

The epidemic threshold of vector-borne diseases with seasonality

The case of cutaneous leishmaniasis in Chichaoua, Morocco

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Abstract Cutaneous leishmaniasis is a vector-borne disease transmitted to humans by sandflies. In this paper, we develop a mathematical model which takes into account the seasonality of the vector population and the distribution of the latent period from infection to symptoms in humans. Parameters are fitted to real data from the province of Chichaoua, Morocco. We also introduce a generalization of the definition of the basic reproduction number R_0 which is adapted to periodic environments. This R_0 is estimated numerically for the epidemic in Chichaoua; $R_0 \simeq 1.94$. The model suggests that the epidemic could be stopped if the vector population were reduced by a factor $(R_0)^2 \simeq 3.76$.

Keywords Vector-borne disease · Seasonality · Epidemic threshold

Mathematics Subject Classification (2000) 92D30 · 35Q80

1 Introduction

Leishmaniasis is a complex of vector-borne diseases caused by protozoa of the genus *Leishmania*. The parasite is transmitted to humans through bites of female sandflies (Diptera: Psychodidae: Phlebotominae). The disease is endemic in many regions of Africa, South and Central America, southern Europe,

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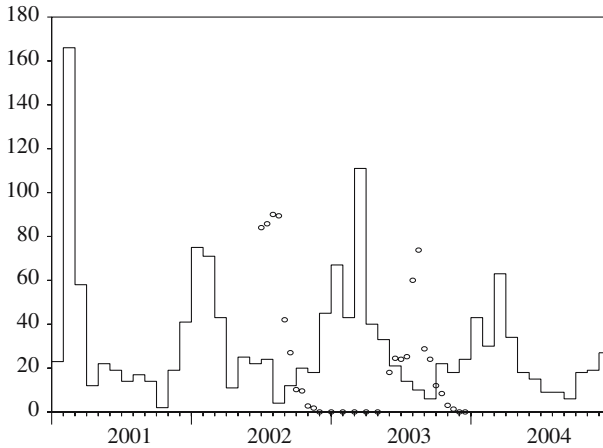


Fig. 1 Horizontal axis: time. Left vertical axis and solid line: monthly number of reported cases of cutaneous leishmaniasis in Imi'Ntanout, province of Chichaoua, Morocco. Dots (scale irrelevant): evolution of the population of *Phlebotomus sergenti*, the probable vector [10]

Asia and the Middle East. Leishmaniasis includes four major eco-epidemiological entities: zoonotic and anthroponotic visceral leishmaniasis (VL), and zoonotic and anthroponotic cutaneous leishmaniasis (CL). In anthroponotic forms, humans are considered to be the sole source of infection for the sandfly vector; in zoonotic transmission cycles, animals are reservoirs which maintain and disseminate the *Leishmania* parasites. Each year, there are about 500,000 new human cases of VL and about 1–1.5 million cases of CL in the world [7]. VL is fatal if untreated. CL is generally self-healing but can leave disfiguring scars.

According to the Moroccan Ministry of Public Health [19], anthroponotic CL due to *Leishmania tropica* is an emerging disease in the province of Chichaoua: 1877 cases have been officially reported between the beginning of 2000 and the end of 2004. Figure. 1 shows the monthly evolution of the number of cases reported in the city of Imi'Ntanout, which represents about 80% of the cases in the province, between the beginning of the year 2001 and the end of the year 2004. A few cases (43 in total) had already been observed in the year 2000, but the detailed monthly report is not available. Field investigation [10] has shown that sandflies of the species *Phlebotomus sergenti* are responsible for the transmission and that the transmission is anthroponotic: no animal reservoir such as dogs has been detected for this particular epidemic. Figure. 1 also shows estimations of the population of *Phlebotomus sergenti* obtained by traps one or two times per month from June 2002 until December 2003 (PhD work of S. Guernaoui). Notice that the population of vectors falls to zero between December and May. This is due to the special life cycle of sandflies in this area: during these months, only the eggs and larvae survive hidden in the ground. As the temperature rises at the beginning of each summer, larvae transform to flying adults. The transformation stops when the cold days reappear.

The purpose of this work is to develop a mathematical model of this epidemic, to estimate some of the parameters of the transmission cycle and to estimate the classical epidemic threshold R_0 which measures in some sense the amount of effort necessary to stop the epidemic. Interestingly, this particular study has led us to a new general definition of the basic reproduction number R_0 in a periodic environment.

Various models have already been developed for epidemics of cutaneous leishmaniasis [3–5, 11, 15, 20]. Only one [3] simulates a fluctuating vector population but without mathematical analysis or field data.

For our model, we emphasize in fact two points. First, there are marked seasonal fluctuations in the population of vectors; the most simple models are obtained by assuming that the population of vectors is periodic with a period equal to one year. Secondly, there is a delay of several months between infection – which occurs in summer or falls when the population of vectors is non-zero – and the number of symptomatic human cases – which is highest in winter and spring (see Fig. 1).

