Threshold dynamics in mathematical models for mosquito- and rodent-borne diseases with seasonality

Outline of Ph.D. Thesis

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Introduction

My thesis is concerned with periodic mathematical models for the spread of two different mosquito-borne diseases and a rodent-borne disease. In particular, it presents compartmental population models for the transmission dynamics of malaria, Zika virus and Lassa virus diseases in a seasonal environment.

The main aim of the thesis was to investigate the impact of the periodicity of weather on the spread of the above mentioned diseases by applying non-autonomous mathematical models with time-dependent parameters. The basic reproduction number $\mathcal{R}_0$ is defined as the spectral radius of a linear integral operator and the global dynamics is determined by this threshold parameter: if $\mathcal{R}_0 < 1$, then the disease-free periodic solution is globally asymptotically stable , while if $\mathcal{R}_0 > 1$, then the disease remains endemic in the population and there exist at least a positive ω-periodic solution. Numerical simulations to illustrate and support the analytical results are given. Additionally, we provide numerical studies and give examples to describe what kind of parameter changes might lead to a periodic recurrence of the disease.

The thesis is based on the following publications of the author:

- M. A. Ibrahim and A. Dénes. A mathematical model for Lassa fever transmission dynamics in a seasonal environment with a view to the 2017–20 epidemic in Nigeria. *Nonlinear Analysis: Real World Applications*, 60:103310, 2021. https://doi.org/10.1016/j.nonrwa.2021.103310.

- M. A. Ibrahim and A. Dénes. Threshold and stability results in a periodic model for malaria transmission with partial immunity in humans. *Applied Mathematics and Computation*, 392:125711, 2021. https://doi.org/10.1016/j.amc.2020.125711

- M. A. Ibrahim and A. Dénes. Threshold dynamics in a model for Zika virus disease with seasonality. *Bulletin of Mathematical Biology*, 83:27, 2021. https://doi.org/10.1007/s11538-020-00844-6

Threshold and stability results in a periodic model for malaria spread with partial immunity in humans

Malaria

Malaria is an acute febrile illness caused by *Plasmodium* microorganisms spread to humans by female *Anopheles* mosquitoes. The latest malaria report of WHO from December 2019 estimated around 230 million malaria cases and more than 400,000

deaths in both of the preceding two years [15]. In a person without immunity, symptoms usually appear ten to fifteen days after infection. The symptoms of the disease, including fever, headache, and chills are often mild, making malaria difficult to recognize at early stages. *P. falciparum* malaria can develop to a serious, often lethal illness if not treated within one day. Children suffering from severe malaria often show severe anemia, respiratory distress or cerebral malaria [15], while multi-organ failure is frequent in infected adults. In regions where the disease is endemic, several years of exposure may contribute to a partial immunity, making asymptomatic infections are possible. It is important to note that heterozygotes for the sickle gene (AS) also have a partial protection against malaria [8].

Mathematical model

In our model, human population is divided into two types based on their immunity level: the non-immune, i.e. those who have not developed any immunity against malaria, and the semi-immune, that is those who have some partial immunity due to their genetics or by contracting the disease earlier in their life. Semi-immune human, non-immune human and mosquito compartments are denoted by the lower indices m, n and v. Susceptible humans (S_m and S_n) can be infected by malaria. Following the infectious mosquito bite, susceptibles proceed to the exposed compartment (E_m, E_n). Individuals in these compartments have no symptoms yet. After the incubation time, exposed individuals proceed to the infectious class (I_m, I_n). For semi-immune, there is an additional immune compartment (R_m). Humans in the class R_m are partially immune to the disease, but their blood stream still has a low level of parasites and they are still able to infect susceptible mosquitoes [5]. We have three compartments for the mosquitoes: susceptibles (S_v), exposed (E_v) and infected (I_v).

We denote the total population of humans by $N_h(t)$ and total population of mosquitoes by $N_v(t)$, that is

$$\begin{aligned} N_h(t) &= S_n(t) + E_n(t) + I_n(t) + S_m(t) + E_m(t) + I_m(t) + R_m(t), \\ N_v(t) &= S_v(t) + E_v(t) + I_v(t). \end{aligned}$$

With the above notations, our model equations can be written as

$$\begin{aligned} S_n^{'}(t) &= \theta\mu_h - \tilde{\alpha}_n(t)\frac{I_v(t)}{N_h(t)}S_n(t) - d_h S_n(t), \\ E_n^{'}(t) &= \tilde{\alpha}_n(t)\frac{I_v(t)}{N_h(t)}S_n(t) - \nu_n E_n(t) - d_h E_n(t), \\ I_n^{'}(t) &= \nu_n E_n(t) - \gamma_n I_n(t) - (d_h + \delta_n) I_n(t), \\ S_m^{'}(t) &= (1-\theta)\mu_h - \tilde{\alpha}_m(t)\frac{I_v(t)}{N_h(t)}S_m(t) - d_h S_m(t) + \beta R_m(t), \end{aligned}$$

$$
\begin{aligned}
E_m^{'}(t) &= \tilde{\alpha}_m(t)\frac{I_v(t)}{N_h(t)}S_m(t) - \nu_m E_m(t) - d_h E_m(t), \\
I_m^{'}(t) &= \nu_m E_m(t) - \gamma_m I_m(t) - (d_h + \delta_m) I_m(t), \\
R_m^{'}(t) &= \gamma_n I_n(t) + \gamma_m I_m(t) - \beta R_m(t) - d_h R_m(t), \\
S_v^{'}(t) &= \tilde{\mu}_v(t) - \tilde{\alpha}_v(t)\frac{\eta_n I_n(t) + \eta_m I_m(t) + \eta_r R_m(t)}{N_h(t)}S_v(t) - \tilde{d}_v(t)S_v(t), \\
E_v^{'}(t) &= \tilde{\alpha}_v(t)\frac{\eta_n I_n(t) + \eta_m I_m(t) + \eta_r R_m(t)}{N_h(t)}S_v(t) - \nu_v E_v(t) - \tilde{d}_v(t)E_v(t), \\
I_v^{'}(t) &= \nu_v E_v(t) - \tilde{d}_v(t) I_v(t),
\end{aligned}
\tag{1}
$$

