessary conditions for the coexistence of stationary states. They can be expressed in terms of the infectivity probability b:

$$b_c < b < 0.5 \tag{S90}$$

where b_c depends on the other 5 model parameters and is given by the expression above. Notice that the critical value in the infectivity probability, b_c, is bounded between 0 and 0.5 (see Eq (S89)).

In figure S4, we show how the intersection of model isolines defines the stationary points in the usual way (upper panels), as well as the effect of superinfection (compare left to right panels). Bifurcation diagrams are represented in the bottom panels. As you see, whenever there is bistability the low equilibrium represents a disease-free equilibrium malaria. This is so because RM model does not consider an external component to the force of infection as we do in the full, more realistic model analyzed throughout this paper.

7 Malaria models of different degrees of complexity

As shown, the coupled models presented here all boil down to the RM seminal model through a sequence of ever simplifying assumptions. These models are used to investigate how the propensity for bistability changes as model complexity and, therefore, the number of model parameters increases. Here we fully specify the models we used to generate Fig 5 in the Main Text. We use stochastic integration to evaluate model propensity to show bistability. This involves to randomly draw parameter sets within the boundaries given in Table S1, and evaluate the fraction of times, out of the total number of draws, that a given model shows bistability. This fraction is what we defined as a propensity, or *probability*, of coexisting stable stationary points.