The oldest mathematical models of vector-borne diseases go back to Ross [21], who studied malaria. Our model can be seen as an extension of the “second” model of Ross, as it is called in the work of Lotka [16]: the population of vectors is split between susceptible vectors and infected vectors, whereas the humans are split between susceptible, infected and immune. Moreover, the population of vectors is assumed to undergo periodic fluctuations. Numerical investigations on the influence of seasonality for vector-borne diseases appear for example in [1, p. 404]; mathematical results in relationship with Floquet’s theory for periodic differential equations appear in [12, 13] and [8, p. 148]. Notice in [13, §2.3] that the definition of the epidemic threshold supposed to replace the basic reproduction number R_0 for a periodic vector population is rather awkward: it is the spectral radius of a matrix which is similar (in the sense of matrix theory) but not equal to the next-generation matrix when specialized to a constant vector population. These works also do not include any delay between infection and symptoms in humans other than an exponentially distributed one. It is clear from Fig. 1 that a constant delay would give a poor fit to data for the epidemic of cutaneous leishmaniasis in Imi’Ntanout since the population of vectors is nonzero during six months but human cases occur all year round. A distributed delay is needed. The first models in epidemiology including distributed delays go back to Kermack and McKendrick [17] and involve partial differential equations. Very few works combine distributed delays with the influence of periodicity in the context of epidemiology: this is the case in [23], but the discussion focuses mainly on exponential distributions. However, several works discuss general distributions in other areas of population dynamics: periodic birth rates in linear continuous-time demographic models were considered by Coale [6] using Fourier techniques; periodic Volterra integral equations were considered by Thieme [22] in an abstract setting with an application to plant populations; branching processes in a periodic environment were considered in [14]; optimal harvesting of an age-structured population with periodic birth

rates was considered in [2]. Reference [22] provides the theoretical background for the study of the linearization of the model we present.

In short, from the general point of view of population dynamics, our contribution is to make more explicit the definition of the epidemic threshold R_0 for vector-borne diseases with a periodic population of vectors – the definition seems to be new even if the incubation period were exponentially distributed so that the model could be reduced to a system of ordinary differential equations – and to provide an algorithm for its computation. From the point of view of epidemiology, our contribution is to estimate some parameters in the transmission of cutaneous leishmaniasis during an epidemic in Morocco: we estimate the time between infection and symptoms by a Gamma distribution with mean 6 months and standard deviation 1.5 months; we finally arrive at the estimate $R_0 \simeq 1.94$. The model suggests that the epidemic could be stopped if the population of vectors were reduced by a factor $(R_0)^2 \simeq 3.76$.

The plan is the following. Section 2 presents the system of differential equations used to model the epidemic. Section 3 analyzes the model, in particular the stability of the infection-free state. Section 4 presents a simulation with parameters chosen so as to fit the epidemic data from the city of Imi’Ntan-out. The epidemic threshold R_0 is then estimated for this particular epidemic. Section 5 introduces a general definition of the basic reproduction number R_0 in a periodic environment and discusses its relationship with some previous works.

2 The model

Set

$s(t)$: number of susceptible sandflies at time t ;

$i(t)$: number of infectious sandflies;

$S(t)$: number of susceptible humans;

$I(t, \tau)$: infectious humans at time t structured by the time τ since infection;

$R(t)$: number of immune humans.

To simplify the model, we have not considered the period of time during which humans or vectors are infected but not yet infectious. The group of “immune” humans contains both humans whose symptoms have recently appeared and have been covered by cloth so that they cannot transmit the disease further, and people whose scars have healed and who have acquired some immunity. The reported cases are the new people entering state R . It is assumed that scars are covered as soon as they appear (this is of course a simplification compared to the real situation). The total number of infectious humans is $I(t) = \int_0^\infty I(t, \tau) d\tau$.

Set

$P = S(t) + I(t) + R(t)$: total human population;

$p(t) = s(t) + i(t)$: total sandfly population;

$\Lambda(t)$: emergence rate of sandflies;

μ : mortality of sandflies;

- β : biting rate of sandflies;
- $\alpha(\tau)$: rate of advance from infection to immunity in humans;
- γ : rate of loss of immunity;
- π : transmission probability of CL per bite from sandfly to human;
- $\widehat{\pi}$: transmission probability of CL per bite from human to sandfly.