where $\tilde{\mu}_v(t)$, $\tilde{\alpha}_n(t)$, $\tilde{\alpha}_m(t)$, $\tilde{\alpha}_v(t)$ and $\tilde{d}_v(t)$ are the mosquito birth rate, the rate of transmission from an infected mosquito to a non-immune susceptible human, transmission rate from an infectious mosquito to susceptible semi-immune humans, the transmission rate from infected humans to susceptible mosquitoes and mosquito death rate, respectively. In our model we assumed $\tilde{\mu}_v(t)$, $\tilde{\alpha}_n(t)$, $\tilde{\alpha}_m(t)$, $\tilde{\alpha}_v(t)$ and $\tilde{d}_v(t)$ to be continuous, positive ω-periodic functions. In our present work, motivated by [3, 7] we set up and study a compartmental population model for malaria transmission in a periodically changing environment: we extend the model given in [7] by including periodicity of the environment.

System (1) has a single disease-free periodic solution

$$
E_0 = \big(S_n^*, 0, 0, S_m^*, 0, 0, 0, S_v^*(t), 0, 0\big),
$$

with $S_n^* = \theta\frac{\mu_h}{d_h}$, $S_m^* = (1-\theta)\frac{\mu_h}{d_h}$ and

$$
S_v^*(t) = \left[\int_0^t \tilde{\mu}_v(r) e^{\int_0^r \tilde{d}_v(s)ds} dr + \frac{\int_0^\omega \tilde{\mu}_v(r) e^{\int_0^r \tilde{d}_v(s)ds} dr}{e^{\int_0^\omega \tilde{d}_v(s)ds} - 1}\right] e^{-\int_0^t \tilde{d}_v(s)ds} > 0.
$$

To introduce the following result, we set $h^L = \sup_{t\in[0,\omega)} h(t)$ and $h^M = \inf_{t\in[0,\omega)} h(t)$ for a positive, continuous ω-periodic function $h(t)$.

Lemma 3.1. *There is $N_v^* = \frac{\mu_v^L}{d_v^M} > 0$ such that each solution in X of (1) eventually enters*

$$
G_{N^*} := \left\{ (S_n, E_n, I_n, S_m, E_m, I_m, R_m, S_v, E_v, I_v) \in \mathbb{R}_+^{10} : \begin{array}{c} N_h \leqslant N_h^*, \\ N_v \leqslant N_v^* \end{array} \right\},
$$

and for each $N_v(t) \geqslant N_v^*$, G_N is positively invariant for system (1). Also, we have that

$$
\lim_{t\to+\infty} (N_v(t) - S_v^*(t)) = 0.
$$

Following the technique introduced by Wang and Zhao [13], we identify the basic reproduction number $\mathcal{R}_0$ for system (1) and show the local stability of the disease-free periodic solution E_0. Based on the results so far, we can formulate the following

theorem concerning the local stability properties of the disease-free periodic solution E_0 of (1).

Theorem 3.1. *The disease-free periodic solution E_0 is locally asymptotically stable if $\mathcal{R}_0 < 1$, while it is unstable in the case $\mathcal{R}_0 > 1$.*

Threshold dynamics

We show the global stability of the disease-free periodic solution E_0 and the extinction of the disease if $\mathcal{R}_0$ is less than 1, as well as the persistence of malaria and the existence of a positive periodic solution of (1) if $\mathcal{R}_0$ is larger than 1.

Theorem 3.2. *If $\delta_n = 0$, $\delta_m = 0$ and $\mathcal{R}_0 < 1$, then the disease-free periodic solution E_0 of (1) is globally asymptotically stable and if $\mathcal{R}_0 > 1$, then it is unstable.*

Let us introduce the notations

$$X := \left\{(S_n, E_n, I_n, S_m, E_m, I_m, R_m, S_v, E_v, I_v) \in \mathbb{R}_+^{10}\right\},$$

$$X_0 := \left\{ (S_n, E_n, I_n, S_m, E_m, I_m, R_m, S_v, E_v, I_v) \in X : \begin{array}{l} E_n > 0, I_n > 0, \\ E_m > 0, I_m > 0, \\ R_m > 0, E_v > 0, \\ I_v > 0 \end{array} \right\},$$

and $\partial X_0 := X \setminus X_0$.

Let $P\colon \mathbb{R}_+^{10} \to \mathbb{R}_+^{10}$ defined as the Poincaré map corresponding to (1), i.e. the map P is defined as

$$P(x^0) = u(\omega, x^0), \qquad x^0 \in \mathbb{R}_+^{10},$$

with $u(t, x^0)$ being the single solution of (1) started from initial condition $x^0 \in \mathbb{R}_+^{10}$.

Lemma 3.2. *If the basic reproduction number $\mathcal{R}_0$ is larger than 1, then there exists a $\sigma > 0$ such that for any $(S_n^0, E_n^0, I_n^0, S_m^0, E_m^0, I_m^0, R_m^0, S_v^0, E_v^0, I_v^0) \in X_0$ with*

$$\| (S_n^0, E_n^0, I_n^0, S_m^0, E_m^0, I_m^0, R_m^0, S_v^0, E_v^0, I_v^0) - E_0 \| \leqslant \sigma,$$

we have $\limsup_{m\to\infty} d\left(P^m\left(S_n^0, E_n^0, I_n^0, S_m^0, E_m^0, I_m^0, R_m^0, S_v^0, E_v^0, I_v^0\right), E_0\right) \geqslant \sigma$.