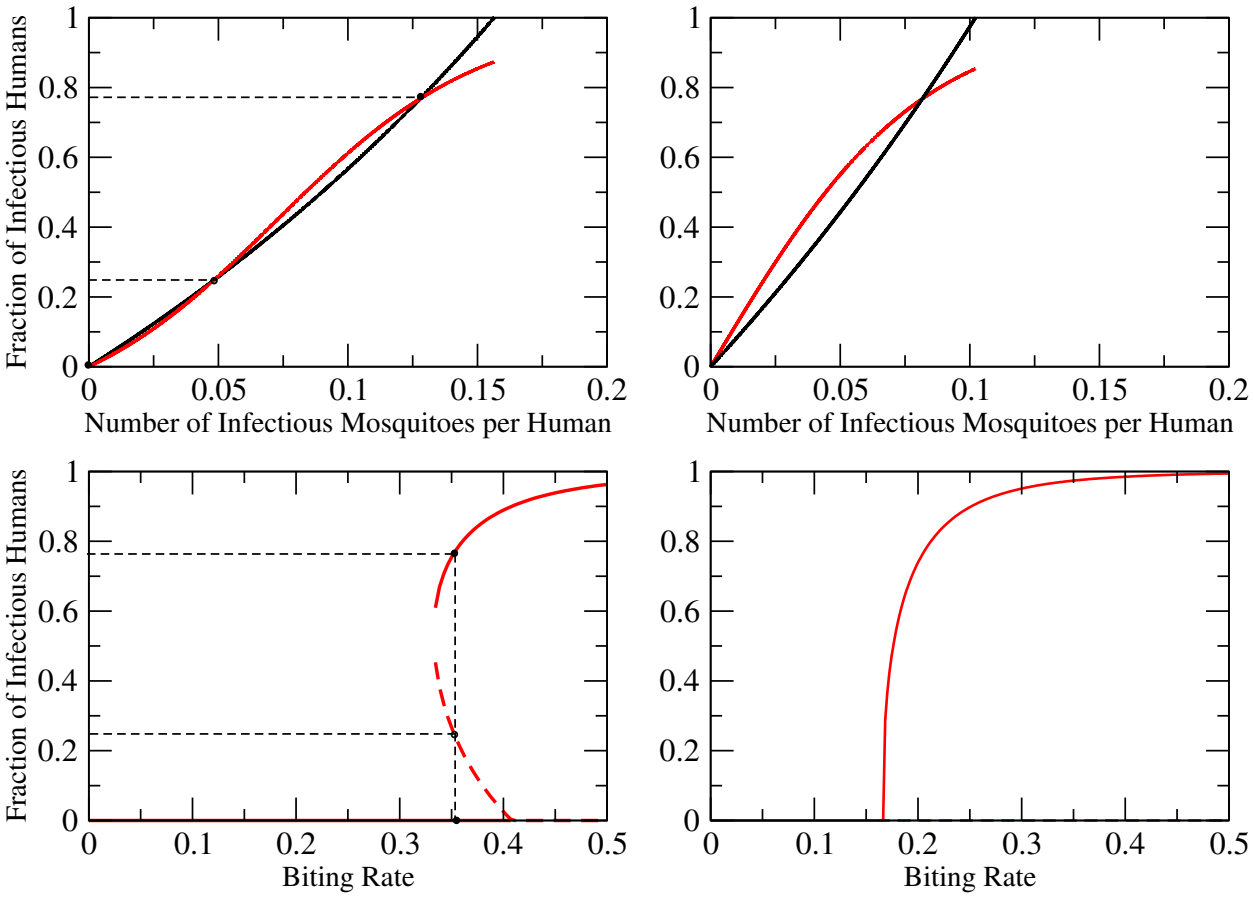

Figure S4: **MacDonald and Ross model with superinfection**. On the left, for $b = 0.1$, there is coexistence of stationary states. On the right, for $b = 0.6$, there is only one endemic equilibrium for every value of the biting rate. The other parameters are kept constant (at values given in Table S2). The corresponding bifurcation diagrams are represented in the bottom panels. Broken red lines indicate unstable equilibrium states.

7.1 Human submodels

$[SE_nCIR\ ]$

$$\begin{aligned}
\frac{dS}{dt} &= B - \beta\ S + \sigma R - \delta_H\, S + \rho\ C \\
\frac{dE_1}{dt} &= \beta\, S - \delta_H\, E_1 - \gamma_H\, n\, E_1 \\
\frac{dE_i}{dt} &= \gamma_H\, n\, E_{i-1} \delta_H\, E_i - \gamma_H\, n\, E_i \\
& \quad i = 2, \ldots, n \\
\frac{dI}{dt} &= (1-\xi)\, \gamma_H\ n\, E_n - \eta\, \beta\ I + \nu\ C - r\ I - \ \delta_H\, I \\
\frac{dR}{dt} &= -\sigma R + r\ I - \delta_H\, R \\
\frac{dC}{dt} &= \xi\, \gamma_H\, n\, E_n + \eta\, \beta\ I - \nu\ C - \rho\ C - \alpha\ C - \delta_H\, C
\end{aligned}$$

where r is represented by the Dietz function (Eq S7), new susceptibles enter the system at a constant "replacement" rate, $B = \delta N$, where N is the total human population, so human population remains constant, and $\beta = b\, aW/N + \beta_e$ is the total force of infection, where β_e is an external force of infection, and W/N is the number of infectious mosquitoes per human, represented by w in Eq (S68) above.

$[SE_nIR\ ]$ A model that does not take into account the state variable for the number of clinical malaria cases, can be readily written:

$$\begin{aligned}
\frac{dS}{dt} &= B - \beta\ S + \sigma R - \delta_H\, S \\
\frac{dE_1}{dt} &= \beta\, S - \delta_H\, E_1 - \gamma_H\, n\, E_1 \\
\frac{dE_i}{dt} &= \gamma_H\, n\, E_{i-1} \delta_H\, E_i - \gamma_H\, n\, E_i \\
& \quad i = 1, \ldots, n \\
\frac{dI}{dt} &= \gamma_H\ n\, E_n + -r\ I - \ \delta_H\, I \\
\frac{dR}{dt} &= -\sigma R + r\ I - \delta_H\, R
\end{aligned}$$

$[SE_nI\ ]$ When no recovery state is considered, then the model becomes even simpler:

$$\begin{aligned}
\frac{dS}{dt} &= B - \beta\ S - \delta_H\, S + r\ I \\
\frac{dE_1}{dt} &= \beta\, S - \delta_H\, E_1 - \gamma_H\, n\, E_1 \\
\frac{dE_i}{dt} &= \gamma_H\, n\, E_{i-1} \delta_H\, E_i - \gamma_H\, n\, E_i \\
& \quad i = 1, \ldots, n \\
\frac{dI}{dt} &= \gamma_H\ n\, E_n - r\ I - \ \delta_H\, I
\end{aligned}$$

[SI] Finally, if no exposed classes are considered, we obtain a minimal model:

$$\begin{aligned}\frac{dS}{dt} &= B - \beta\ S - \delta_H\, S + r\ I \\ \frac{dI}{dt} &= +\beta\ S - r\ I - \delta_H\, I\end{aligned}$$

Of course, since $N = S + I$, these two Eqs can collapse into one, which corresponds to the equation for infectious humans in the seminal Ross and MacDonald model when expressed in population fractions.

