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

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ABSTRACT

In this paper, we formulate and study a compartmental model for Lassa fever transmission dynamics considering human-to-human, rodent-to-human transmission and the vertical transmission of the virus in rodents. To incorporate the impact of periodicity of weather on the spread of Lassa, we introduce a non-autonomous model with time-dependent parameters for rodent birth rate and carrying capacity of the environment with respect to rodents. We introduce the basic reproduction number and show that it can be used as a threshold parameter concerning the global dynamics. It also shown that the disease-free periodic solution is globally asymptotically stable in the case of $\mathcal{R}_0 < 1$ and if $\mathcal{R}_0 > 1$, then the disease persists. We show numerical studies for the Lassa fever in Nigeria and give examples to describe what kind of parameter changes might trigger the periodic recurrence of Lassa fever.

1. Introduction

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 [1]. The disease was first described in the 1950s, though the virus causing it was only identified in 1969 [2]. The disease was named after the Nigerian town Lassa, where the first cases were observed. 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 [3]. 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 [3]. 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

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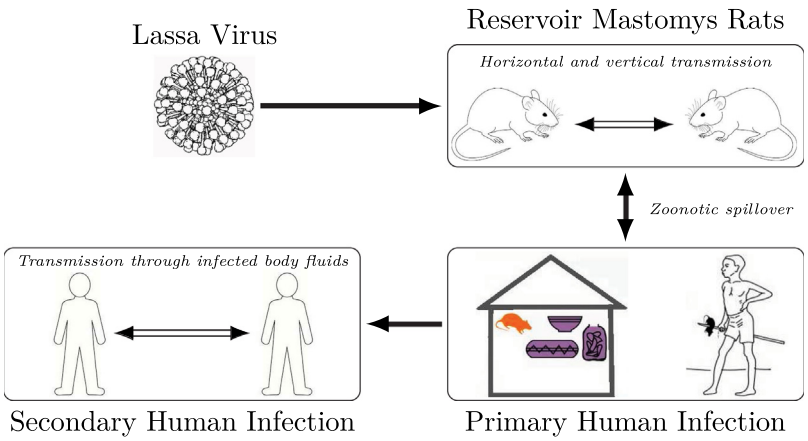


Fig. 1. Lassa fever transmission. The figure shows modes of transmission (human-to-human, human-to-rodent, rodent-to-human and rodent-to-rodent).

per year is estimated between 100,000 and 300,000, with around 5000 deaths. Lassa menaces mostly those who live in rural areas where multimammate rats are present, especially where poor sanitation and crowded living conditions are typical. Fig. 1 shows the possible methods of LHF transmission.

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. Approximately 1% of infections result in death due to multi-organ failure. However, the disease is particularly severe in women in the third trimester of their pregnancy, with high rates of maternal death (29%) observed, while an estimated 80%–95% fetal and neonatal mortality is reported [1,4,5].

Treatment of Lassa fever includes antiviral medication, fluid replacement and blood transfusions. For women in late pregnancy, inducing delivery is necessary.

Although Lassa fever appears in WHO's Blueprint list of diseases to be prioritized for research and development [6], compared with other infectious diseases, a relatively small number of mathematical modelling studies have been published up to now. Onah et al. [7] extended an *SIR*–*SI*-type compartmental model by introducing different control intervention measures, e.g. external protection, treatment, isolation and rodent control. They used optimal control theory to determine how to reduce disease transmission with minimal cost. Musa et al. [8] established a model describing the interaction between humans and rodents including quarantine, isolation and hospitalization. The authors showed the presence of a forward bifurcation with a stability switch between the disease-free and the endemic equilibrium. Also, they fitted the model to data from 2016–19 to find that initial susceptibility increased across the three outbreaks in these years. Zhao et al. [9] studied the epidemiological features of Lassa epidemics in various regions of Nigeria. They assessed the connection between the reproduction number and rainfall. They determined the infectivity of Lassa by the reproduction number estimated from four types of growth models. They fitted the models to Lassa surveillance data and estimated the reproduction number in various regions. Akhmetzanov et al. [10] applied a model to study the datasets of human infection, population changes of rodents as well as weather changes to quantify the seasonal drivers of Lassa fever transmission. They obtained that seasonal migration of rats plays a key role in regulating the periodicity of Lassa epidemics. The peak exposure of humans to rats is shortly after the beginning of the dry season and correlates with the mating period of rodents.

Although some of the above works put an emphasis on the time-changing nature of Lassa transmission dynamics, so far, no compartmental model with time-dependent parameters has been established. In

this work, we set up and study a compartmental epidemic model for Lassa fever transmission dynamics considering infected humans with mild or severe symptoms, treatment, human-to-human and rodent-to human transmission as well as time-dependent parameters. Namely, modelling the annual periodic change of weather, we introduce time-periodic parameters for rodent birth rate and carrying capacity of the environment with respect to rodents. To study the dynamics of our time-periodic model, we will apply the theory initiated in [11–15], later applied in several periodic epidemic models (see, e.g. [16–23]). Here we adapt these methods to our system with human-to-human and rodent-to-human transmission with a logistic growth of rodents.

The rest of the paper is structured as follows. In the next section we introduce the time-dependent mathematical model for Lassa fever transmission dynamics. In Section 3 we study the existence of the disease-free periodic solution. In Section 4 we calculate the basic reproduction number of our model using various methods. In Section 5, we show that depending on the basic reproduction number, either the disease-free periodic solution is globally asymptotically stable or the disease persists in the population. In Section 6 we provide numerical simulations for both scenarios supporting the theoretical results.

2. 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.

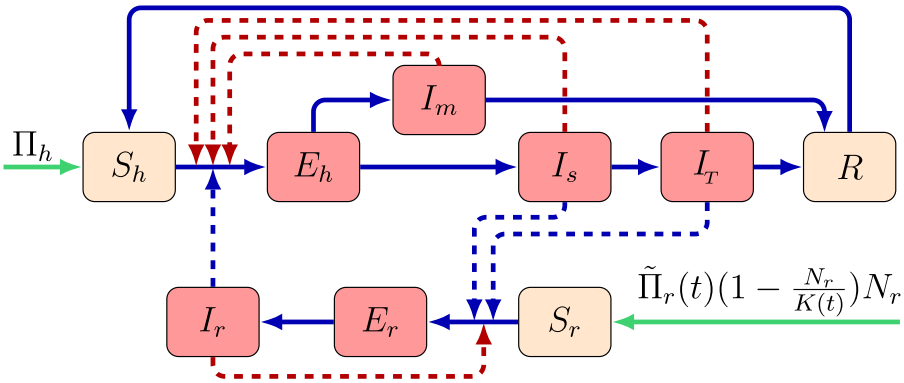


Fig. 2. Schematic diagram of the LHF transmission among rodents and humans. Red nodes denote infectious, brown nodes denote non-infectious states. Blue solid arrows demonstrate infection progress, while red dashed arrows represent direction of human-to-human transmission and rodent-to-rodent transmission. Blue dashed arrows show direction of transmission between humans and rodents. Green arrows show recruitment rate for humans and maximum growth rate of the rodents. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

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

$$N_r(t) = S_r(t) + E_r(t) + I_r(t).$$

Table 1
Description of parameters of model (1).

Parameters	Description
Π_h	Recruitment rate for humans
d	Natural death rates of humans
δ_s, δ_T	Disease-induced death rates for humans
$\beta_m, \beta_s, \beta_T$	Transmission rates from human-to-human
β_{hr}	Transmission rate from human-to-rodent
β_{rh}	Transmission rate from rodent-to-human
β_r	Transmission rate from rodent-to-rodent
η_s, η_T	Relative transmissibility of infectious human-to-rodent
θ	Proportion of mild infections
γ_s	Progression rate from I_s to I_T
γ_m, γ_T	Recovery rates
ν_h	Humans incubation rate
ν_r	Rodents incubation rate
ξ	Rate of relapse from R to S_h
K_r	Average carrying capacity of the environment for the rodents
Π_r	Baseline value of rodents birth rate
μ	Natural death rates of rodents
b	Phase angle (month of peak in seasonal forcing)
Λ	Amplitude of seasonality

The transmission dynamics is shown in the flow diagram (see Fig. 2) and our model takes the form

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

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 δ_T for those in the compartments I_s and I_T, respectively. The description of the model parameters are summarized in Table 1.

3. The disease-free periodic solution

3.1. Existence of the disease-free ω-periodic solution

In this section, we study the existence and uniqueness of the disease-free periodic solution of system (1). Define

$$\phi = \big(S_h(0), E_h(0), I_m(0), I_s(0), I_T(0), R(0), S_r(0), E_r(0), I_r(0)\big) \in \mathbb{R}_+^9.$$

In case of no disease, for the total human population N_h with a positive initial condition $\phi \in \mathbb{R}_+^9$, we have the equation

$$\frac{\mathrm{d}N_h(t)}{\mathrm{d}t} = \Pi_h - dN_h(t), \tag{2}$$

from which we obtain

$$N_h(t) = N_h(0)e^{-dt} + \frac{\Pi_h}{d}(1 - e^{-dt}). \tag{3}$$

with an arbitrary initial value $N_h(0)$. Eq. (3) has a unique equilibrium $N_h^* = \frac{\Pi_h}{d}$ in $\mathbb{R}_+$. Consequently, $|N_h(t) - N_h^*| \to 0$ as $t \to \infty$ and N_h^* is globally attractive on $\mathbb{R}_+$.