Lemma 3.1. *X_0 and ∂X_0 are positively invariant w.r.t. the flow defined by (1).*

Theorem 3.3. *Assume $\mathcal{R}_0 > 1$. Then (1) admits at least one positive periodic solution and there is an $\varepsilon > 0$ s.t.*

$$\liminf_{t\to\infty} E_n(t) \geqslant \varepsilon, \quad \liminf_{t\to\infty} I_n(t) \geqslant \varepsilon, \quad \liminf_{t\to\infty} E_m(t) \geqslant \varepsilon, \quad \liminf_{t\to\infty} I_m(t) \geqslant \varepsilon,$$
$$\liminf_{t\to\infty} R_m(t) \geqslant \varepsilon, \quad \liminf_{t\to\infty} E_v(t) \geqslant \varepsilon, \quad \liminf_{t\to\infty} I_v(t) \geqslant \varepsilon,$$

for all $(S_n^0, E_n^0, I_n^0, S_m^0, E_m^0, I_m^0, R_m^0, S_v^0, E_v^0, I_v^0) \in X_0$.

Numerical simulations

Here we show numerical simulations regarding our model to illustrate and support the theoretical results of the previous sections. We show some simulations to demonstrate that our time-periodic model is in accordance with seasonally fluctuation. The functions $\tilde{\mu}_v(t)$, $\tilde{\alpha}_n(t)$, $\tilde{\alpha}_m(t)$, $\tilde{\alpha}_v(t)$ and $\tilde{d}_v(t)$ are time-periodic with one year as a period and, following e.g. [3], they are assumed to be of the form

$$\begin{aligned} \tilde{\alpha}_i(t) =& \alpha_i \cdot \left(\sin\left(\tfrac{2\pi}{p}t + b\right) + a\right), \qquad i = n, m, v, \\ \tilde{\mu}_v(t) =& \mu_v \cdot \left(\sin\left(\tfrac{2\pi}{p}t + b\right) + a\right), \qquad \tilde{d}_v(t) = d_v \cdot \left(\cos\left(\tfrac{2\pi}{p}t + b\right) + a\right), \end{aligned}$$

where p is period length (given in months), a, b are free adjustment parameters and μ_v, α_n, α_m, α_v and d_v are the (constant) baseline values of the corresponding time-dependent parameters.

In order to show that the single disease-free periodic solution E_0 is globally asymptotically stable if the basic reproduction number is less than unity, we provide a couple of examples. Our first example, was created with $\mathcal{R}_0 = 0.625 < 1$. In our second example, was created with another set of parameters and $\mathcal{R}_0 = 0.913 < 1$. By Theorem 3.3, system (1) has a positive ω-periodic solution if $\mathcal{R}_0 > 1$. Accordingly, one can see that, the disease compartments are persistent and the epidemic becomes endemic in the population recurring periodically every year.

The reproduction numbers were calculated as a function of the parameters α_n, α_m, α_v, μ_v and d_v. Our simulations suggest that vector control is an important factor in malaria transmission and that mosquito control, above all the control of mosquito births, may prove to be sufficient in controlling the disease. At the same time, personal protection resulting in a decrease of transmission rates is also an important tool to reduce the basic reproduction number.

Threshold dynamics in a model for Zika virus disease with seasonality

Zika virus disease

Zika virus disease or Zika fever is a mosquito-borne disease caused by the Zika virus (ZIKV). Zika virus is chiefly spread in tropical and subtropical regions by the bite of infected female mosquitoes from the *Aedes* genus (by *Aedes aegypti* above all) [see, e.g., 10], the same species that is responsible for dengue, chikungunya and yellow fever transmission. Zika virus is also spread via sexual contacts, principally from men to women. Studies suggest that ZIKV might remain in male genital secretions for a longer period (up to six months) than in other bodily fluids, hence,

in this way, a transmission of the disease is possible even several months after recovery. Mothers can transmit the disease to their fetus during pregnancy or during delivery. This transmission might result in microcephaly and further congenital malformations. These are collectively denominated as congenital Zika syndrome. The incubation period of Zika virus disease is around 3–14 days. Most of the infected people do not show any symptoms or only mild ones including fever, rash, muscle and joint pain, conjunctivitis and headache, in general lasting for 2–7 days [14].

Mathematical model

We divide the total human population into six compartments: susceptible $S_h(t)$, exposed $E_h(t)$, symptomatically infected $I_s(t)$, asymptomatically infected $I_a(t)$, convalescent $I_r(t)$, and recovered $R(t)$ at time $t > 0$, while the vector population is divided into three classes: susceptible $S_v(t)$, exposed $E_v(t)$ and infectious $I_v(t)$ individuals.

The total human population $N_h(t)$ and the total mosquito population $N_v(t)$ are given by:

$$\begin{aligned} N_h(t) &= S_h(t) + E_h(t) + I_a(t) + I_s(t) + I_r(t) + R(t), \\ N_v(t) &= S_v(t) + E_v(t) + I_v(t). \end{aligned}$$

Our model takes the form

$$\begin{aligned} S_h'(t) &= \mu_h - \beta \frac{\tau_e E_h(t) + \tau_a I_a(t) + I_s(t) + \tau_r I_r(t)}{N_h(t)} S_h(t) - \frac{\tilde{\alpha}_h(t)}{N_h(t)} I_v(t) S_h(t) \\ &\quad - d_h S_h(t), \\ E_h'(t) &= \beta \frac{\tau_e E_h(t) + \tau_a I_a(t) + I_s(t) + \tau_r I_r(t)}{N_h(t)} S_h(t) + \frac{\tilde{\alpha}_h(t)}{N_h(t)} I_v(t) S_h(t) \\ &\quad - \nu_h E_h(t) - d_h E_h(t), \\ I_a'(t) &= q\nu_h E_h(t) - \gamma_a I_a(t) - d_h I_a(t), \\ I_s'(t) &= (1-q)\nu_h E_h(t) - \gamma_s I_s(t) - d_h I_s(t), \\ I_r'(t) &= \gamma_a I_a(t) + \gamma_s I_s(t) - \gamma_r I_r(t) - d_h I_r(t), \\ R'(t) &= \gamma_r I_r(t) - d_h R(t), \\ S_v'(t) &= \tilde{\mu}_v(t) - \tilde{\alpha}_v(t) \frac{\eta_e E_h(t) + \eta_a I_a(t) + I_s(t)}{N_h(t)} S_v(t) - \tilde{d}_v(t) S_v(t), \\ E_v'(t) &= \tilde{\alpha}_v(t) \frac{\eta_e E_h(t) + \eta_a I_a(t) + I_s(t)}{N_h(t)} S_v(t) - \nu_v E_v(t) - \tilde{d}_v(t) E_v(t), \\ I_v'(t) &= \nu_v E_v(t) - \tilde{d}_v(t) I_v(t), \end{aligned} \tag{2}$$