The model consists of the following equations

$$s'(t) = \Lambda(t) - \mu s(t) - \beta \widehat{\pi} s(t) \frac{I(t)}{P}, \tag{1}$$

$$i'(t) = \beta \widehat{\pi} s(t) \frac{I(t)}{P} - \mu i(t), \tag{2}$$

$$S'(t) = -\beta \pi i(t) \frac{S(t)}{P} + \gamma R(t), \tag{3}$$

$$I(t, 0) = \beta \pi i(t) \frac{S(t)}{P}, \quad \frac{\partial I}{\partial t}(t, \tau) + \frac{\partial I}{\partial \tau}(t, \tau) = -\alpha(\tau) I(t, \tau), \tag{4}$$

$$R'(t) = \int_0^\infty \alpha(\tau) I(t, \tau) d\tau - \gamma R(t), \tag{5}$$

with some initial conditions $s(0), i(0), S(0), I(0, \tau)$ and $R(0)$. Notice that $p(t) = s(t) + i(t)$ satisfies $p'(t) = \Lambda(t) - \mu p(t)$, and that $P = S(t) + I(t) + R(t)$ is indeed a constant. If $f(\tau)$ is the probability distribution of the time elapsed from infection to symptoms in humans and $g(\tau)$ the probability of not having developed symptoms τ units of time after infection, then

$$g(\tau) = 1 - \int_0^\tau f(\sigma) d\sigma = \exp\left(-\int_0^\tau \alpha(\sigma) d\sigma\right). \tag{6}$$

Therefore, $\alpha(\tau) = f(\tau)/[1 - \int_0^\tau f(\sigma) d\sigma]$.

3 Analysis

Assume that $\Lambda(t)$ is a periodic function of period T . Then system (1)–(5) has an infection-free periodic solution given by $s(t) = p(t), i(t) = 0, S(t) = P, I(t) = R(t) = 0$, where $p(t)$ is the unique periodic solution of $p'(t) = \Lambda(t) - \mu p(t)$. Its stability can be studied by linearizing the system. One gets

$$\tilde{i}'(t) = \beta \widehat{\pi} p(t) \frac{\tilde{I}(t)}{P} - \mu \tilde{i}(t), \tag{7}$$

$$\tilde{I}(t, 0) = \beta \pi \tilde{i}(t), \quad \frac{\partial \tilde{I}}{\partial t}(t, \tau) + \frac{\partial \tilde{I}}{\partial \tau}(t, \tau) = -\alpha(\tau) \tilde{I}(t, \tau), \tag{8}$$

with an initial condition $\tilde{i}(0, \tau) = \tilde{i}_0(\tau)$ and $\tilde{I}(0, \tau) = \tilde{I}_0(\tau)$. This system involves both a linear ordinary differential equation and a linear partial differential equation. To have a more symmetric discussion, let us introduce $i(t, \tau)$, where τ is the time since infection in sandflies, and the column vector $J(t, \tau) = (\tilde{i}(t, \tau), \tilde{I}(t, \tau))$. Then

$$\begin{aligned} \frac{\partial J}{\partial t}(t, \tau) + \frac{\partial J}{\partial \tau}(t, \tau) &= \begin{pmatrix} -\mu & 0 \\ 0 & -\alpha(\tau) \end{pmatrix} J(t, \tau) \\ J(t, 0) &= \begin{pmatrix} 0 & \frac{\beta \widehat{\pi} p(t)}{P} \\ \beta \pi & 0 \end{pmatrix} \int_0^\infty J(t, \tau) \, d\tau, \end{aligned}$$

with $J(0, \tau) = J_0(\tau) = (\tilde{i}_0(\tau), \tilde{I}_0(\tau))$. Hence,

$$\begin{aligned} J(t, 0) &= \int_0^t \begin{pmatrix} 0 & \frac{\beta \widehat{\pi} p(t)}{P} e^{-\int_0^\tau \alpha(\sigma) \, d\sigma} \\ \beta \pi e^{-\mu \tau} & 0 \end{pmatrix} J(t - \tau, 0) \, d\tau \\ &+ \int_t^\infty \begin{pmatrix} 0 & \frac{\beta \widehat{\pi} p(t)}{P} e^{-\int_{t-t}^\tau \alpha(\sigma) \, d\sigma} \\ \beta \pi e^{-\mu t} & 0 \end{pmatrix} J_0(\tau - t) \, d\tau. \end{aligned}$$

Set $u(t) = J(t, 0)$. Then the previous equation is of the form

$$u(t) = \int_0^t A(t, \tau) u(t - \tau) \, d\tau + \bar{u}(t), \tag{9}$$

where $A(t, \tau)$ is T -periodic in t and $\bar{u}(t)$ is a given function. Notice that the coefficient $A_{i,j}(t, \tau)$ in line i and column j of the matrix $A(t, \tau)$ is the expected number of individuals of type i (type 1 stands for vectors, type 2 for humans) that one infected individual of type j will infect per unit of time at time t if it was infected at time $t - \tau$.

Let \mathcal{E} be the set of T -periodic continuous functions with values in \mathbb{R}^2 ; with the supremum norm, this is a Banach space. The asymptotic behavior of equations such as (9) has been investigated in [22]: $u(t) \sim e^{\lambda^* t} v(t)$, where λ^* is a real number and $v \in \mathcal{E}$ is nonnegative, nonzero, and such that

$$v(t) = \int_0^\infty e^{-\lambda^* \tau} A(t, \tau) v(t - \tau) \, d\tau. \tag{10}$$

In fact, there is a unique real number λ^* for which such a nonnegative and nonzero element of \mathcal{E} can be found [14,22].