To identify the disease-free periodic solution of (1), consider

$$\frac{\mathrm{d}S_r(t)}{\mathrm{d}t} = \tilde{\Pi}_r(t)\left(1 - \frac{S_r(t)}{K(t)}\right)S_r(t) - \mu S_r(t), \tag{4}$$

with initial condition $S_r(0) \in \mathbb{R}_+$. Eq. (4) has a unique positive ω-periodic solution

$$S_r^*(t) = \frac{e^{\int_0^t (\tilde{\Pi}_r(s)-\mu)\,ds}}{\int_0^t \frac{\tilde{\Pi}_r(\tau)}{K(\tau)} e^{\int_0^\tau (\tilde{\Pi}_r(s)-\mu)\,ds}\,d\tau + \frac{\int_0^\omega \frac{\tilde{\Pi}_r(\tau)}{K(\tau)} e^{\int_0^\tau (\tilde{\Pi}_r(s)-\mu)\,ds}\,d\tau}{e^{\int_0^\omega (\tilde{\Pi}_r(s)-\mu)\,ds} - 1}} > 0, \tag{5}$$

which is globally attractive in $\mathbb{R}_+$. Thus, system (1) has a unique disease-free periodic solution $E_0 = \big(S_h^*, 0, 0, 0, 0, 0, S_r^*(t), 0, 0\big)$, where $S_h^* = \frac{\Pi_h}{d}$.

Lemma 3.1. *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 (1) 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. (1). Further, it holds that

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

Proof. From (1), we have

$$\begin{aligned}\frac{\mathrm{d}N_r(t)}{\mathrm{d}t} &= \tilde{\Pi}_r(t)\left(1 - \frac{N_r(t)}{K(t)}\right)N_r(t) - \mu N_r(t)\\ &\leqslant \left(\tilde{\Pi}_r(t) - \mu - \frac{\tilde{\Pi}_r(t)}{K(t)}N_r(t)\right)N_r(t) \leqslant 0 \quad \text{if } N_r(t) \geqslant N_r^*,\end{aligned}$$

which implies that Ω_N, $N_r(t) \geqslant N_r^*$, is positively invariant and each forward orbit enters Ω_{N^*} eventually. For the second part of the proof, let us assume that $z(t) = N_r(t) - S_r^*(t),\ t \geqslant 0$. Then, it follows that

$$\frac{\mathrm{d}z(t)}{\mathrm{d}t} = -\mu z(t),$$

which implies that $\lim_{t\to+\infty} z(t) = 0$. □

4. Basic reproduction numbers and local stability

Based on the method established by Wang and Zhao [14], we demonstrate the local stability of the disease-free periodic equilibrium E_0 of (1) in terms of the basic reproduction number $\mathcal{R}_0$.

Linearizing the system (1) at E_0, we obtain the equations for exposed and infectious human and rodent populations, respectively:

$$\begin{aligned}
\frac{\mathrm{d}E_h(t)}{\mathrm{d}t} &= \frac{\beta_m I_m(t) + \beta_s I_s(t) + \beta_T I_T(t)}{N_h^*} S_h^* - \beta_{rh} \frac{I_r(t)}{N_h^*} S_h^* - (\nu_h + d) E_h(t),\\
\frac{\mathrm{d}I_m(t)}{\mathrm{d}t} &= \theta \nu_h E_h(t) - \gamma_m I_m(t) - d I_m(t),\\
\frac{\mathrm{d}I_s(t)}{\mathrm{d}t} &= (1-\theta)\nu_h E_h(t) - \gamma_s I_s(t) - (d+\delta_s) I_s(t),\\
\frac{\mathrm{d}I_T(t)}{\mathrm{d}t} &= \gamma_s I_s(t) - \gamma_T I_T(t) - (d+\delta_T) I_T(t),\\
\frac{\mathrm{d}E_r(t)}{\mathrm{d}t} &= \beta_{hr} \frac{\eta_s I_s(t) + \eta_T I_T(t)}{N_h^*} S_r^*(t) + \beta_r \frac{I_r(t)}{N_r^*} S_r^*(t) - (\nu_r + \mu) E_r(t),\\
\frac{\mathrm{d}I_r(t)}{\mathrm{d}t} &= \nu_r E_r(t) - \mu I_r(t).
\end{aligned}$$

Let us introduce the matrix functions $F(t)$ and $V(t)$ of dimension 7×7 as

$$F(t) = \begin{bmatrix}
0 & \beta_m \frac{S_h^*}{N_h^*} & \beta_s \frac{S_h^*}{N_h^*} & \beta_T \frac{S_h^*}{N_h^*} & 0 & \beta_{rh} \frac{S_h^*}{N_h^*}\\
0 & 0 & 0 & 0 & 0 & 0\\
0 & 0 & 0 & 0 & 0 & 0\\
0 & 0 & 0 & 0 & 0 & 0\\
0 & 0 & \beta hr \frac{\eta_s}{N_h^*} S_r^*(t) & \beta hr \frac{\eta_T}{N_h^*} S_r^*(t) & 0 & \beta_r \frac{S_r^*(t)}{N_r^*}\\
0 & 0 & 0 & 0 & 0 & 0
\end{bmatrix},$$

$$V(t) = \begin{bmatrix}
\nu_h + d & 0 & 0 & 0 & 0 & 0\\
-\theta \nu_h & \gamma_m + d & 0 & 0 & 0 & 0\\
-(1-\theta)\nu_h & 0 & \gamma_s + d + \delta_s & 0 & 0 & 0\\
0 & 0 & -\gamma_s & \gamma_T + d + \delta_T & 0 & 0\\
0 & 0 & 0 & 0 & \nu_r + \mu & 0\\
0 & 0 & 0 & 0 & -\nu_r & \mu
\end{bmatrix}.$$

Note that $F(t)$ is a non-negative matrix function, while $-V(t)$ is cooperative.

Suppose $Z(t,s), t \geqslant s$, is the evolution operator of the linear system

$$\frac{\mathrm{d}y}{\mathrm{d}t} = -V(t)y. \tag{6}$$

Thus, for $s \in \mathbb{R}$, $Z(t,s)$ satisfies the equation

$$\frac{\mathrm{d}Z(t,s)}{\mathrm{d}t} = -V(t)Z(t,s), \qquad \forall t \geqslant s,\ Z(s,s) = I,$$

where I stands for the 6×6 identity matrix.

Assume $\phi(s)$ is the initial distribution of infected, ω-periodic in s. Then, $F(s)\phi(s)$ provides the rate of new cases due to those infected who were introduced at time s. For $t \geqslant s$, the term $Z(t,s)F(s)\phi(s)$ provides us the distribution of the infectious individuals who newly became infected at time s and who are still infected at time t. Therefore,

$$\psi(t) := \int_{-\infty}^{t} Z(t,s)F(s)\phi(s)ds = \int_0^{\infty} Z(t,t-a)F(t-a)\phi(t-a)da,$$

gives the distribution of accumulative new infections at t generated by all infected $\phi(s)$ who were introduced at any time $s \leqslant t$.

Let us assume that C_ω is the ordered Banach space of ω-periodic functions from $\mathbb{R}$ to $\mathbb{R}^6$, endowed with the usual maximum norm $\|\cdot\|_\infty$ and introduce the positive cone

$$C_\omega^+ := \{\phi \in C_\omega : \phi(t) \geqslant 0,\ \forall t \in \mathbb{R}\}.$$

Define the linear next infection operator $\mathcal{L}\colon C_\omega \to C_\omega$ by

$$(\mathcal{L}\phi)(t) = \int_0^\infty Z(t, t-a)F(t-a)\phi(t-a)da, \qquad \forall t \in \mathbb{R},\ \phi \in C_\omega. \tag{7}$$

Then, the basic reproduction number of (1) is $\mathcal{R}_0 := \rho(\mathcal{L})$, the spectral radius of $\mathcal{L}$ [14].

Let $W(t, \lambda)$ be the monodromy matrix of the linear ω-periodic equation

$$\frac{\mathrm{d}w}{\mathrm{d}t} = \left(-V(t) + \frac{1}{\lambda}F(t)\right)w, \qquad \forall t \in \mathbb{R},$$

with parameter $\lambda \in (0, \infty)$.

To numerically approximate the basic reproduction number, we will apply the following theorem from [14].

Theorem 4.1 (*[14, Theorem 2.1]*)**.** *The following statements are valid.*

(i) If $\rho(W(\omega, \lambda)) = 1$ has a positive solution λ_0, then λ_0 is an eigenvalue of operator L, and hence $\mathcal{R}_0 > 0$.
(ii) If $\mathcal{R}_0 > 0$, then $\lambda = \mathcal{R}_0$ is the unique solution of $\rho(W(\omega, \lambda)) = 1$.
(iii) $\mathcal{R}_0 = 0$ if and only if $\rho(W(\omega, \lambda)) < 1$ for all $\lambda > 0$.