7.2 Mosquito submodels

Mosquito submodels can incorporate several complexities, according to the number of life stages considered, from eggs to adult mosquitoes, the presence of density dependence regulation, etc. We present here four possibilities:

[LXV_nW] If only larvae and adult mosquitoes are taken into account, with density-dependent regulation in the larval stage, we obtain:

$$\begin{aligned}\frac{dL}{dt} &= f\, M\, \left(\frac{K-L}{K}\right) - \delta_L\, L - d_L\, L \\ \frac{dX}{dt} &= -c\, a\, y\, X - \delta_M\, X + d_L\, L \\ \frac{dV_1}{dt} &= +c\, a\, y\, X - \gamma_P\, n V_1 - \delta_M\, V \\ \frac{dV_i}{dt} &= \gamma_P\, n\, V_{i-1} \delta_M\, V_i - \gamma_P\, n\, V_i \\ & \quad i = 2, \ldots, n \\ \frac{dW}{dt} &= \gamma_P\, n\, V_n - \delta_M\, W\end{aligned}$$

where y is the fraction of infectious humans, and M is the total number of adult mosquitoes in the system.

[$X_K V_n W$] If we do not consider larvae, and introduce density-dependent regulation in the adult level, we obtain:

$$\begin{aligned}\frac{dX}{dt} &= f\, M\, \left(\frac{K-M}{M}\right) - c\, a\, y\, X - \delta_M\, X \\ \frac{dV_1}{dt} &= +c\, a\, y\, X - -\delta_M\, V_1 \\ \frac{dV_i}{dt} &= \gamma_P\, n\, V_{i-1} \delta_M\, V_i - \gamma_P\, n\, V_i \\ & \quad i = 2, \ldots, n \\ \frac{dW}{dt} &= \gamma_P\, n\, V_n - \delta_M\, W\end{aligned}$$

where K is a carrying capacity for the population of adult mosquitoes.

[XV_nW] If we consider that the adult mosquito population is constant, we can simply write:

$$\begin{aligned}
\frac{dX}{dt} &= fM - c\,a\,y\,X - \delta_M\,X \\
\frac{dV_1}{dt} &= +c\,a\,y\,X - -\delta_M\,V_1 \\
\frac{dV_i}{dt} &= \gamma_P\,n\,V_{i-1}\delta_M\,V_i - \gamma_P\,n\,V_i \\
&\quad i = 2, \ldots, n \\
\frac{dW}{dt} &= \gamma_P\,n\,V_n - \delta_M\,W
\end{aligned}$$

where f is the per capita fecundity of adult mosquitoes balancing out deaths ($f = \delta_M$) so that the size of the adult population is maintained constant.

[XW] Finally, if we do not consider *Plasmodium*'s development within adult mosquitoes, we obtain the following minimal model:

$$\begin{aligned}
\frac{dX}{dt} &= fM - c\,a\,y\,X - \delta_M\,X \\
\frac{dW}{dt} &= c\,a\,y\,X - \delta_M\,W
\end{aligned}$$

Since total mosquito population is held constant ($M = X + W$), again these two equations can be collapsed into just one, which corresponds to the first equation of the RM model. In fact, that seminal model can be labelled as $SI - XW$ in our nomenclature.

These submodels can be combined into 4×4 different coupled models and sorted in descending order in terms of their number of parameters (see Table S3). These models are all related in a hierarchical way since simpler ones are derived from more complex ones by equating to zero some of the parameters. The number of parameters for the sixteen model combinations are specified, from the more complex one with a total of 21 parameters (12 human-related + 9 mosquito-related) ($SE_nCIR - LXV_nW$) to the minimal one —which corresponds to the RM model— with only 8 (4 + 4) ($SI - XW$) model parameters.