Now let R_0 be the spectral radius of the linear operator which maps $w \in \mathcal{E}$ to the function $t \mapsto \int_0^\infty A(t, \tau) w(t - \tau) \, d\tau$, also in \mathcal{E} . Recall that since this linear

operator is nonnegative, R_0 can also be characterized by the existence of a nonnegative and nonzero $w \in \mathcal{E}$ such that

$$\int_0^\infty A(t, \tau) w(t - \tau) \, d\tau = R_0 w(t). \tag{11}$$

Then R_0 has the properties of an epidemic threshold: $\lambda^* > 0$ if $R_0 > 1$, and $\lambda^* < 0$ if $R_0 < 1$.

Indeed, for all real number λ , let \mathcal{A}_λ be the linear operator which maps $w \in \mathcal{E}$ to the function $t \mapsto \int_0^\infty e^{-\lambda\tau} A(t, \tau) v(t - \tau) \, d\tau$, also in \mathcal{E} . Let R_λ be the spectral radius of \mathcal{A}_λ . Notice that this definition is consistent with the definition of R_0 . Notice also that for all λ , the linear operator \mathcal{A}_λ is nonnegative. Moreover, $\lambda_1 \leq \lambda_2$ implies $\mathcal{A}_{\lambda_1} \geq \mathcal{A}_{\lambda_2}$. The properties of the spectral radius imply that the function $\lambda \mapsto R_\lambda$ from \mathbb{R} to \mathbb{R} is decreasing. But according to equation (10), $R_{\lambda^*} = 1$. So if $R_0 > 1$, then $\lambda^* > 0$. And if $R_0 < 1$, then $\lambda^* < 0$. QED.

Notice that if $p(t)$ is a constant p , then $A(t, \tau)$ does not depend on t . In this case, considering a constant function $w(t)$ equal to a nonnegative eigenvector of the nonnegative matrix $\int_0^\infty A(\tau) \, d\tau$, we see that R_0 is the spectral radius of this matrix, which is generally called the next-generation matrix [8, p. 74]. More precisely, we get

$$R_0 = \sqrt{\frac{\beta^2 \pi \widehat{\pi}}{P} \times \frac{p}{\mu} \int_0^\infty g(\tau) \, d\tau}, \tag{12}$$

where we see the product of the mean number of humans infected by one infectious sandfly $\frac{\beta\pi}{\mu}$ with the mean number of sandflies infected by one infectious human $(\beta\widehat{\pi}p/P) \int_0^\infty g(\tau) \, d\tau$.

If $p(t)$ is not constant but T -periodic, then setting $w = (w_1, w_2)$, (11) can be rewritten as

$$\begin{aligned} \frac{\beta \widehat{\pi} p(t)}{P} \int_0^\infty g(\tau) w_2(t - \tau) \, d\tau &= R_0 w_1(t) \\ \beta \pi \int_0^\infty e^{-\mu\tau} w_1(t - \tau) \, d\tau &= R_0 w_2(t). \end{aligned}$$

Inserting the second equation into the first one, we see that if r_0 is such that there exists a nonnegative and nonzero T -periodic function $w_1(t)$ satisfying

$$p(t) \int_0^\infty g(\tau) \int_0^\infty e^{-\mu\sigma} w_1(t - \tau - \sigma) \, d\sigma \, d\tau = r_0 w_1(t), \tag{13}$$

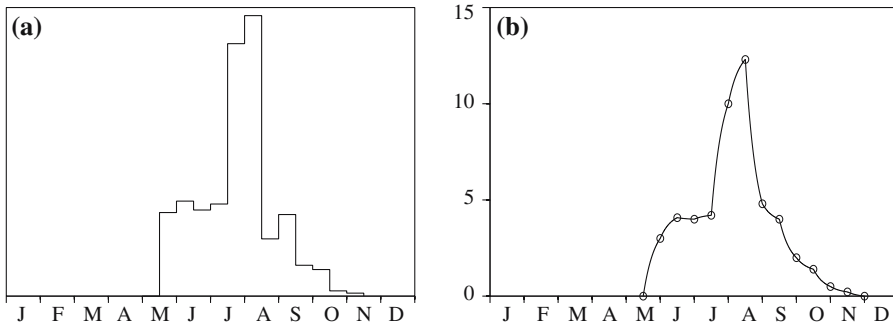


Fig. 2 **a**: emergence rate of sandflies $\bar{\lambda}(t)$. **b**: population of sandflies $\bar{p}(t)$. The line was computed using $\bar{p}'(t) = \bar{\lambda}(t) - \mu \bar{p}(t)$. The dots represent data from [10]

then

$$R_0 = \sqrt{\frac{\beta^2 \pi \hat{\pi}}{P}} \times r_0. \tag{14}$$

Formula (14) generalizes the classical formula (12) for vector-borne diseases with a seasonal (periodic) population of vectors. Notice that r_0 is a complex function of $p(t)$, $g(x)$ and μ . Obviously, r_0 is a decreasing function of μ . Besides, if $p(t)$ is replaced by $\varepsilon p(t)$, then r_0 becomes εr_0 . So the classical conclusion saying that a vector-borne disease can be eradicated if the population of vectors is divided by $(R_0)^2$ – valid a priori only for a constant population of vectors – remains true if the population of vectors is periodic provided that the definition of R_0 presented above is used.