4.1. Local stability of the disease-free periodic solution

First we recall the following theorem from [14].

Theorem 4.2 (*[14, Theorem 2.2]*)**.** *The following statements are valid:*

(i) $\mathcal{R}_0 = 1$ if and only if $\rho(\Phi_{F-V}(\omega)) = 1$.
(ii) $\mathcal{R}_0 > 1$ if and only if $\rho(\Phi_{F-V}(\omega)) > 1$.
(iii) $\mathcal{R}_0 < 1$ if and only if $\rho(\Phi_{F-V}(\omega)) < 1$.

As per the above discussion, the following theorem concerns the local stability of the disease-free periodic solution E_0 of (1).

Theorem 4.3. *The disease-free periodic solution E_0 of (1) is locally asymptotically stable if $\mathcal{R}_0 < 1$, whereas it is unstable if $\mathcal{R}_0 > 1$.*

Proof. The Jacobian matrix of (1) calculated at E_0 is given by.

$$J(t) = \begin{bmatrix} F(t)-V(t) & 0 \\ A(t) & M \end{bmatrix},$$

where

$$A(t) = \begin{bmatrix} 0 & \beta_m & \beta_s & \beta_T & 0 & \beta_{rh} \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & \beta hr\frac{\eta_s}{N_h^*}S_r^*(t) & \beta hr\frac{\eta_T}{N_h^*}S_r^*(t) & 0 & \beta_r \end{bmatrix} \text{ and } M = \begin{bmatrix} -d & \xi & 0 \\ 0 & -\xi-d & 0 \\ 0 & 0 & -\mu \end{bmatrix}.$$

According to [24], E_0 is LAS if $\rho(\Phi_M(\omega)) < 1$ and $\rho(\Phi_{F-V}(\omega)) < 1$. M is a constant matrix and its eigenvalues are $\lambda_1 = -d < 0$, $\lambda_2 = -\xi - d < 0$ and $\lambda_3 = -\mu < 0$. Since λ_1, λ_2 and λ_3 are negative, we have $\rho(\Phi_M) < 1$. Consequently, the stability of E_0 depends on $\rho(\Phi_{F-V}(\omega))$. Thus, E_0 is locally asymptotically stable if $\rho(\Phi_{F-V}(\omega)) < 1$, and unstable if $\rho(\Phi_{F-V}(\omega)) > 1$. Hence, we complete the proof by applying Theorem 4.2. □

4.2. The time-average basic reproduction number

Using the general method introduced in [25], we calculate the basic reproduction number of the autonomous model obtain from (1) by setting the time-varying parameters $\tilde{\Pi}_r(t) \equiv \Pi_r$ and $K(t) \equiv K_r$ to constant.

Substituting the value of $S_r^*(t) \equiv S_r^* = K_r\left(\frac{\Pi_r-\mu}{\Pi_r}\right)$ in the disease-free equilibrium for all $t \geqslant 0$, we obtain the Jacobian F given by

$$F = \begin{bmatrix} 0 & \beta_m & \beta_s & \beta_T & 0 & \beta_{rh} \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & \beta hr\frac{\eta_s}{N_h^*}S_r^* & \beta hr\frac{\eta_T}{N_h^*}S_r^* & 0 & \beta_r \\ 0 & 0 & 0 & 0 & 0 & 0 \end{bmatrix},$$

and the Jacobian V given by

$$V = \begin{bmatrix} \nu_h+d & 0 & 0 & 0 & 0 & 0 \\ -\theta\nu_h & \gamma_m+d & 0 & 0 & 0 & 0 \\ -(1-\theta)\nu_h & 0 & \gamma_s+d+\delta_s & 0 & 0 & 0 \\ 0 & 0 & -\gamma_s & \gamma_T+d+\delta_T & 0 & 0 \\ 0 & 0 & 0 & 0 & \nu_r+\mu & 0 \\ 0 & 0 & 0 & 0 & -\nu_r & \mu \end{bmatrix},$$

thus the characteristic polynomial of FV^{-1} is

$$\lambda^4\left(\lambda^2 - (\mathcal{R}_{hh}+\mathcal{R}_{rr})\lambda + \mathcal{R}_{hh}\mathcal{R}_{rr} - \mathcal{R}_{hr}\mathcal{R}_{rh}\right) = 0, \tag{8}$$

where

$$\begin{aligned} \mathcal{R}_{hh} &= \frac{\nu_h}{d+\nu_h}\left(\frac{\theta\beta_m}{\gamma_m+d} + \frac{(1-\theta)\beta_s}{\gamma_s+d+\delta_s} + \frac{(1-\theta)\gamma_s\beta_T}{(\gamma_s+d+\delta_s)(\gamma_T+d+\delta_T)}\right), \\ \mathcal{R}_{hr} &= \frac{(1-\theta)\nu_h\beta_{hr}S_r^*}{\frac{\Pi_h}{d}(\gamma_s+d+\delta_s)(d+\nu_h)}\left(\eta_s + \frac{\gamma_s\eta_T}{\gamma_T+d+\delta_T}\right), \\ \mathcal{R}_{rh} &= \frac{\beta_{rh}\nu_r}{\mu(\mu+\nu_r)}, \\ \mathcal{R}_{rr} &= \frac{\beta_r\nu_r}{\mu(\mu+\nu_r)}. \end{aligned}$$

The characteristic polynomial therefore is the quadratic equation

$$\lambda^2 - (\mathcal{R}_{hh}+\mathcal{R}_{rr})\lambda + \mathcal{R}_{hh}\mathcal{R}_{rr} - \mathcal{R}_{hr}\mathcal{R}_{rh} = 0. \tag{9}$$

According to [25], the basic reproduction number is the largest absolute eigenvalue of FV^{-1} and therefore, it is given by the root of the quadratic equation (9),

$$\mathcal{R}_0^A = \rho(FV^{-1}) = \frac{\mathcal{R}_{hh}+\mathcal{R}_{rr}+\sqrt{\left(\mathcal{R}_{hh}-\mathcal{R}_{rr}\right)^2+4\mathcal{R}_v^2}}{2}, \tag{10}$$

where $\mathcal{R}_{hh}$, $\mathcal{R}_{rr}$ and $\mathcal{R}_v = \sqrt{\mathcal{R}_{hr}\mathcal{R}_{rh}}$ are the basic reproduction numbers of human-to-human transmission, rodent-to-rodent transmission and vectorial transmission, respectively. From (10) one can see that $\frac{\mathcal{R}_{hh}+\mathcal{R}_{rr}+\mathcal{R}_v^2}{\mathcal{R}_{hh}\mathcal{R}_{rr}+1} > 1$ is the necessary and sufficient condition for $\mathcal{R}_0^A > 1$.

To calculate the time-average basic reproduction number, $[\mathcal{R}_0]$, of the associated non-autonomous system, we use the following remark.

Remark 4.4. For a continuous ω-periodic function $g(t)$, define its average (using the notation presented in [26]) as

$$[g] := \frac{1}{\omega}\int_0^\omega g(t)\,dt.$$

Then, the time-average basic reproduction number is given by

$$[\mathcal{R}_0] = \frac{\mathcal{R}_{hh} + \mathcal{R}_{rr} + \sqrt{\left(\mathcal{R}_{hh} - \mathcal{R}_{rr}\right)^2 + 4[\mathcal{R}_{hr}]\mathcal{R}_{rh}}}{2}, \tag{11}$$

where

$$[\mathcal{R}_{hr}] = \frac{(1-\theta)\nu_h\beta_{hr}[S_r^*]}{\frac{\Pi_h}{d}(\gamma_s + d + \delta_s)(d+\nu_h)}\left(\eta_s + \frac{\gamma_s\eta_T}{\gamma_T + d + \delta_T}\right),$$
$$[S_r^*] = [K]\left(\frac{[\tilde{\Pi}_r] - \mu}{[\tilde{\Pi}_r]}\right).$$

5. Threshold dynamics

In this section, we show the dynamics of our model depending on the basic reproduction number. We prove the existence of a positive periodic solution of model (1) 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.

We will need the following lemma to show the global stability of E_0 and the persistence of the disease.