where $\tilde{\mu}_v(t)$, $\tilde{\alpha}_h(t)$, $\tilde{\alpha}_v(t)$ and $\tilde{d}_v(t)$ denote mosquito birth rate, transmission rate from an infectious mosquito to a susceptible human, the transmission rate from infected humans to susceptible mosquitoes and mosquito death rate, respectively. In our

model we assumed $\tilde{\mu}_v(t)$, $\tilde{\alpha}_h(t)$, $\tilde{\alpha}_v(t)$ and $\tilde{d}_v(t)$ to be continuous, positive ω-periodic functions. An individual may progress from susceptible (S_h) to exposed (E_h) upon contracting the disease. An exposed individual moves either to the symptomatically infected class I_s or to the asymptomatically infected class I_a, depending on whether that person shows symptoms or not. Infected people with or without symptoms move to the convalescent compartment I_r including those who have already recovered, but who can still transmit the disease via sexual contact. After the convalescent period, one moves to the recovered compartment R. Mosquitoes may progress from susceptible (S_v) to exposed (E_v) and then to infectious (I_v) class.

To determine the disease-free periodic solution of (2), we study equation

$$S_v'(t) = \tilde{\mu}_v(t) - \tilde{d}_v(t)S_v(t) \tag{3}$$

with initial value $S_v(0) \in \mathbb{R}_+$. Equation (3) has a single positive ω-periodic solution $S_v^*(t)$, globally attractive in $\mathbb{R}_+$ and thus, system (2) has a single disease-free periodic solution $E_0 = \big(N_h^*, 0, 0, 0, 0, N_h^*, S_v^*(t), 0, 0\big)$.

Lemma 4.1. *There exists an* $N_v^* = \frac{\tilde{\mu}_v^L}{\tilde{d}_v^L} > 0$ *such that every forward solution in*

$$X := \left\{ (S_h, E_h, I_a, I_s, I_r, N_h, S_v, E_v, I_v) \in \mathbb{R}_+^9 : \begin{array}{l} N_h \geqslant S_h + E_h + I_a + I_s + I_r, \\ N_v \geqslant S_v + E_v + I_v \end{array} \right\},$$

of (2) *eventually enters*

$$G_{N^*} := \{(S_h, E_h, I_a, I_s, I_r, N_h, S_v, E_v, I_v) \in X : N_h \leqslant N_h^*,\ S_v + E_v + I_v \leqslant N_v^* < \infty\}$$

and for each $N_v(t) \geqslant N_v^*$, G_N *is positively invariant for* (2). *Further, it holds that*

$$\lim_{t \to +\infty} (N_v(t) - S_v^*(t)) = 0.$$

Threshold dynamics

Here we study the global stability of the disease-free equilibrium of model (2) and the persistence of the infectious compartments. We use the general theory for the extinction or persistence of infectious given by [11] to show that if the basic reproduction ratio $\mathcal{R}_0$ is less than 1, then the unique disease-free equilibrium $\mathcal{X}^*(t) = \big(0, 0, 0, 0, 0, 0, N_h^*, N_h^*, S_v^*(t)\big)$ is globally asymptotically stable (G.A.S.) and the disease dies out, while if the basic reproduction ratio $\mathcal{R}_0$ is larger than 1, the disease persists. Moreover, we prove the existence of a positive periodic solution of (2) if $\mathcal{R}_0 > 1$.

Theorem 4.1. *If $\mathcal{R}_0 < 1$, then the disease-free periodic solution $\mathcal{X}^*(t)$ is globally asymptotically stable and if $\mathcal{R}_0 > 1$, then it is unstable.*

Theorem 4.2. *If $\mathcal{R}_0 > 1$ then system (2) is persistent with respect to E_h, I_a, I_s, I_r, E_v and I_v.*

Define

$$X := \left\{(S_h, E_h, I_a, I_s, I_r, N_h, S_v, E_v, I_v) \in \mathbb{R}^9_+\right\},$$
$$X_0 := \left\{(S_h, E_h, I_a, I_s, I_r, N_h, S_v, E_v, I_v) \in \mathbb{R}_+ \times \mathrm{Int}(\mathbb{R}^4_+) \times \mathbb{R}^2_+ \times \mathrm{Int}(\mathbb{R}^2_+)\right\}$$

and

$$\partial X_0 := X \setminus X_0 = \{(S_h, E_h, I_a, I_s, I_r, N_h, S_v, E_v, I_v) : E_h I_a I_s I_r E_v I_v = 0\}.$$