To avoid misunderstanding, let us recall that some authors call R_0 what appears here as R_0^2 . This point is discussed briefly in [13, §2.1].

4 Simulation and estimation of R_0

Now we turn to the estimation of the parameters of the model.

The total population of Imi’Ntanout is about 5,000. However, some parts of the city are more affected than others because sandflies prefer areas where they can lay eggs, for example near garbage deposits. The present model considers only one homogeneous group. One way to deal with this is to consider that the initial susceptible population P is unknown but with the constraint $P \leq 5,000$, and should be determined in the process of fitting the epidemic curve with data.

According to current knowledge about sandflies, the life expectation $1/\mu$ of an adult sandfly is about 10 days. So we took $\mu = 3$ per month.

The sampling in Fig. 1 shows the seasonal fluctuations of the vector population up to a constant multiplicative factor from June 2002 until December 2003. We will take as the basis for the periodic population of the model the data from January to December 2003. Of course, the vector population from June to

December 2002 was not absolutely the same as from June to December 2003 because the mean monthly temperature for example can be slightly different from year to year. Let us call p_{\max} the maximum number of sandflies during the year, $\bar{p}(t) = p(t)/p_{\max}$, $\bar{\Lambda}(t) = \Lambda(t)/p_{\max}$, $\bar{s}(t) = s(t)/p_{\max}$ and $\bar{i}(t) = i(t)/p_{\max}$. Assuming that the sandfly emergence rate per month $\bar{\Lambda}(t)$ is a step function, the width of the steps being equal to the time between two observations of sandfly population, it is easy to fit the heights of the steps so that $\bar{p}(t)$ given by $\bar{p}'(t) = \bar{\Lambda}(t) - \mu \bar{p}(t)$ coincides with the data (see Fig. 2a, b). More precisely, if $\theta_k < \theta_{k+1}$ are two successive observation times, then

$$\bar{\Lambda}(t) = \bar{\Lambda}_k = \mu \frac{\exp(\mu \theta_{k+1}) \bar{p}(\theta_{k+1}) - \exp(\mu \theta_k) \bar{p}(\theta_k)}{\exp(\mu \theta_{k+1}) - \exp(\mu \theta_k)} \tag{15}$$

on the interval (θ_k, θ_{k+1}) . This choice turned out to be consistent with the data in the sense that we found $\bar{\Lambda} \geq 0$ for each interval except of course for the last interval at the end of the transmission season for which $\bar{p}(\theta_k) > 0$ and $\bar{p}(\theta_{k+1}) = 0$, and for which we took $\bar{\Lambda}(t) = 0$.

We assume that at $t = 0$, say at the beginning of the year 2000, one human imports the infection into the susceptible population. At that time, the population of vectors is zero. The initial condition will be: $s(0) = 0$, $i(0) = 0$, $S(0) = P - 1$, $I(0, \tau) = \delta_{\tau=0}$ (Dirac's mass at $\tau = 0$), and $R(0) = 0$.

To get $\alpha(\tau)$, one assumes that $f(\tau)$, the probability distribution of the time elapsed from infection to symptoms in humans, is a Gamma distribution:

$$f(\tau) = a^\nu \tau^{\nu-1} e^{-a\tau} / \Gamma(\nu). \tag{16}$$

For computational purposes, notice that when $\tau \rightarrow +\infty$:

$$\alpha(\tau) = \frac{f(\tau)}{1 - \int_0^\tau f(\sigma) d\sigma} \simeq -\frac{f'(\tau)}{f(\tau)} = a - \frac{\nu - 1}{\tau}.$$