Lemma 5.1 ([15, Lemma 2.1]). *Let $\mu = \frac{1}{\omega}\ln\rho(\Phi_{A(\cdot)}(\omega))$. Then there exists a positive, ω-periodic function $v(t)$ such that $e^{\mu t}v(t)$ is a positive solution of $x' = A(t)x$.*

5.1. Global stability of the disease-free equilibrium

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

Proof. We realize from Theorem 4.3 that if $\mathcal{R}_0 > 1$, then E_0 is unstable and if $\mathcal{R}_0 < 1$, then E_0 is locally asymptotically stable. Consequently, it remains only to show that for $\mathcal{R}_0 < 1$, E_0 is globally attractive. For any ε_1, from Lemma 3.1 and Eq. (2), there exists $T_1 > 0$ such that $S_r(t) \leqslant S_r^*(t) + \varepsilon_1$, $N_r(t) \geqslant S_r^*(t) - \varepsilon_1$ and $N_h(t) \geqslant N_h^* - \varepsilon_1$ for $t > T_1$. Thus, we get

$$\frac{S_h(t)}{N_h(t)} \leqslant \frac{S_h^*}{N_h^* - \varepsilon_1}, \quad \frac{S_r(t)}{N_h(t)} \leqslant \frac{S_r^* + \varepsilon_1}{N_h^* - \varepsilon_1} \quad \text{and} \quad \frac{S_r(t)}{N_r(t)} \leqslant \frac{S_r^* + \varepsilon_1}{N_r^*(t) - \varepsilon_1}.$$

From (1), we obtain

$$\begin{aligned}
\frac{\mathrm{d}E_h(t)}{\mathrm{d}t} &\leqslant \big(\beta_m I_m(t) + \beta_s I_s(t) + \beta_T I_T(t) - \beta_{rh} I_r(t)\big)\frac{S_h^*}{N_h^* - \varepsilon_1} - (\nu_h + d)E_h(t),\\
\frac{\mathrm{d}I_m(t)}{\mathrm{d}t} &= \theta\nu_h E_h(t) - \gamma_m I_m(t) - dI_m(t),\\
\frac{\mathrm{d}I_s(t)}{\mathrm{d}t} &= (1-\theta)\nu_h E_h(t) - \gamma_s I_s(t) - (d + \delta_s)I_s(t),\\
\frac{\mathrm{d}I_T(t)}{\mathrm{d}t} &= \gamma_s I_s(t) - \gamma_T I_T(t) - (d + \delta_T)I_T(t),\\
\frac{\mathrm{d}R(t)}{\mathrm{d}t} &= \gamma_m I_m(t) + \gamma_T I_T(t) - \xi R(t) - dR(t),\\
\frac{\mathrm{d}E_r(t)}{\mathrm{d}t} &\leqslant \beta_{hr}\big(\eta_s I_s(t) + \eta_T I_T(t)\big)\frac{S_r^*(t) + \varepsilon_1}{N_h^* - \varepsilon_1} + \beta_r I_r(t)\frac{S_r^*(t) + \varepsilon_1}{N_r^* - \varepsilon_1} - (\nu_r + \mu)E_r(t),\\
\frac{\mathrm{d}I_r(t)}{\mathrm{d}t} &= \nu_r E_r(t) - \mu I_r(t),
\end{aligned}$$

for $t > T_1$. Let $M_{\varepsilon_1}(t)$ be the 6×6 matrix function defined by

$$\begin{bmatrix} -\nu_h - d & \beta_m \frac{S_h^*}{N_h^* - \varepsilon_1} & \beta_s \frac{S_h^*}{N_h^* - \varepsilon_1} & \beta_T \frac{S_h^*}{N_h^* - \varepsilon_1} & 0 & \beta_{rh} \frac{S_h^*}{N_h^* - \varepsilon_1} \\ \theta\nu_h & -\gamma_m - d & 0 & 0 & 0 & 0 \\ (1-\theta)\nu_h & 0 & -\gamma_s - d - \delta_s & 0 & 0 & 0 \\ 0 & 0 & \gamma_s & -\gamma_T - d - \delta_T & 0 & 0 \\ 0 & 0 & \beta h r \eta_s \frac{S_r^* + \varepsilon_1}{N_h^* - \varepsilon_1} & \beta h r \eta_T \frac{S_r^* + \varepsilon_1}{N_h^* - \varepsilon_1} & -\nu_r - \mu & \beta_r \frac{S_r^* + \varepsilon_1}{N_r^*(t) - \varepsilon_1} \\ 0 & 0 & 0 & 0 & \nu_r & -\mu \end{bmatrix}.$$

Consider the following auxiliary system:

$$\frac{\mathrm{d}\tilde{U}(t)}{\mathrm{d}t} = M_{\varepsilon_1}(t)\tilde{U}(t), \tag{12}$$

where $\tilde{U}(t) = \left(\tilde{E_h}(t), \tilde{I_m}(t), \tilde{I_s}(t), \tilde{I_T}(t), \tilde{E_r}(t), \tilde{I_r}(t)\right)$.

Applying Theorem 4.2, it flows that $\mathcal{R}_0 < 1$ if and only if $\rho(\Phi_{F-V}(\omega)) < 1$. It is obvious that $\lim_{\varepsilon_1 \to 0} \Phi_{M_{\varepsilon_1}}(\omega) = \Phi_{F-V}(\omega)$. As $\rho(\Phi_{F-V}(\omega))$ is continuous, we can choose $\varepsilon_1 > 0$ small enough such that $\rho(\Phi_{M_{\varepsilon_1}}(\omega)) < 1$.

From Lemma 5.1, there is an ω-periodic positive function $p_1(t)$ such that $p_1(t)e^{\xi_1 t}$ is a solution of (12) and $\xi_1 = \frac{1}{\omega} \ln \rho(\Phi_{M_{\varepsilon_1}}(\omega)) < 0$. For any $h(0) \in \mathbb{R}_+^6$, we can choose $n^* > 0$ s.t. $h(0) \leqslant n^* p_1(0)$ where

$$h(t) = (E_h(t), I_m(t), I_s(t), I_T(t), E_r(t), I_r(t))^T.$$

Applying the comparison principle [27, Theorem B.1], we obtain $h(t) \leqslant p_1(t)e^{\xi_1 t}$ for all $t > 0$. Therefore, we get

$$\lim_{t \to \infty} (E_h(t), I_m(t), I_s(t), I_T(t), E_r(t), I_r(t))^T = (0, 0, 0, 0, 0, 0)^T.$$

One can easily find that $N_h(t) \to N_h^*$ as $t \to \infty$. Let $\varepsilon_1 > 0$, we can find $t_{\varepsilon_1} > 0$ such that $I_m(t) \leqslant \varepsilon_1$ and $I_T(t) \leqslant \varepsilon_1$ for all $t \geqslant t_{\varepsilon_1}$. Then, the equation for $R'(t)$ of (1) gives $\frac{\mathrm{d}R(t)}{\mathrm{d}t} \leqslant (\gamma_m + \gamma_T)\varepsilon_1 - \xi R(t) - dR(t)$, for large t. From where $R(t) \to 0$ as $t \to +\infty$. Thus, from (5) and the first equation of (1), we obtain that

$$\lim_{t \to \infty} S_h(t) = S_h^* \quad \text{and} \quad \lim_{t \to \infty} S_r(t) = S_r^*(t),$$

and the proof is complete. □

5.2. Existence of positive periodic solutions

Define

$$X := \left\{(S_h, E_h, I_m, I_s, I_T, R, S_r, E_r, I_r) \in \mathbb{R}_+^9\right\},$$
$$X_0 := \left\{(S_h, E_h, I_m, I_s, I_T, R, S_r, E_r, I_r) \in X : \begin{array}{l} E_h > 0, I_m > 0, I_s > 0, \\ I_T > 0, E_r > 0, I_r > 0 \end{array}\right\},$$

and

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

Let $P \colon \mathbb{R}_+^9 \to \mathbb{R}_+^9$ denote the Poincaré map corresponding to (1), 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 (1) with initial condition $x^0 \in X$. Clearly,

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

Proposition 5.3. *The sets X_0 and ∂X_0 are both positively invariant w.r.t. the flow defined by (1).*

Proof. Let $\phi \in X_0$ be any initial condition. By solving (1) for all $t > 0$, we get that

$$S_h(t) = e^{\int_0^t -(a_1(s)+d)\,ds}\left[S_h(0) + \int_0^t \big(\Pi_h + \xi R(t)\big) e^{\int_0^s (a_1(r)+d)\,dr}\,ds\right] > 0, \tag{13}$$

$$E_h(t) = e^{-(\nu_h+d)t}\left[E_h(0) + \int_0^t a_1(s) S_h(s) e^{(\nu_n+d)s}\,ds\right] > 0, \tag{14}$$

$$I_m(t) = e^{-(\gamma_m+d)t}\left[I_m(0) + \theta\nu_h \int_0^t E_h(s) e^{(\gamma_m+d)s}\,ds\right] > 0, \tag{15}$$

$$I_s(t) = e^{-(\gamma_m+d+\delta_s)t}\left[I_m(0) + (1-\theta)\nu_h \int_0^t E_h(s) e^{(\gamma_m+d+\delta_s)s}\,ds\right] > 0, \tag{16}$$

$$I_T(t) = e^{-(\gamma_T+d+\delta_T)t}\left[I_T(0) + \gamma_s \int_0^t I_s(r) e^{(\gamma_T+d+\delta_T)r}\,dr\right] > 0, \tag{17}$$

$$R_h(t) = e^{-(\xi+d)t}\left[R(0) + \int_0^t \left(\gamma_s I_s(r) + \gamma_T I_T(r)\right) e^{(\xi+d)r}\,dr\right] > 0, \tag{18}$$

$$S_r(t) = e^{\int_0^t -(a_2(s)+\mu)\,ds}\left[S_r(0) + \int_0^t \tilde{\Pi}_r(s)\big(1 - \tfrac{N_r(s)}{K(s)}\big) N_r(s) e^{\int_0^s (a_2(r)+\mu)\,dr}\,ds\right] > 0 \tag{19}$$

$$E_r(t) = e^{-(\nu_r+\mu)t}\left[E_r(0) + \int_0^t a_2(s) S_r(s) e^{(\nu_r+\mu)s}\,ds\right] > 0, \tag{20}$$

$$I_r(t) = e^{-\mu t}\left[I_r(0) + \nu_r \int_0^t E_r(s) e^{-\mu s}\,ds\right] > 0, \tag{21}$$

where

$$a_1(t) = \frac{\beta_m I_m(t) + \beta_s I_s(t) + \beta_T I_T(t)}{N_h(t)} + \beta_{rh}\frac{I_r(t)}{N_h(t)},$$
$$a_2(t) = \beta_{hr}\frac{\eta_s I_s(t) + \eta_T I_T(t)}{N_h(t)} + \beta_r \frac{I_r(t)}{N_r(t)}.$$