Let $P\colon \mathbb{R}^9_+ \to \mathbb{R}^9_+$ be the Poincaré map associated with (2), that is,

$$P(x^0) = u(\omega, x^0), \quad \text{for } x^0 \in \mathbb{R}^9_+,$$

where $u(t, x^0)$ is the unique solution of (2) with $u(0, x^0) = x^0$. It is easy to see that

$$P^m(x^0) = u(m\omega, x^0), \qquad \forall m \geqslant 0.$$

Lemma 4.2. *If $\mathcal{R}_0 > 1$, then there exists a $\sigma^* > 0$ such that for any $x^0 \in X_0$, with $\|x^0 - E_0\| \leqslant \sigma^*$ we have*

$$\limsup_{m\to\infty} d\left(P^m(x^0), E_0\right) \geqslant \sigma^*.$$

Theorem 4.3. *Assume that $\mathcal{R}_0 > 1$. Then system (2) has at least one positive periodic solution and there exists an $\varepsilon > 0$ such that*

$$\liminf_{t\to\infty} E_h(t) \geqslant \varepsilon, \quad \liminf_{t\to\infty} I_a(t) \geqslant \varepsilon, \quad \liminf_{t\to\infty} I_s(t) \geqslant \varepsilon, \quad \liminf_{t\to\infty} I_r(t) \geqslant \varepsilon,$$
$$\liminf_{t\to\infty} E_v(t) \geqslant \varepsilon, \quad \liminf_{t\to\infty} I_v(t) \geqslant \varepsilon,$$

for all $(S_h(0), E_h(0), I_a(0), I_s(0), I_r(0), N_h(0), S_v(0), E_v(0), I_v(0)) \in X_0$.

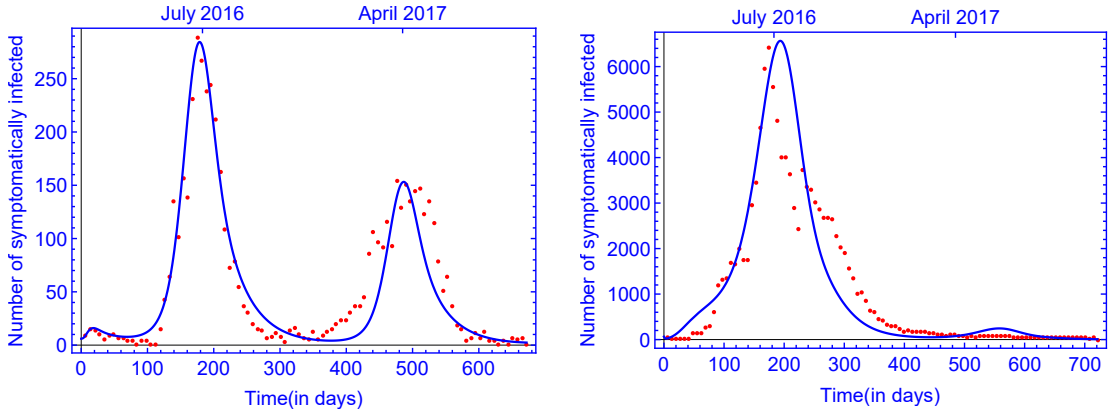
Case study for Ecuador and Colombia: what changes in the parameters might lead to a regular recurrence of Zika fever?

In this section, we apply our model to study the spread of Zika in Ecuador during the 2015–17 and in Colombia during the 2015–17 Zika virus epidemic. From Section , we see that $\mathcal{R}_0$ is a threshold parameter for the persistence of the disease in the population (see Theorems 4.1 and 4.3). The functions $\tilde{\mu}_v(t)$, $\tilde{\alpha}_h(t)$, $\tilde{\alpha}_v(t)$ and $\tilde{d}_v(t)$ are assumed to be time-periodic with one year as a period and, following e.g. [3], they are assumed to be of the form $\mu_v \cdot \left(\sin\left(\frac{2\pi}{p}t + b\right) + a\right)$, $\alpha_h \cdot \left(\sin\left(\frac{2\pi}{p}t + b\right) + a\right)$,

$\alpha_v \cdot \left(\sin\left(\frac{2\pi}{p}t + b\right) + a\right)$ and $d_v \cdot \left(\cos\left(\frac{2\pi}{p}t + b\right) + a\right)$ where p is period length, a, b are free adjustment parameters and $\mu_v, \alpha_h, \alpha_v, d_v$ are the (constant) baseline values of the corresponding time-dependent parameters.

Parameter estimation for Ecuador and Colombia

Figure 1 shows model (2) fitted to data from Ecuador and Colombia. Our model gives a reasonably good fit for both countries, reproducing the single peak of Zika fever in Colombia and the two peaks of Zika fever experienced in Ecuador in two subsequent years. This shows that model (2) is able to reproduce the two types of outcomes of the Zika epidemic observed in South America. Figure 1 is in accordance with the analytic results stating that the unique disease-free equilibrium E_0 is globally asymptotically stable when $\mathcal{R}_0 < 1$. By Theorem 4.2, system (2) is persistent with respect to the infective compartments if $\mathcal{R}_0 > 1$. We present how changes in some of



(a) *The model fitted to 2016–17 data from Ecuador when* $\mathcal{R}_0 = 0.945 < 1$.

(b) *The model fitted to 2015–17 data from colombia when* $\mathcal{R}_0 = 0.989 < 1$.

Figure 1: *The model fitted to in (a) 2016–17 data from Ecuador and in (b) 2015–17 data from Colombia when* $\mathcal{R}_0 < 1$.

the key parameters (human-to-human, human-to-mosquito and mosquito-to human transmission rates as well as mosquito birth rates) might affect the course of Zika epidemics. The simulations suggest that an increase of any of these four parameters–either due to climate change or to genetic mutation of the virus–can lead to a periodic annual reappearance of the epidemic.

For a better assessment of the effect of additional mosquito killing, we assume a periodic recurrence of the disease. We show some seasonal measures to control Zika virus disease both in Ecuador and Colombia. The result suggests that even a mosquito control limited to the peak period of mosquito abundance might have a significant impact to control the disease.