Consider system (1)–(5). Dividing the first two equations by p_{\max} , we see that

$$\bar{s}'(t) = \bar{\Lambda}(t) - \mu \bar{s}(t) - \beta \hat{\pi} \bar{s}(t) \frac{I(t)}{P}, \quad \bar{i}'(t) = \beta \hat{\pi} \bar{s}(t) \frac{I(t)}{P} - \mu \bar{i}(t), \tag{17}$$

$$S'(t) = -\beta \pi p_{\max} \bar{i}(t) \frac{S(t)}{P} + \gamma R(t), \tag{18}$$

$$I(t, 0) = \beta \pi p_{\max} \bar{i}(t) \frac{S(t)}{P}, \quad \frac{\partial I}{\partial t}(t, \tau) + \frac{\partial I}{\partial \tau}(t, \tau) = -\alpha(\tau) I(t, \tau), \tag{19}$$

$$R'(t) = \int_0^\infty \alpha(\tau) I(t, \tau) d\tau - \gamma R(t). \tag{20}$$

Hence, $\bar{\Lambda}(t)$ and μ being known, the only unknown parameters left are: P , the product $\beta \hat{\pi}$, the product $\beta \pi p_{\max}$, γ , and the two parameters a and ν which

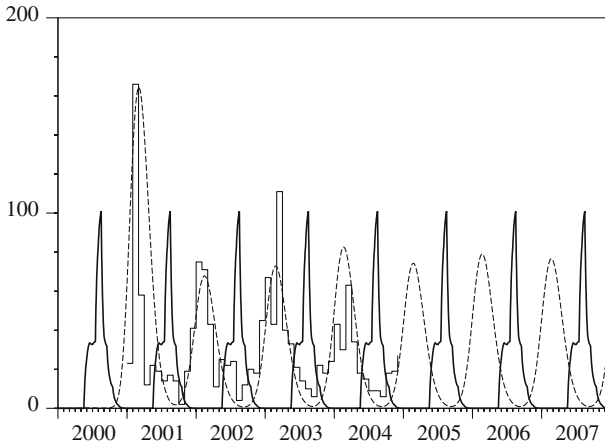


Fig. 3 Number of new cases of cutaneous leishmaniasis per month computed from the model (dotted line) and number of reported cases (step function). The population of sandflies (bold solid line) is also shown (scale irrelevant)

define $\alpha(x)$. Recall that for the Gamma distribution, v/a is the mean and \sqrt{v}/a the standard error.

Simulating system (17)–(20) with different sets of parameter values, we found that a relative good fit to the number of cases reported each month between January 2001 and December 2004 (i.e. to the data shown in Fig. 1) was obtained with $P = 800$, $\beta \hat{\pi} = 1.1$ per month, $\beta \pi p_{\max} = 16,230$ per month, $1/\gamma = 1.2$ years, $v/a = 6$ months and $\sqrt{v}/a = 1.5$ month (see Fig. 3).

Using these parameter values, one can compute numerically R_0 as defined in the previous section. First, in order to simplify Eq. (13), we use the change of variable $\theta = \tau + \sigma$ to get

$$p(t) \int_0^\infty g(\tau) e^{\mu\tau} \int_\tau^\infty e^{-\mu\theta} w_1(t - \theta) d\theta d\tau = r_0 w_1(t).$$

Integrating by parts and noticing that the “integrated term” vanishes, we arrive at

$$p(t) \int_0^\infty h(\tau) w_1(t - \tau) d\tau = r_0 w_1(t), \tag{21}$$

where we set

$$h(\tau) = e^{-\mu\tau} \int_0^\tau e^{\mu\sigma} g(\sigma) d\sigma. \tag{22}$$

Since $w_1(t)$ is T -periodic, it follows that

$$\begin{aligned} \int_0^\infty h(\tau) w_1(t - \tau) d\tau &= \int_{-\infty}^t h(t - \theta) w_1(\theta) d\theta \\ &= \int_0^t h(t - \theta) w_1(t - \theta) d\theta \\ &\quad + \sum_{n=0}^\infty \int_0^T h(t + (n + 1)T - \theta) w_1(\theta) d\theta \\ &= \int_0^t H(t - \theta) w_1(\theta) d\theta + \int_t^T H(t - \theta + T) w_1(\theta) d\theta, \end{aligned}$$

where we set

$$H(\tau) = \sum_{n=0}^\infty h(\tau + nT). \tag{23}$$

So the eigenvalue problem (21) is equivalent to

$$p(t) \left\{ \int_0^t H(t - \theta) w_1(\theta) d\theta + \int_t^T H(t - \theta + T) w_1(\theta) d\theta \right\} = r_0 w_1(t), \tag{24}$$

which can be easily approximated since it involves only the values of $w_1(t)$ on the interval $(0, T)$. Indeed, let N be a large integer, set $t_i = (i - 1)T/N$ for $i = 1 \dots N$, and let $\bar{\rho}_0$ be the spectral radius of the following matrix eigenvalue problem

$$\bar{p}(t_i) \frac{T}{N} \left\{ \sum_{j=1}^{i-1} H(t_i - t_j) W_j + \sum_{j=i}^N H(t_i - t_j + T) W_j \right\} = \bar{\rho}_0 W_i, \tag{25}$$

which is of the form $\mathcal{A} W = \bar{\rho}_0 W$, where \mathcal{A} is a $N \times N$ nonnegative matrix and $W = (W_1, \dots, W_N)$. Considering the relation (14) between R_0 and r_0 , one can conclude that

$$\sqrt{(\beta \hat{\pi}) \times (\beta \pi p_{\max}) \times \bar{\rho}_0/P} \xrightarrow{N \rightarrow +\infty} R_0.$$