Thus, X_0 is a positively invariant set. Since X is also positively invariant and ∂X_0 is relatively closed in X, it gives ∂X_0 is positively invariant. □

Lemma 5.4. *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*

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

Proof. We recognize from Theorem 4.2 that $\rho(\Phi_{F-V}(\omega)) > 1$ if $\mathcal{R}_0 > 1$. Then, we can select $\kappa > 0$ small enough such that we have $\rho(\Phi_{F-V-M_\kappa}(\omega)) > 1$, where $M_\kappa(t)$ is the 6×6 matrix function defined by

$$\begin{bmatrix} 0 & \beta_m\kappa & \beta_s\kappa & \beta_T\kappa & 0 & \beta_{rh}\kappa \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & \beta hr\eta_s\kappa & \beta hr\eta_T\kappa & 0 & \beta_r\kappa \\ 0 & 0 & 0 & 0 & 0 & 0 \end{bmatrix}.$$

Using the continuous dependence of the solutions on initial values, we find a $\sigma = \sigma(\kappa) > 0$ such that for all $\phi \in X_0$ with $\|\phi - E_0\| \leqslant \sigma$, it holds that

$$\|u(t,\phi) - u(t,E_0)\| \leqslant \kappa, \text{ for } 0 \leqslant t \leqslant \omega.$$

We further claim that

$$\limsup_{m\to\infty} d\left(P^m(\phi), E_0\right) \geqslant \sigma. \tag{22}$$

By contradiction suppose that (22) does not hold. Then

$$\limsup_{m\to\infty} d\left(P^m(\phi), E_0\right) < \sigma, \tag{23}$$

for some $\phi \in X_0$. Without loss of generality, we may assume

$$d\left(P^m(\phi), E_0\right) < \sigma,\ \forall m \geq 0.$$

Then, from the above discussion, we have that

$$\|u(t, P^m(\phi) - u(t, E_0))\| < \sigma,\ \forall m \geq 0,\ t \in [0, \omega]\,.$$

For any $t \geqslant 0$, let $t = m\omega + t_1$, where $t_1 \in [0, \omega)$ and $m = [\frac{t}{\omega}]$, which is the largest integer less than or equal to $\frac{t}{\omega}$. Then, we get

$$\|u\left(t, \phi\right) - u\left(t, E_0\right)\| = \|u\left(t_1, P^m(\phi)\right) - u(t_1, E_0)\| < \sigma,$$

for all $t \geqslant 0$, which implies that

$$\frac{S_h(t)}{N_h(t)} \geqslant \frac{S_h^*}{N_h^*} - \kappa, \quad \frac{S_r(t)}{N_h(t)} \geqslant \frac{S_r^*}{N_h^*} - \kappa \quad \text{and} \quad \frac{S_r(t)}{N_r(t)} \geqslant \frac{S_r^*(t)}{N_r^*} - \kappa.$$

Then for $\|\phi - E_0\| \leqslant \sigma$, we obtain

$$\begin{aligned}
\frac{\mathrm{d}E_h(t)}{\mathrm{d}t} &\geqslant \left(\beta_m I_m(t) + \beta_s I_s(t) + \beta_T I_T(t) - \beta_{rh} I_r(t)\right)\left(\frac{S_h^*}{N_h^*} - \kappa\right) - (\nu_h + d)E_h(t),\\
\frac{\mathrm{d}I_m(t)}{\mathrm{d}t} &= \theta\nu_h E_h(t) - \gamma_m I_m(t) - dI_m(t),\\
\frac{\mathrm{d}I_s(t)}{\mathrm{d}t} &= (1-\theta)\nu_h E_h(t) - \gamma_s I_s(t) - (d + \delta_s)I_s(t),\\
\frac{\mathrm{d}I_T(t)}{\mathrm{d}t} &= \gamma_s I_s(t) - \gamma_T I_T(t) - (d + \delta_T)I_T(t),\\
\frac{\mathrm{d}E_r(t)}{\mathrm{d}t} &\geqslant \beta_{hr}\left(\eta_s I_s(t) + \eta_T I_T(t)\right)\left(\frac{S_r^*}{N_h^*} - \kappa\right) + \beta_r I_r(t)\left(\frac{S_r^*}{N_r^*} - \kappa\right) - (\nu_r + \mu)E_r(t),\\
\frac{\mathrm{d}I_r(t)}{\mathrm{d}t} &= \nu_r E_r(t) - \mu I_r(t).
\end{aligned}$$

Next we consider the auxiliary linear system

$$\frac{\mathrm{d}\hat{U}(t)}{\mathrm{d}t} = \big(F(t) - V(t) - M_\kappa(t)\big)\hat{U}(t), \tag{24}$$

where $\hat{U}(t) = \big(\hat{E_h}(t), \hat{I_m}(t), \hat{I_s}(t), \hat{I_T}(t), \hat{E_r}(t), \hat{I_r}(t)\big)$.

Now we have that $\rho(\Phi_{F-V-M_\kappa}(\omega)) > 1$. Again, we have from Lemma 5.1 that there exists a positive, ω-periodic function $p_2(t)$ such that $h(t) = e^{\xi_2 t}p_2(t)$ is a solution of (24) and $\xi_2 = \frac{1}{\omega}\ln\rho(\Phi_{F-V+M_\kappa}(\omega)) > 0$. Let $t = n\omega$ and n be non-negative integer, we obtain

$$h(n\omega) = e^{n\omega\xi_2}p_2(n\omega) \to \big(\infty, \infty, \infty, \infty, \infty, \infty\big)^T.$$

For any $h(0) \in \mathbb{R}_+^6$, we can choose a real number $n_0 > 0$ such that $h(0) \geqslant n_0 p_2(0)$ where

$$h(t) = (E_h(t), I_m(t), I_s(t), I_T(t), E_r(t), I_r(t))^T.$$

Applying the comparison principle [27, Theorem B.1], we obtain $h(t) \geqslant p_2(t)e^{\xi_2 t}$ for all $t > 0$, which implies that

$$\lim_{t\to\infty}\big(E_h(t), I_m(t), I_s(t), I_T(t), E_r(t), I_r(t)\big)^T = \big(\infty, \infty, \infty, \infty, \infty, \infty\big)^T.$$

This leads to a contradiction that completes the proof. □

Theorem 5.5. *Assume that $\mathcal{R}_0 > 1$. Then system (1) has at least one positive periodic solution and there exists an $\varepsilon > 0$ such that*

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

for all $\phi \in X_0$.

Proof. First, we prove that P is uniformly persistent with respect to $(X_0, \partial X_0)$, as from this, applying [28, Theorem 3.1.1], it follows that the solution of (1) is uniformly persistent with respect to $(X_0, \partial X_0)$.

From Proposition 5.3, we have that both X and X_0 are positively invariant and ∂X_0 is relatively closed in X. Furthermore, from Lemma 3.1 it follows that system (1) is point dissipative. Let us introduce

$$M_\partial = \left\{x^0 \in \partial X_0 : P^m(x^0) \in \partial X_0,\ \forall m \geqslant 0\right\},$$

where $x^0 = \phi$. We will apply the theory developed in [28] (see also [15, Theorem 2.3]). In order to do so, we first show that

$$M_\partial = \{(S_h, 0, 0, 0, 0, 0, S_r, 0, 0) : S_h \geqslant 0,\ S_r \geqslant 0\}. \tag{25}$$

Let us note that $M_\partial \supseteq \{(S_h, 0, 0, 0, 0, 0, S_r, 0, 0) : S_h \geqslant 0,\ S_r \geqslant 0\}$. It suffices to prove that $M_\partial \subset \{(S_h, 0, 0, 0, 0, 0, S_r, 0, 0) : S_h \geqslant 0,\ S_r \geqslant 0\}$, i.e., for arbitrary initial condition $\phi \in \partial X_0$, $E_h(n\omega) = 0$ or $I_m(n\omega) = 0$ or $I_s(n\omega) = 0$ or$I_T(n\omega) = 0$ or $R(n\omega) = 0$ or $E_r(n\omega) = 0$ or $I_r(n\omega) = 0$, for all $n \geqslant 0$.