Sensitivity analysis

The PRCC-based sensitivity analysis measures the effect of the parameters on the response function (in our cases, the number of infected cases), while we vary the parameters (relevant to the dynamics of the diseases in Ecuador and Colombia) in the given ranges. Figure 2 shows the comparison of the PRCC values obtained for

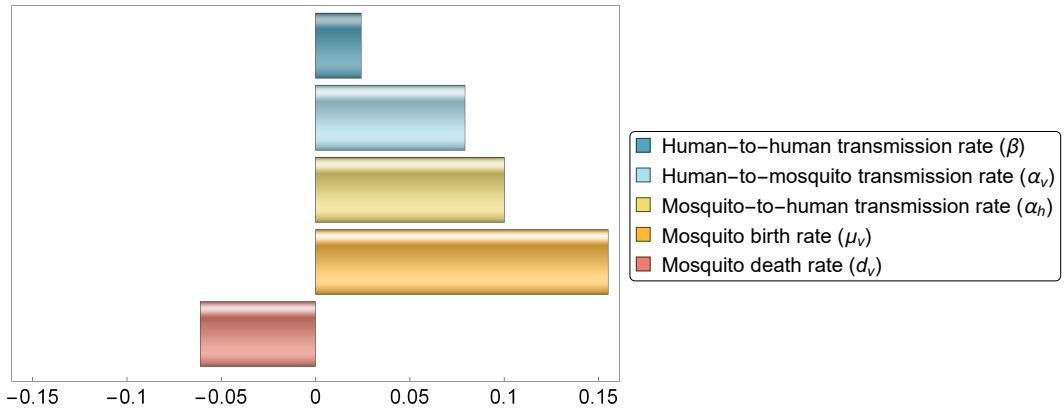


Figure 2: *Partial rank correlation coefficients of the five parameters subject to intervention measures.*

the parameters $\beta, \alpha_h, \alpha_v, \mu_v$ and d_v, i.e. those parameters which can typically be affected by control measures. The results suggest that the most relevant factors in Zika transmission, and hence in the elevation of the number of infected cases are birth and death rates of mosquitoes. Spread via sexual contacts is shown to have a smaller effect, however, it is still an important factor. Based on the sensitivity analysis, we can assess that the most effective measures to reduce transmission are control of mosquito populations and protection against their bites.

Further, by numerical calculations we get the curves of the basic reproduction ratio $\mathcal{R}_0$, the time-average basic reproduction number $[\mathcal{R}_0]$ (using the notation presented by [9]) and the basic reproduction number $\mathcal{R}_0^A$ of the autonomous model with respect to baseline value of mosquito birth rate (μ_v), human-to-human transmission rate (β), baseline value of mosquito-to-human transmission rate (α_h) and baseline value of human-to-mosquito transmission rate (α_v), respectively. The calculations show that the time-average basic reproduction number $[\mathcal{R}_0]$ is always less than the basic reproduction ratio $\mathcal{R}_0$, suggesting that the time-average basic reproduction number underestimates the disease transmission risk. From this aspect, our results are similar to those of [13]. We note that there are some other cases of underestimation and overestimation for the average basic reproduction number can be found in [1], where an approximate formula of the basic reproduction number was obtained for a class of periodic vector-borne disease models with a small perturbation parameter.

A mathematical model for Lassa fever transmission dynamics in a seasonal environment with a view to the 2017–20 epidemic in Nigeria

Lassa fever

Lassa haemorrhagic fever (LHF), or Lassa fever for short is a zoonotic, acute viral hemorrhagic fever caused by the Lassa virus from the *Arenaviridae* family [16]. LHF is usually transmitted to humans via direct or indirect exposure to food or other items contaminated with urine or feces of infected multimammate rats (*Mastomys natalensis*), through the respiratory or gastrointestinal tracts. Person-to-person transmission has also been observed [12]. The virus remains in body fluids even after recovery: in urine for 3–9 weeks from infection and for three months in male genital secretions [12]. Lassa fever is endemic among rats in parts of West Africa, while it is endemic in humans in several countries of the region. In these regions, the number of infections per year is estimated between 100,000 and 300,000, with around 5,000 deaths.

About 80% of people infected with Lassa fever have only mild or no symptoms. Symptom onset occurs usually 1–3 weeks after exposure, these include fever, tiredness, weakness, and headache. 20% of infected develop a severe multisystem disease with symptoms including bleeding gums, respiratory distress, vomiting, chest, back and abdomen pain, facial swelling, low blood pressure. Neurological problems can also be observed, such as hear loss, tremors, encephalitis [16].

Seasonal model for Lassa fever transmission

We divide the human population into six compartments: susceptible $S_h(t)$, exposed $E_h(t)$, symptomatically infected $I_s(t)$, mildly infected $I_m(t)$, treated $I_T(t)$, and recovered individuals with temporary immunity $R(t)$. The total size of the human population at any time t is denoted by

$$N_h(t) = S_h(t) + E_h(t) + I_m(t) + I_s(t) + I_T(t) + R(t).$$

An individual may proceed from susceptible (S_h) to exposed (E_h) upon contracting the disease. Individuals in the exposed compartment have no symptoms yet. After the incubation time, an exposed individual moves either to the symptomatically infected class (I_s) or to the mildly infected class (I_m), depending on whether that person shows symptoms or not. Infected people from I_s may move to the treated compartment (I_T), including those who need hospital treatment. After the infection period, recovered persons move to the class R.

The vector population (*Mastomys natalensis* rat) at time t, denoted by $N_r(t)$, is divided into three compartments: susceptible $S_r(t)$, exposed $E_r(t)$ and infectious $I_r(t)$, respectively. Thus $N_r(t) = S_r(t) + E_r(t) + I_r(t)$.