Human Submodel	Mosquito Submodel			
	LXV_nW	X_KV_nW	XV_nW	XW
SE_nCIR	(12,9)	(12,7)	(11,6)	(11,4)
SE_nIR	(8,9)	(8,7)	(7,6)	(7,4)
SE_nI	(7,9)	(7,7)	(6,6)	(6,4)
SI	(5,9)	(5,7)	(4,6)	(4,4)

Table S3: **Malaria Human-Mosquito coupled Models.** Model complexity increases from the bottom-right cell to the upper-left one in the table. The light gray shaded cell in the bottom-right corner corresponds to the RM model described by Eqs (S68)-(S69), whose 8 parameters are described in Table S2. Human population is maintained constant in all models. Human population size N only plays a role in the first two columns. The last two columns correspond to models where the mosquito population is also held constant. In these cases, we can define a new model parameter, m, the total number of adult mosquitoes per human, which reduces by one the total number of human-related model parameters.

A1 Appendix

In this appendix, we show the equivalence of our mosquito submodel to Eq. (S16) of the RM model under the assumptions 1 to 5 (see page 6). The key point is to be able to identify the rate $F(t)$, initially appearing in Eq. (S91) in terms of the probability distribution of the extrinsic incubation period, T_D, which can be written as:

$$F(t) = \int_{t_0}^{t} a\, c\, y(\hat{t})\, X(\hat{t})\, \exp(-\delta_M\,(t-\hat{t}))\, f(t-\hat{t})\, d\hat{t} \tag{A1}$$

For certain simple density functions, $f(x)$, the total rate $F(t)$ above can be calculated analytically (see below). If, for instance, we assume that the extrinsic incubation period takes always the same value, t_D, so that $\mathbf{Pr}\{T_D < t_D\}$ is equal to zero if $T_D < t_D$ and to 1, otherwise, then, the derivative of such step probability distribution function is a Dirac δ_L function (see Fig. A1). In that case, $F(t)$ can be written as:

$$F(t) = a\, c\, y(t-t_D)\, X(t-t_D)\, \exp(-\delta_M\, t_D) \tag{A2}$$

which, can be introduced back into Eq. S91 to give rise to:

$$\frac{dW}{dt} = a\, c\, y(t-t_D)\, X(t-t_D)\, \exp(-\delta_M\, t_D) - \delta_M W \tag{A3}$$

Finally, by considering no delays, i.e., instantaneous extrinsic incubation periods ($t_D = 0$) so that there is no mosquito infected phase, V, and, by remembering that mosquito population is constant ($W+X = M$), we obtain a simple equation fully describing the temporal evolution of the mosquito population:

$$\frac{dW}{dt} = a\, c\, y(t)\, (M - W(t)) - \delta_M W(t) \tag{A4}$$

which is equivalent to the initial Eq. (S16) of the Ross-MacDonald model, after dividing by total human population, as we wanted to show.

Other classical models can also be considered within this framework. For instance, if we maintain a fixed extrinsic incubation period, and still assume a constant mosquito population ($V+W+X = M$), then our mosquito submodel, Eqs. (S11)-(S91), simplifies into two delayed ODEs of the kind widely used in malaria models [8]:

$$\begin{aligned}
\frac{dV}{dt} &= +cay(t)(M-V-W) - acy(t-t_D)(M-V(t-t_D)-W(t-t_D))\exp(-\delta_M\, t_D) - \delta_M\, V \\
\frac{dW}{dt} &= acy(t-t_D)(M-V(t-t_D)-W(t-t_D))\exp(-\delta_M\, t_D) - \delta_M\, W
\end{aligned} \tag{A5}$$

For instance, the model above corresponds to Koella's [8] mosquito submodel, which, coupled to a SIR human model through the same force of infection considered here, was used as a starting point to study the co-evolution of immunity and immune-evasion in vector-borne diseases [9].