Assume by contradiction the existence of an integer $n_1 \geqslant 0$ for which $E_h(n_1\omega) > 0$, $I_m(n_1\omega) > 0$, $I_s(n_1\omega) > 0$, $I_T(n_1\omega) > 0$, $R(n_1\omega) > 0$,$E_r(n_1\omega) > 0$ and $I_r(n_1\omega) > 0$. Then, by putting $t = n_1\omega$ into the place of the initial time $t = 0$ in (13)–(21), we get that $S_h(t) > 0$, $E_h(t) > 0$, $I_m(t) > 0$, $I_s(t) > 0$, $I_T(t) > 0$, $R(t) > 0$, $S_r(t) > 0$, $E_r(t) > 0$, $I_r(t) > 0$. This is in contradiction with the positive invariance of ∂X_0.

By Lemma 5.4, P is weakly uniformly persistent w.r.t. $(X_0, \partial X_0)$. Lemma 3.1 guarantees the existence of a global attractor of P. Then E_0 is an isolated invariant set in X and $W^s(E_0) \cap X_0 = \emptyset$. Each solution in M_∂ tends to E_0 and E_0 is clearly acyclic in M_∂. By [28, Theorem 1.3.1 and Remark 1.3.1], we can deduce that P is uniformly (strongly) persistent w.r.t. $(X_0, \partial X_0)$. Hence, there exists an $\varepsilon > 0$ such that

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

for all $\phi \in X_0$. By [28, Theorem 1.3.6], P has a fixed point $\bar{\phi} \in X_0$, and hence system (1) has at least one periodic solution $u(t, \bar{\phi})$ with

$$\bar{\phi} = \big(\bar{S}_h(0), \bar{E}_h(0), \bar{I}_a(0), \bar{I}_a(0), \bar{I}_s(0), \bar{R}_h(0), \bar{S}_r(0), \bar{E}_r(0), \bar{I}_r(0)\big) \in X_0.$$

Now, let us prove that $\bar{S}_h(0)$ and $\bar{S}_r(0)$ are positive. If $\bar{S}_h(0) = 0 = \bar{S}_r(0)$, then we obtain that $\bar{S}_h(0) > 0$ and $\bar{S}_r(0) > 0$ for all $t > 0$. However, using the periodicity of solution, we have $\bar{S}_h(0) = \bar{S}_h(n\omega) = 0$, and $\bar{S}_r(0) = \bar{S}_r(n\omega) = 0$, that is a contradiction. □

6. A case study — Lassa fever in Nigeria 2017–2020

In this section, we use our model to study the spread of Lassa fever in Nigeria during the epidemic in November 2017 to May 2020. From Section 5, we see that $\mathcal{R}_0$ is a threshold parameter for the persistence of the disease in the population (see Theorems 5.2 and 5.5). 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. [29,30], they are supposed to be of the form

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

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.

Fig. 3 shows the weekly confirmed cases of 2017–2020 Lassa outbreak in Nigeria [31].

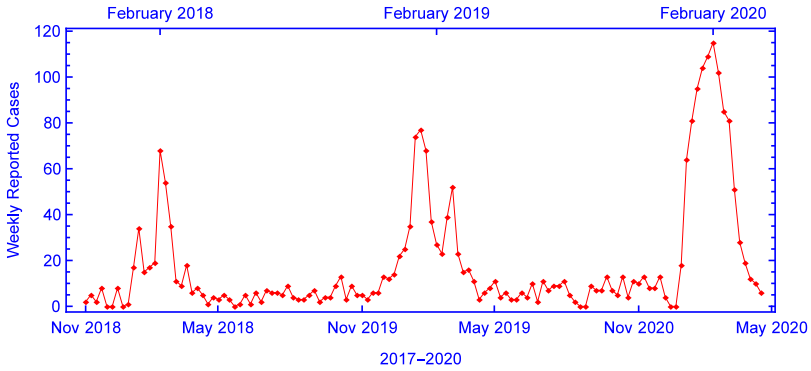


Fig. 3. Confirmed number of cases reported of the November 2017–May 2020 Lassa fever epidemic in Nigeria [31].

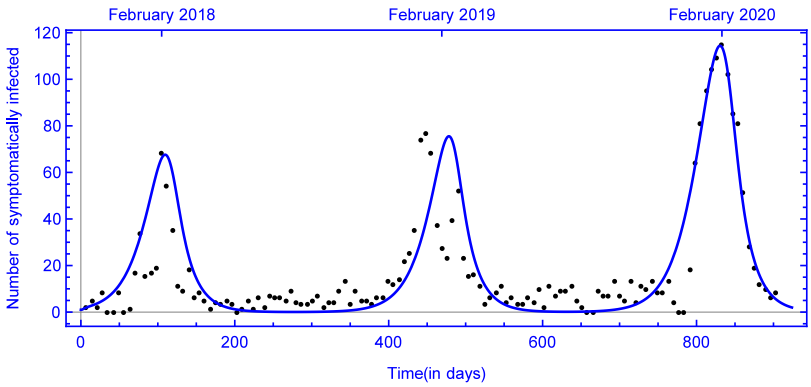


Fig. 4. Fitting the model to the data for the 2017–2020 Lassa outbreaks in Nigeria with parameter values in Table 2 and initial condition $(S_h, E_h, I_m, I_s, I_T, R, S_r, E_r, I_r)(0) = (2 \times 10^8, 40, 49, 2, 20, 14 \times 10^3, 5 \times 10^8, 10^6, 10^3)$.

6.1. Parameter estimation for Nigeria

We used Latin Hypercube Sampling, a sampling tool applied in statistics to quantify simultaneous variation of many parameter values (see, e.g., [34]), as a way to estimate the parameters providing the best fit. The method consists of generating a representative sample set for all parameters shown in Table 2 from parameter ranges obtained from literature and the World Bank website [32] as shown in Table 2. Then the solutions of model (1) with the specified parameters value are determined numerically for all elements of this representative sample set. Finally, the least squares method is used to get the best fit.

Fig. 4 shows model (1) fitted to data from Nigeria [31]. Our model provides a reasonably good fit, generating the three peaks of Lassa fever happened in the last three seasons in Nigeria.

Fig. 5 shows the long-term behaviour of infectious humans and rodents with the best fit parameters given in Table 2 (see baseline). The results indicate that Lassa fever in Nigeria will persist and show periodic fluctuations in the coming years unless additional measures are taken.

6.2. Long-term behaviour

We compute the basic reproduction $\mathcal{R}_0$ numerically by using the method developed in [26, Section 2]. By Theorem 5.2, we know that the disease will die out if $\mathcal{R}_0 < 1$. We obtain $\mathcal{R}_0 = 0.7165 < 1$ with the set of parameter values in Table 2 (see Extinction). In this case, the long-term behaviours of the infectious

Table 2
Baseline values, ranges, units and values for extinction and persistence of model (1) parameters.

Parameter	Baseline	Range	Units	Value for		Source
				Extinction	Persistence	
N_h	2×10^8	–	Persons	2×10^8	2×10^8	[32]
Π_h	10,000	–	Persons day^{-1}	10,000	10,000	[32]
d	0.00005	–	Day^{-1}	0.00005	0.00005	[32]
δ_s	0.485	0.1–0.5	Day^{-1}	0.201	0.201	[8]
δ_T	0.269	0.1–0.5	Day^{-1}	0.224	0.224	[8]
β_m	0.0637	0.03–0.5	Day^{-1}	0.181	0.181	[8,33]
β_s	0.221	0.03–0.5	Day^{-1}	0.275	0.367	[8,33]
β_T	0.206	0.03–0.5	Day^{-1}	0.259	0.259	[8,33]
β_{hr}	0.259	0.03–0.5	Day^{-1}	0.242	0.242	[8]
β_{rh}	0.0296	0.1–0.8	Day^{-1}	0.216	0.373	[8]
β_r	0.052	0.005–0.4	Day^{-1}	0.007	0.02	[8,29]
η_s	0.238	0.1–0.5	Day^{-1}	0.392	0.392	Assumed
η_T	0.319	0.1–0.5	Day^{-1}	0.344	0.344	Assumed
θ	0.815	0.7–0.9	Day^{-1}	0.802	0.802	[32]
γ_m	0.108	0–1	Day^{-1}	0.433	0.433	[8]
γ_s	0.024	0.001–0.025	Day^{-1}	0.0123	0.0123	[8]
γ_T	0.446	0–1	Day^{-1}	0.256	0.256	[8]
ν_h	0.528	0.1–1	Day^{-1}	0.515	0.515	[8,29]
ν_r	0.32	0.1–1	Day^{-1}	0.299	0.299	[8,29]
ξ	0.00578	0.0035–0.03	Day^{-1}	0.00578	0.00578	[8]
Π_r	0.172	–	–	0.2	0.146	Assumed
μ	0.003	0.001–0.006	Day^{-1}	0.005	0.006	[8,29]
K_r	20,000	–	–	198,000	342,000	Assumed
a	0.31	0–1	–	0.31	0.31	Assumed
Λ	0.31	0–1	–	0.31	0.31	[29]
b	134.8	0–365	–	249	163.5	[29]