The results are presented in Table 1. In practice, the terms in (25) were computed in the following way:

Table 1 Estimation of R_0 . N is the number of points discretizing the interval $(0, T)$, which represents 1 year

N	25	50	100	200	400
R_0	1.901	1.926	1.938	1.940	1.940

- For the normalized vector population $\bar{p}(t_i)$, the equation $\bar{p}'(t) = \bar{\Lambda}(t) - \mu \bar{p}(t)$ and the assumption saying that $\bar{\Lambda}(t)$ is a step function given by formula (15) imply that $\bar{p}(t_i) = e^{-\mu(t_i-\theta_k)}[\bar{p}(\theta_k) - \bar{\Lambda}_k/\mu] + \bar{\Lambda}_k/\mu$ if $\theta_k \leq t_i < \theta_{k+1}$. Recall that $\bar{p}(t)$ is shown in Fig. 2b.
- For the function $H(\tau)$, we truncated the sum (23), keeping only the first two terms. Taking more than the first two terms in the sum did not change any of the digits in Table 1. For the function $h(\tau)$, which is necessary to compute $H(\tau)$, we used equations (6) and (22) and an integration by parts to get the more practical form $h(\tau) = [e^{-\mu\tau} \int_0^\tau e^{\mu\sigma} f(\sigma) d\sigma + 1 - e^{-\mu\tau} - \int_0^\tau f(\sigma) d\sigma]/\mu$.
- The spectral radius $\bar{\rho}_0$ can be computed using numerical mathematics software such as Scilab (www.scilab.org).

Finally, it seems that $R_0 \simeq 1.94$. The epidemic could be stopped if the population of vectors were reduced by a factor $(R_0)^2 \simeq 3.76$. We have checked numerically that a simulation of system (17)–(20) of partial differential equations with the product $\beta \pi p_{\max}$ divided by 3.7 still yields an epidemic, while there is no epidemic if it is divided by 3.9. If instead of using the complicated method of this section, we had used as an approximation formula (12) with the symbol p replaced by the mean of the fluctuating $p(t)$, we would have found $R_0 \simeq 2.76$, which overestimates the effort necessary to stop the epidemic.

Currently, there are no prophylactic drugs or vaccines that can be used to prevent leishmaniasis. The breeding sites of sandflies are generally unknown, and control efforts that focus on immature stages are generally not feasible [9]. The control of leishmaniasis therefore relies upon measures taken to reduce sandfly density. Such a reduction in the number of vectors could be achieved by spraying insecticides. However, the province of Chichaoua is a poor rural area, and this solution requires probably too much money and effort compared to local resources. Nevertheless, its geographic position, halfway between two major touristic zones of Morocco, Marrakesh and Agadir, would certainly justify such an intervention even from a purely economic point of view at the national level.

5 Generalization and other possible applications

The definition of the basic reproduction number R_0 presented in this work can be generalized as follows. Let $A(t, \tau)$ be an $n \times n$ nonnegative and continuous matrix function, with $A_{i,j}(t, \tau)$ representing the expected number of individuals of type i infected per unit of time at time t by one individual of type j that was infected at time $t - \tau$. Assume that $A(t, \tau)$ is T -periodic with respect to t for all

τ , and that $\int_0^\infty A(t, \tau) d\tau$ is finite for all t . Under suitable positivity assumptions on the matrix function $A(t, \tau)$, there exists a unique real number R_0 such that there exists a nonnegative, nonzero, continuous and T -periodic vector function $w(t)$ such that

$$\int_0^\infty A(t, \tau) w(t - \tau) d\tau = R_0 w(t).$$

Moreover, if $\bar{u}(t)$ is a given vector function and $u(t)$ satisfies

$$u(t) = \int_0^t A(t, \tau) u(t - \tau) d\tau + \bar{u}(t), \tag{26}$$

then $u(t) \sim e^{\lambda^* t} v(t)$ as $t \rightarrow +\infty$, where $v(t)$ is a nonnegative T -periodic vector function such that

$$\int_0^\infty e^{-\lambda^* \tau} A(t, \tau) v(t - \tau) d\tau = v(t). \tag{27}$$

Finally, $\lambda^* > 0$ if $R_0 > 1$ and $\lambda^* < 0$ if $R_0 < 1$. The definition of R_0 can be also used in other fields of population dynamics, e.g. demography (the verb ‘‘to infect’’ should then replaced by ‘‘to give birth’’).