A1.1 Calculation of $F(t)$

In order to show the equivalence of the mosquito submodel to the single Eq. (S16) of the RM model under the assumptions listed in the main text, we need first to derive a useful expression for $F(t)$, the rate at which the number of infectious mosquitoes increases. Let us start by writing an integral version of Eq. (S15):

$$W(t) = W(t_0) + \int_{t_0}^{t} a\, c\, y(\hat{t})\, X(\hat{t})\, p(t-\hat{t})\, d\hat{t} \tag{A6}$$

where $p(t-\hat{t})$ is the probability for an infected mosquito at time $\hat{t}$ to be still alive and infectious at time t. After being infected, mosquitoes would become infectious after certain time, T_D, the extrinsic incubation period, but, only if they are still alive at this time. In general, the variable T_D will follow certain probability distribution (see Fig A1). Since mosquito life span, T_S, is not reduced by the *Plasmodium* incubation process, the probability kernel, $p(t-t_0)$, factorizes as a product of two probabilities:

$$p(t-t_0) = \mathbf{Pr}\left\{T_D < t-t_0\right\}\, \mathbf{Pr}\left\{T_S > t-t_0\right\} \tag{A7}$$

The first factor in Eq (A7) is, by definition, the probability distribution function (pdf) of the extrinsic incubation period. The second is the probability of mosquito living longer than $t-t_0$, which is trivially related to the pdf of mosquito live span, T_s, which, under a density-independent, constant death rate, is described by the exponential distribution:

$$\mathbf{Pr}\left\{T_S > t-t_0\right\} = 1 - \mathbf{Pr}\left\{T_S < t-t_0\right\} = \exp(-\delta_M(t-t_0)) \tag{A8}$$

The rate at which infectious mosquito population increases, $F(t)$ (see Eq. (S91)) can be obtained from Eq. (A6). For simplicity, let us choose t_0 as the time at which there are no infectious mosquitoes in the sytem ($W(t_0)=0$), and take time derivatives of Eq. (A6):

$$\frac{dW}{dt} = \int_{t_0}^{t} a\, c\, y(\hat{t})\, X(\hat{t})\, \frac{dp}{dt}\, d\hat{t} \tag{A9}$$

where we have used the fact that the evaluation of the integrand at the upper boundary, t, of the integral is equal to zero. The time derivative of the probability kernel produces two terms:

$$\frac{dp}{dt} = \exp(-\delta_M\, x)\, \frac{d\Phi}{dx} - \delta_M\, p(x) \tag{A10}$$

where $x = t-\hat{t}$ and $\Phi(x) = \mathbf{Pr}\left\{T_D < x\right\}$, whose derivative is a probability density function, $f(x)$, the one associated to the extrinsic incubation period. By introducing Eq. (A10) into (A9), and remembering $W(t_0)=0$, we obtain:

$$\frac{dW}{dt} = \int_{t_0}^{t} a\, c\, y(\hat{t})\, X(\hat{t})\, \exp(-\delta_M\,(t-\hat{t}))\, f(t-\hat{t})\, d\hat{t} - \delta_M W(t) \tag{A11}$$

Therefore, we can identify the rate $F(t)$, initially appearing in Eq. (S91), as:

$$F(t) = \int_{t_0}^{t} a\, c\, y(\hat{t})\, X(\hat{t})\, \exp(-\delta_M\, (t - \hat{t}))\, f(t - \hat{t})\, d\hat{t} \tag{A12}$$

which is the expression in the main text (see Eq. (A1)) as we wanted to show.

The rate $F(t)$ involves a probability density, $f(\tau)$, describing the extrinsic incubation period T_D. This time period has been modeled by using a gamma distribution (see Fig A1) throughout our work.