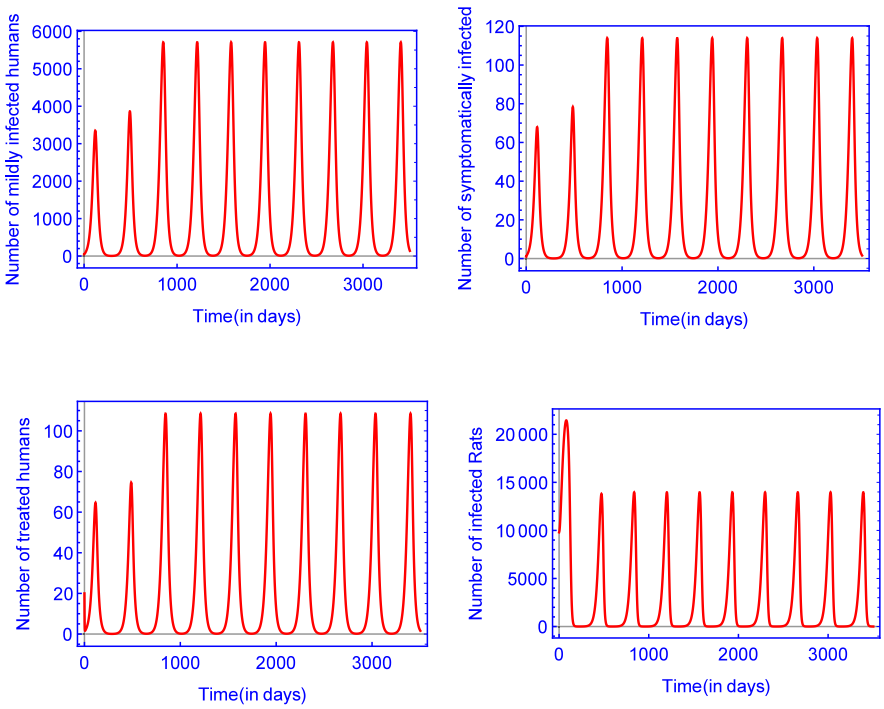


Fig. 5. The long-term dynamic behaviour of the model (1) variables with parameter values in Table 2 (see baseline).

humans and rodents are shown in Fig. 6, which implies that the unique disease-free equilibrium E_0 is globally asymptotically stable when $\mathcal{R}_0 < 1$.

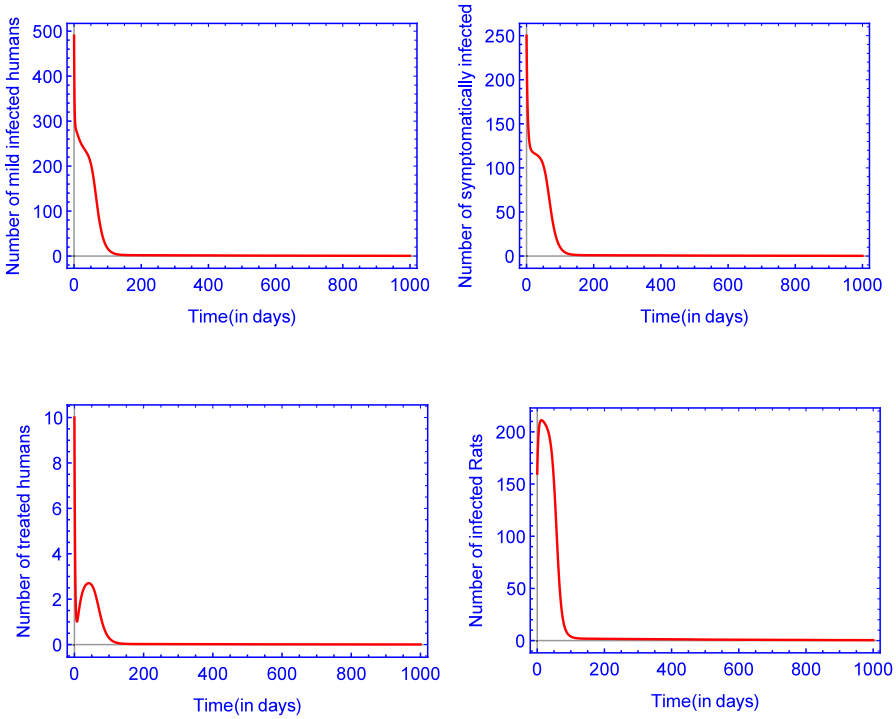


Fig. 6. Extinction of Lassa fever for $\mathcal{R}_0 = 0.7165 < 1$ with parameters given in Table 2 (see Extinction).

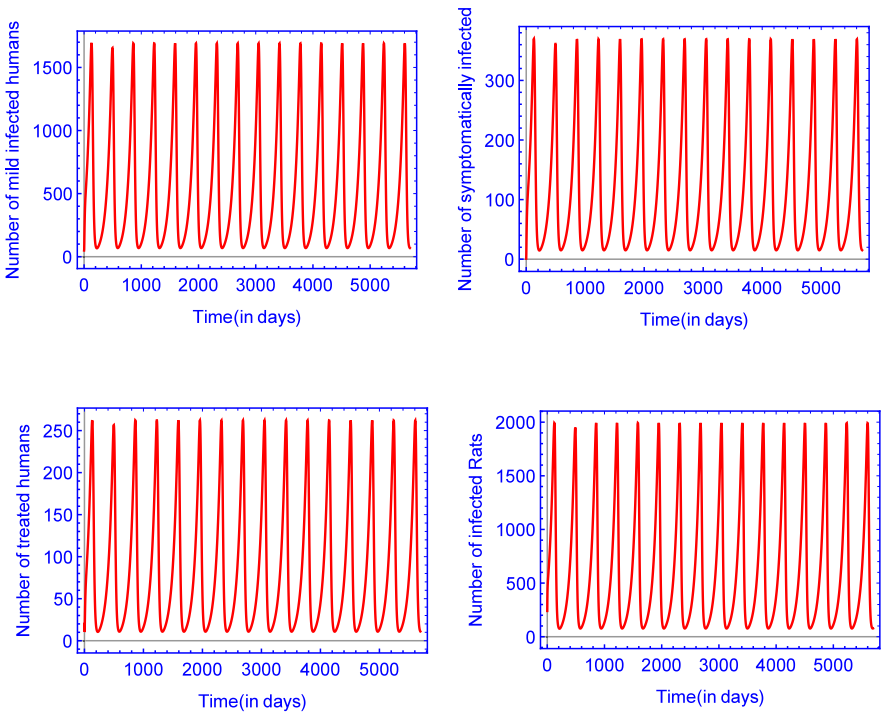
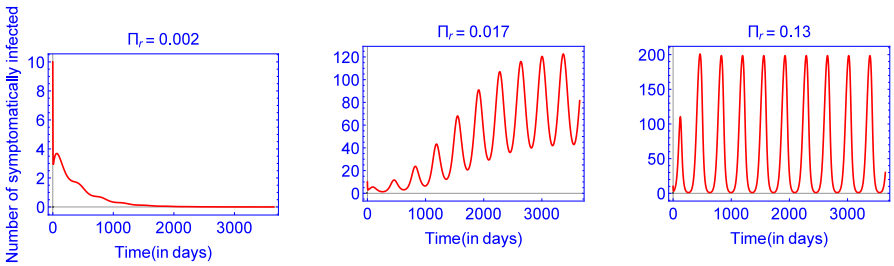
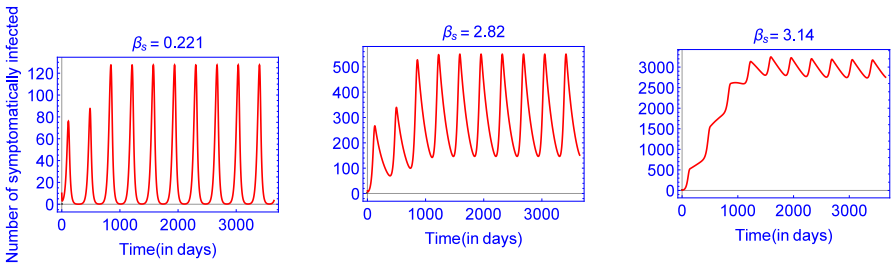


Fig. 7. Uniform persistence of Lassa fever for $\mathcal{R}_0 = 3.2678 > 1$ with parameters given in Table 2 (see Persistence).

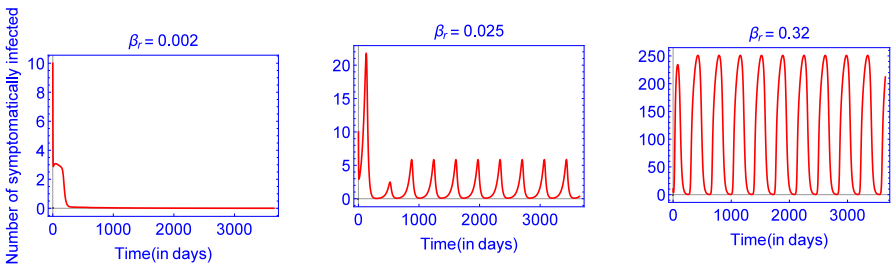
By Theorem 5.5, system (1) has a positive ω-periodic solution if $\mathcal{R}_0 > 1$. Fig. 7 illustrates the uniform persistence of the disease when $\mathcal{R}_0 = 3.2678 > 1$ with the set of parameter values in Table 2 (see Persistence). These simulations correspond to our theoretical results.