Our model takes the form

$$
\begin{aligned}
\frac{\mathrm{d}S_h(t)}{\mathrm{d}t} &= \Pi_h - \frac{\beta_m I_m(t) + \beta_s I_s(t) + \beta_{_T} I_{_T}(t)}{N_h(t)} S_h(t) - \beta_{rh}\frac{I_r(t)}{N_h(t)} S_h(t) - dS_h(t) \\
&\quad + \xi R(t), \\
\frac{\mathrm{d}E_h(t)}{\mathrm{d}t} &= \frac{\beta_m I_m(t) + \beta_s I_s(t) + \beta_{_T} I_{_T}(t)}{N_h(t)} S_h(t) + \beta_{rh}\frac{I_r(t)}{N_h(t)} S_h(t) - \nu_h E_h(t) \\
&\quad - dE_h(t), \\
\frac{\mathrm{d}I_m(t)}{\mathrm{d}t} &= \theta\nu_h E_h(t) - \gamma_m I_m(t) - dI_m(t), \\
\frac{\mathrm{d}I_s(t)}{\mathrm{d}t} &= (1-\theta)\nu_h E_h(t) - \gamma_s I_s(t) - (d+\delta_s) I_s(t), \\
\frac{\mathrm{d}I_{_T}(t)}{\mathrm{d}t} &= \gamma_s I_s(t) - \gamma_{_T} I_{_T}(t) - (d+\delta_{_T}) I_{_T}(t), \\
\frac{\mathrm{d}R(t)}{\mathrm{d}t} &= \gamma_m I_m(t) + \gamma_{_T} I_{_T}(t) - \xi R(t) - dR(t), \\
\frac{\mathrm{d}S_r(t)}{\mathrm{d}t} &= \tilde{\Pi}_r(t)\left(1 - \frac{N_r(t)}{K(t)}\right) N_r(t) - \beta_{hr}\frac{\eta_s I_s(t) + \eta_{_T} I_{_T}(t)}{N_h(t)} S_r(t) - \mu S_r(t) \\
&\quad - \beta_r \frac{I_r(t)}{N_r(t)} S_r(t), \\
\frac{\mathrm{d}E_r(t)}{\mathrm{d}t} &= \beta_{hr}\frac{\eta_s I_s(t) + \eta_{_T} I_{_T}(t)}{N_h(t)} S_r(t) + \beta_r \frac{I_r(t)}{N_r(t)} S_r(t) - \nu_r E_r(t) - \mu E_r(t), \\
\frac{\mathrm{d}I_r(t)}{\mathrm{d}t} &= \nu_r E_r(t) - \mu I_r(t),
\end{aligned}
\tag{4}
$$

where $\tilde{\Pi}_r(t)$ and $K(t)$ denote the time-dependent per capita birth rate and maximal carrying capacity of the *Mastomys natalensis* rats. In our model we assumed $\tilde{\Pi}_r(t)$ and $K(t)$ are continuous, positive ω-periodic functions. We denote by Π_h and d the human birth and death rate, respectively. There is also an additional disease-induced death rate, denoted by δ_s and $\delta_{_T}$ for those in the compartments I_s and $I_{_T}$, respectively.

To identify the disease-free periodic solution of (4), consider

$$
\frac{\mathrm{d}S_r(t)}{\mathrm{d}t} = \tilde{\Pi}_r(t)\left(1 - \frac{S_r(t)}{K(t)}\right) S_r(t) - \mu S_r(t), \tag{5}
$$

with initial condition $S_r(0) \in \mathbb{R}_+$. Equation (5) has a unique positive ω-periodic solution $S_r^*(t)$. Thus, system (4) has a unique disease-free periodic solution $E_0 = \left(S_h^*, 0, 0, 0, 0, 0, S_r^*(t), 0, 0\right)$, where $S_h^* = \frac{\Pi_h}{d}$.

Lemma 5.1. *There is* $N_r^* = \limsup_{t\to\infty} \frac{K(t)(\tilde{\Pi}_r(t)-\mu)}{\tilde{\Pi}_r(t)} > 0$ *such that any forward solution in* $\mathbb{R}_+^9$ *of* (4) *enters eventually*

$$
\Omega_{N_r^*} := \left\{(S_h, E_h, I_m, I_s, I_{_T}, R, S_r, E_r, I_r) \in \mathbb{R}_+^9 : N_h \leqslant N_h^*,\ N_r \leqslant N_r^*\right\},
$$

and for each $N_r(t) \geqslant N_r^*$, Ω_N *is a positively invariant set w.r.t.* (4). *Further, it holds that*

$$\lim_{t\to+\infty} (N_r(t) - S_r^*(t)) = 0.$$

Based on the method established by Wang and Zhao [13], we demonstrate the local stability of the disease-free periodic equilibrium E_0 of (4) in terms of the basic reproduction number $\mathcal{R}_0$.

Theorem 5.1. *The disease-free periodic solution* E_0 *of* (4) *is locally asymptotically stable if* $\mathcal{R}_0 < 1$, *whereas it is unstable if* $\mathcal{R}_0 > 1$.

Threshold dynamics

We show the dynamics of our model depending on the basic reproduction number. We prove the existence of a positive periodic solution of model (4) if the basic reproduction number $\mathcal{R}_0 > 1$. In this case, the disease persists, whereas if the basic reproduction number $\mathcal{R}_0 < 1$, then the unique disease-free equilibrium E_0 is globally asymptotically stable and the disease goes extinct.

Theorem 5.2. *If* $\mathcal{R}_0 < 1$, *then the disease-free periodic solution* E_0 *of* (4) *is globally asymptotically stable and if* $\mathcal{R}_0 > 1$, *then it is unstable.*

Define

$$X \coloneqq \left\{(S_h, E_h, I_m, I_s, I_T, R, S_r, E_r, I_r) \in \mathbb{R}_+^9\right\},$$

$$X_0 \coloneqq \left\{(S_h, E_h, I_m, I_s, I_T, R, S_r, E_r, I_r) \in X : \begin{array}{l} E_h > 0, I_m > 0, I_s > 0, \\ I_T > 0, E_r > 0, I_r > 0 \end{array}\right\},$$

and

$\partial X_0 \coloneqq X \setminus X_0$.

Let $P\colon \mathbb{R}_+^9 \to \mathbb{R}_+^9$ denote the Poincaré map corresponding to (4), then P is given by

$$P(x^0) = u(\omega, x^0), \quad \text{for } x^0 \in \mathbb{R}_+^9,$$

where $u(t, x^0)$ is the unique solution of (4) with initial condition $x^0 \in X$. Clearly,

$$P^m(x^0) = u(m\omega, x^0), \qquad \forall m \geqslant 0.$$

Lemma 5.1. *The sets* X_0 *and* ∂X_0 *are both positively invariant w.r.t. the flow defined by* (4).