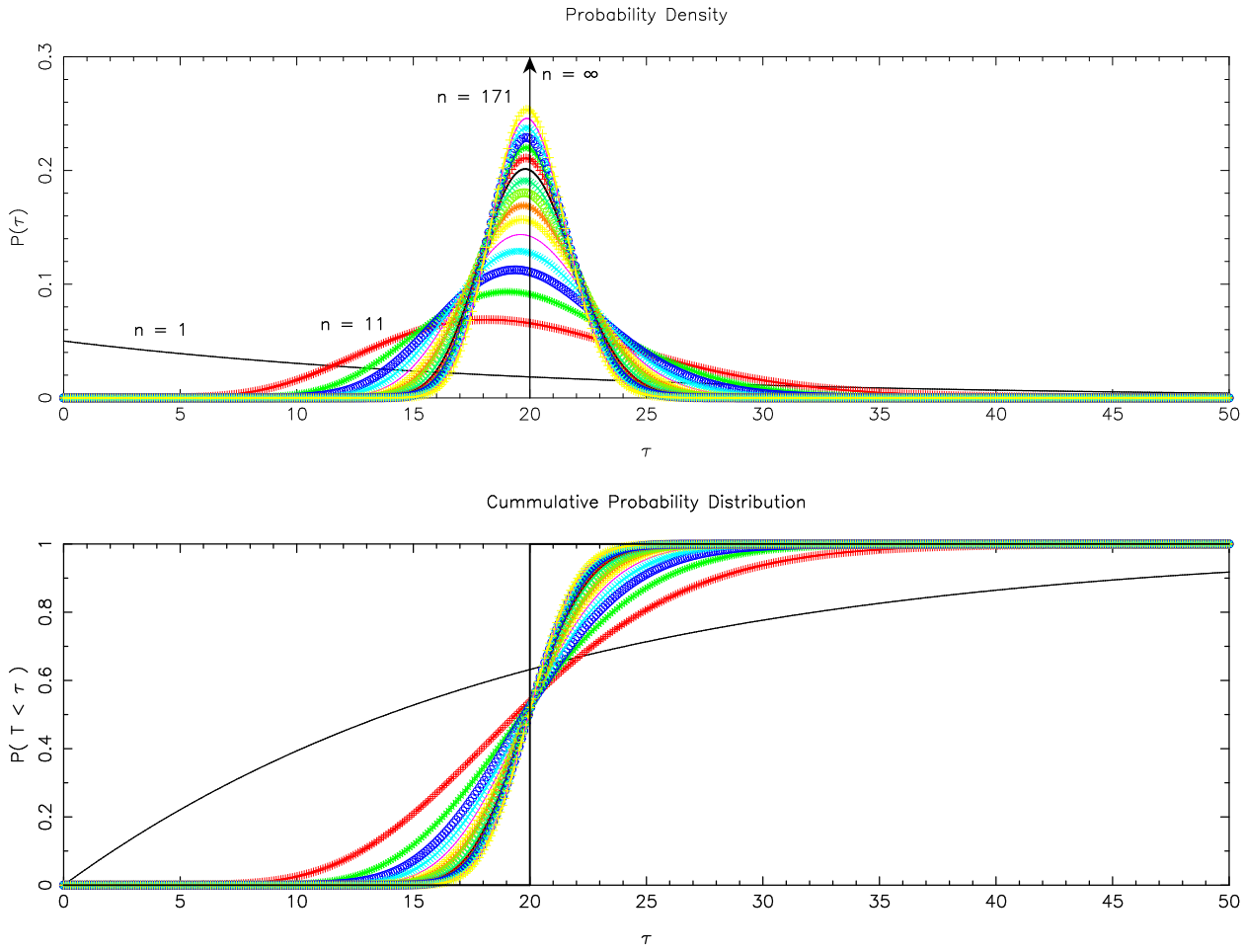

Figure A1: **The gamma distribution.** In the upper panel, we represent the gamma probability density for increasing values the parameter n, for $n = 1, 11, 21, \ldots, 171$. All probability densisty functions share the same expected value, $\langle \tau \rangle = 20.0$. In our paper, they have been used to model both the extrinsic incubation period, T_D, and the human incubation period. The probability density with $n = 1$ corresponds to an exponential distribution. The limit case $n = \infty$ corresponds to a Dirac δ distribution —represented by the vertical arrow— for which the variance of the probability distribution has collapsed to zero, and the value $\tau = 20$ has probability one. In the lower panel, we show the corresponding cummulative distribution functions in the same color codes. The corresponding distribution in the limit $n = \infty$ is a step function (thick black line).

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