If $A(t, \tau)$ does not depend on t , i.e. $A(t, \tau) = A(\tau)$, then taking for $w(t)$ an eigenvector of the matrix $\int_0^\infty A(\tau) d\tau$, we see that R_0 is the spectral radius of this matrix. Besides, λ^* is the unique real number such that the spectral radius of the matrix $\int_0^\infty e^{-\lambda^* \tau} A(\tau) d\tau$ is equal to 1. Any eigenvector associated to the eigenvalue 1 of this matrix can be chosen for $v(t)$ to satisfy (27).

There is another special case for which the basic reproduction number R_0 can be computed easily, namely the case where $n = 1$ and

$$A(t, \tau) = p(t) e^{-\int_{t-\tau}^t \phi(\sigma) d\sigma} \tag{28}$$

with T -periodic functions $p(t)$ and $\phi(t)$. Indeed, the eigenvalue problem can then be rewritten as

$$p(t) \int_0^\infty e^{-\int_{t-\tau}^t \phi(\tau) d\tau} w(t - \tau) d\tau = R_0 w(t). \tag{29}$$

Deriving this equation and integrating by parts, one gets

$$\begin{aligned}
 R_0 w'(t) &= p'(t) \int_0^\infty e^{-\int_{t-\tau}^t \phi(\sigma) d\sigma} w(t-\tau) d\tau + p(t) \int_0^\infty e^{-\int_{t-\tau}^t \phi(\sigma) d\sigma} w'(t-\tau) d\tau \\
 &\quad + p(t) \int_0^\infty e^{-\int_{t-\tau}^t \phi(\sigma) d\sigma} [\phi(t-\tau) - \phi(t)] w(t-\tau) d\tau \\
 &= p'(t) \frac{R_0 w(t)}{p(t)} - p(t) \int_0^\infty \phi(t-\tau) e^{-\int_{t-\tau}^t \phi(\sigma) d\sigma} w(t-\tau) d\tau \\
 &\quad - p(t) \left[e^{-\int_{t-\tau}^t \phi(\sigma) d\sigma} w(t-\tau) \right]_0^\infty \\
 &\quad + p(t) \int_0^\infty e^{-\int_{t-\tau}^t \phi(\sigma) d\sigma} [\phi(t-\tau) - \phi(t)] w(t-\tau) d\tau \\
 &= \frac{p'(t)}{p(t)} R_0 w(t) - \phi(t) R_0 w(t) + p(t) w(t).
 \end{aligned}$$

The previous equation can be rewritten as

$$\frac{w'(t)}{w(t)} = \frac{p'(t)}{p(t)} - \phi(t) + \frac{p(t)}{R_0},$$

which can be integrated to get

$$w(t) = K p(t) e^{-\int_0^t \phi(\tau) d\tau + \frac{1}{R_0} \int_0^t p(\tau) d\tau} \tag{30}$$

where K is a positive constant. The function $w(t)$ thus obtained is T -periodic if $w(t + T) = w(t)$ for all t . Using the periodicity of $p(t)$ and $\phi(t)$, we see that this condition holds if and only if

$$R_0 = \frac{\int_0^T p(\tau) d\tau}{\int_0^T \phi(\tau) d\tau}. \tag{31}$$

Conversely, the function $w(t)$ given by (30) with R_0 given by (31) satisfies equation (29). Formula (31) appears in [18, §3.1] for an SIR epidemic model with periodic contact rate and death rate, whose linear stability analysis can be put in the form (26) with $A(t, \tau)$ of the form (28). But the authors hesitate to call R_0 the right-hand side of (31) (they call it \bar{R}) because they do not have a general definition of R_0 . This expression ‘‘appears’’ just at the end of their analysis.

The same computation (derivation, integration by parts, etc) starting from (27) shows that

$$v(t) = K p(t) e^{-\lambda^* t - \int_0^t \phi(\tau) d\tau + \int_0^t p(\tau) d\tau},$$

which is T -periodic if and only if

$$\lambda^* = \frac{1}{T} \int_0^T p(\tau) d\tau - \frac{1}{T} \int_0^T \phi(\tau) d\tau. \quad (32)$$

For this case, the epidemic threshold ($R_0 > 1$ or $\lambda^* > 0$) depends only on the mean value of $p(t)$ and $\phi(t)$. For the even more particular case where $\phi(t)$ is constant, formula (32) is the result “proved” in [23] using Fourier techniques and divergent series!

We also mention that the linear stability of the SEIR epidemic model with periodic contact rate in [18, §2] can be put in the form (26) with a 2×2 matrix $A(t, \tau)$ similar to the one from Sect. 3. As in the present paper, no closed formula for R_0 can be expected, but numerical estimation is possible.

From the point of view of applications, the definition of R_0 we propose might be used to evaluate the risk for vector-borne diseases to appear in areas that have been disease-free until now, provided that enough information is known about the vector population and the disease. This has become a popular topic in epidemiology because many people believe that the climate is getting warmer and that the tropical diseases from the “South” could appear or reappear in the “North”. We mention in particular the project called EDEN (“Emerging Diseases in a changing European eNvironment”, www.eden-fp6project.net).

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