Lemma 5.2. *If* $\mathcal{R}_0 > 1$, *then there exists a* $\sigma > 0$ *such that for any* $\phi \in X_0$ *with* $\|\phi - E_0\| \leqslant \sigma$, *we have*

$$\limsup_{m\to\infty} d\left(P^m(\phi), E_0\right) \geqslant \sigma.$$

Theorem 5.3. *Assume that $\mathcal{R}_0 > 1$. Then system (4) has at least one positive periodic solution and there exists an $\varepsilon > 0$ such that*

$$\liminf_{t\to\infty} \left(E_h(t), I_m(t), I_s(t), I_T(t), R(t), E_r(t), I_r(t)\right)^T \geqslant \left(\varepsilon, \varepsilon, \varepsilon, \varepsilon, \varepsilon, \varepsilon, \varepsilon\right)^T,$$

for all $\phi \in X_0$.

A case study – Lassa fever in Nigeria 2017–2020

We use our model to study the spread of Lassa fever in Nigeria during the epidemic in November 2017 to May 2020. Simulation results are provided to demonstrate that our model with periodic parameters is well aligned with seasonal fluctuation data.

The functions $\tilde{\Pi}_r(t)$ and $K(t)$ are assumed to be time-periodic with one year as a period and, following e.g. [2, 6], they are supposed to be of the form

$$\tilde{\Pi}_r(t) = \Pi_r \cdot \left(a + \sin\left(\tfrac{2\pi(t+b)}{p}\right)\right) \quad \text{and} \quad K(t) = K_r \cdot \left(1 - \Lambda\cos\left(\tfrac{2\pi(t+b)}{p}\right)\right),$$

where p is period length, a is free adjustment parameter, Λ is the amplitude of seasonality, b is phase angle and (Π_r, K_r) are the (constant) baseline values of the corresponding time-dependent parameters.

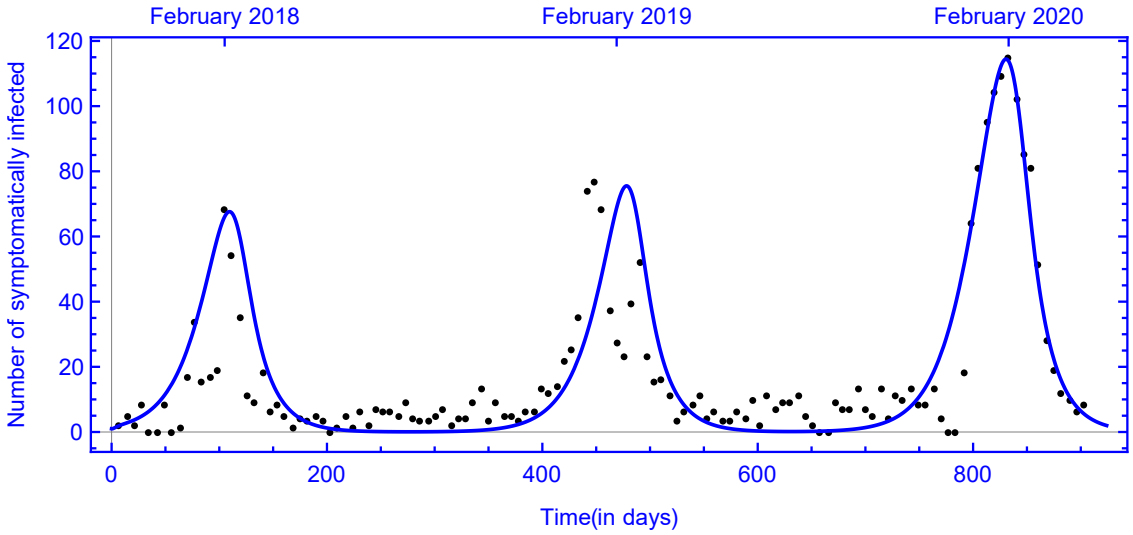


Figure 3: *Fitting the model to the data for the 2017-2020 Lassa outbreaks in Nigeria.*

Figure 3 shows model (4) fitted to data from Nigeria [4]. Our model provides a reasonably good fit, generating the three peaks of Lassa fever happened in the last three seasons in Nigeria.

In this study, one of our core concerns was to see what changes in the parameters might trigger a periodic reappearance of the epidemic. Since we have a large number

of parameters, it is not easy to rigorously determine which of the parameters play the most important role in the variation of the dynamics, so we are just attempting to explain the possible changes through a few examples.

Numerically, with the same set of parameter values used in the extinction case except human-to-human transmission (β_s) and the rodent-related parameters ($\beta_{rh}, \beta_r, \Pi_r, \mu, K_r$), we calculated the value of the basic reproduction number $\mathcal{R}_0 = 3.2678 > 1$, i.e. we increased human-to-human, rodent-to-human and rodent-to-rodent transmission rates, rodent death rate and maximal carrying capacity of rodents, while rodent birth rate was decreased. Accordingly, it can be seen that the disease compartments are persistent with these parameters, and the epidemic becomes endemic in the population periodically recurring annually. We have computed all constant and periodic parameters by using some published data and studied LHF in Nigeria. The fitted curve based on our model reflects the seasonal fluctuation and coincide in quite well with the reported data. The reproduction numbers were estimated as a function of the parameters $K_r, \Pi_r, \beta_s, \beta_{hr}, \beta_{rh}$ and β_r. The calculations show that the basic reproduction number $\mathcal{R}_0^A$ underestimates the disease transmission risk.

Our model enables us to evaluate what kind of parameter changes might trigger a periodic recurrence of LHF. Using numerical simulations, we observed that the human-to-human transmission rate has a substantial impact on the prevalence of the disease, but the most significant factors in Lassa's periodic recurrence are the rodent related parameters.

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