(a) Model (1) solution with distinct Π_r–values.



(b) Model (1) solution with distinct β_s–values.



(c) Model (1) solution with distinct β_r–values.

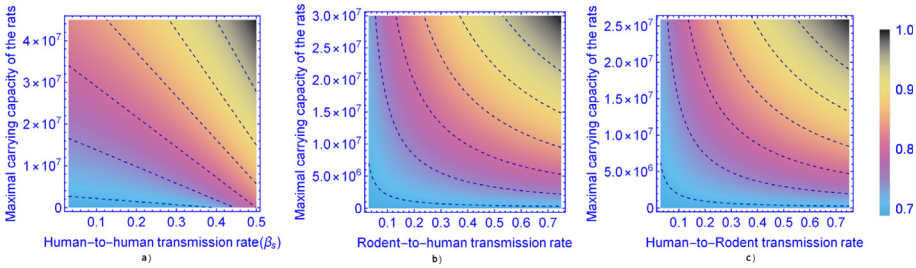
Fig. 8. The number sympatrically infected humans with three different values of in (a) rodent birth rate (Π_r), in (b) human-to-human transmission rate (β_s) and in (c) rodent-to-rodent transmission rate (β_r) with parameter values are given in Table 2.

6.3. Parameter changes for Nigeria

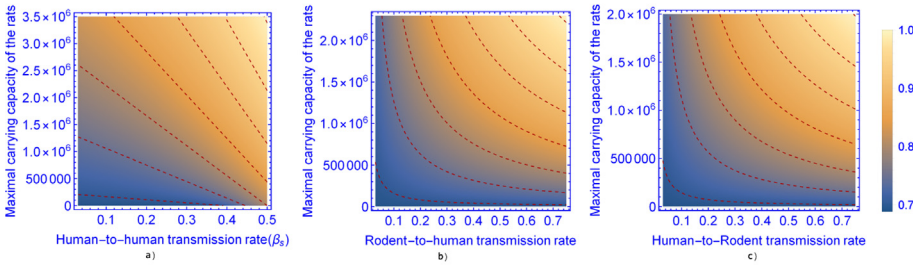
In this study, one of our core concerns was to see what changes in the parameters might trigger a periodic reappearance of the epidemic. Since we have a large number of parameters, it is not easy to rigorously determine which of the parameters play the most important role in the variation of the dynamics, 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 (see Fig. 6) 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 (see Fig. 7).

For a further illustration to explain the impact of parameter changes on the spread of Lassa fever, we plotted the solution of our model with three different values for a rodent birth rate (Π_r), human-to-human transmission rate (β_s) and rodent-to-rodent transmission rate (β_r) in Fig. 8. As is observed, the number of



(a)



(b)

Fig. 9. The contour plot of the time-average basic reproduction number, $[\mathcal{R}_0]$ in (a) and the basic reproduction number, $\mathcal{R}_0^A$ of the autonomous model in (b), as a function of maximal carrying capacity of the rats (K_r) and in a) human-to-human transmission rate (β_s), b) rodent-to-human transmission rate (β_{rh}) and c) human-to-rodent transmission rate (β_{hr}).

symptomatically infected people increases by raising any term of Π_r or β_s or β_r, and the disease becomes recurring periodically every year.

6.4. Sensitivity analysis of $\mathcal{R}_0$

In any given time, formula (10) gives us with the basic reproduction number, $\mathcal{R}_0^A$, of the associated autonomous system by substituting the parameter values in it, along with the value of the time-dependent parameters at that time. Moreover, formula (11) provides us the time-average basic reproduction number, $[\mathcal{R}_0]$, of the associated non autonomous system which can be calculated using the notation in Remark 4.4.

In Fig. 9, we plot the time-average basic reproduction number $[\mathcal{R}_0]$ (see Fig. 9(a)) and the basic reproduction number $\mathcal{R}_0^A$ (see Fig. 9(b)), as a function of maximal carrying capacity of the rodents (K_r), and human-to-human transmission rate (β_s), rodent-to-human transmission rate (β_{rh}) and human-to-rodent transmission rate (β_{hr}). The rest of the parameters are set as obtained in the fitting of symptomatically infected cases in Table 2 (see baseline). As can be observed, both reproduction numbers increase by increasing the transmission rates β_s, β_{rh} and β_{hr}. Increasing rodent birth rates also increase reproduction numbers. Although human-to-human and human-to-rodent transmission rates have a notable impact on the increase in both reproduction numbers, the figure indicates that rodent control is a significant factor in Lassa's spread and that vector control might be necessary to suppress the disease.

In Fig. 10, we plot the curves of the time-average basic reproduction number $[\mathcal{R}_0]$, and the basic reproduction number $\mathcal{R}_0^A$ with respect to maximal carrying capacity of rodents (K_r), rodents birth rate (Π_r), human-to-human transmission rate (β_s), human-to-rodent transmission rate (β_{hr}), rodent-to-human transmission rate (β_{rh}) and rodent-to-rodent transmission rate (β_r), respectively. The calculations show that $[\mathcal{R}_0] \geqslant \mathcal{R}_0^A$, suggesting that $\mathcal{R}_0^A$ provides an underestimation of the risk of disease transmission.

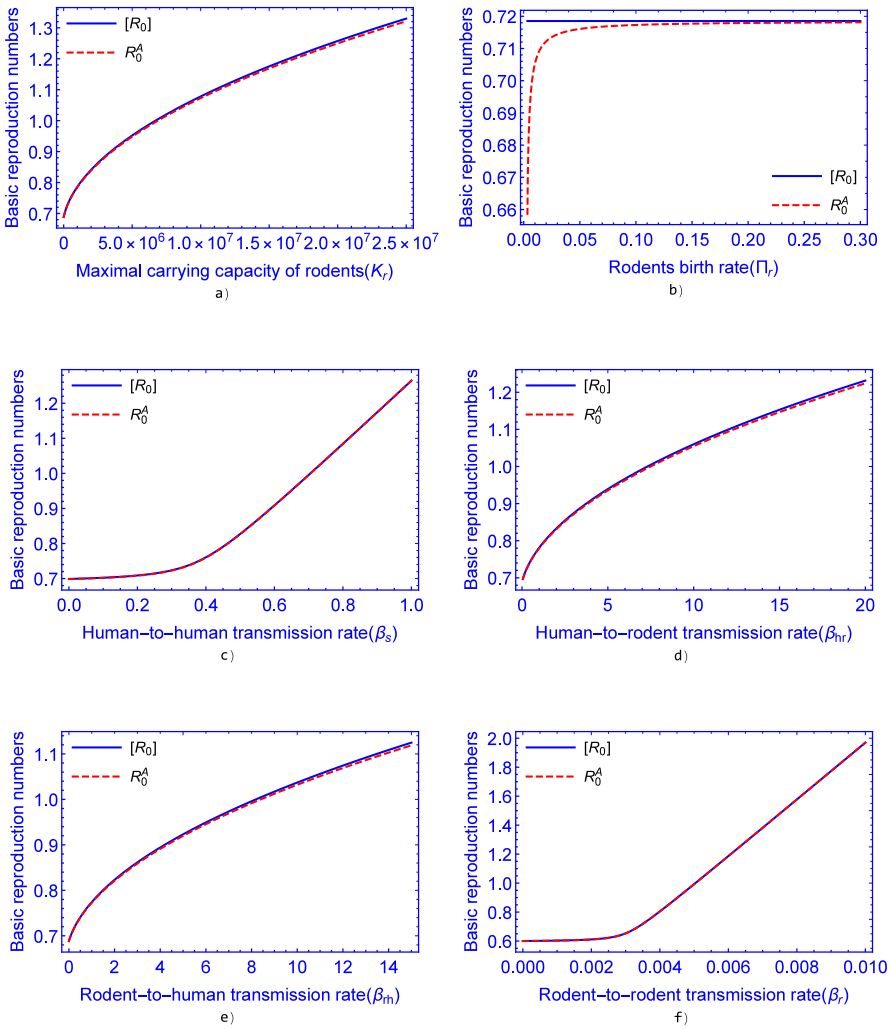


Fig. 10. The curves of the time-average basic reproduction number $[\mathcal{R}_0]$ and the basic reproduction number of the autonomous model $\mathcal{R}_0^A$ versus in a) maximal carrying capacity of rodents (K_r), b) rodents birth rate (Π_r), c) human-to-human transmission rate (β_s), d) human-to-rodent transmission rate (β_{hr}), e) rodent-to-human transmission rate (β_{rh}) and f) rodent-to-rodent transmission rate (β_r).

We mention that numerous papers have results on under- and overestimation of the average basic reproduction number. For instance, it was shown in [14] that $\mathcal{R}_0 > [\mathcal{R}_0]$, while in [21] the authors gave an example with $\mathcal{R}_0 < [\mathcal{R}_0]$. In general, $\mathcal{R}_0 \neq [\mathcal{R}_0]$ and more details can also be found in [14,35].

7. Discussion

We formulated and analysed a periodic LHF transmission model between humans and rodents that involves the seasonal effects (by including periodic coefficients), human-to-human transmission and the vertical transmission of the virus in rodents. By using the theory presented in [14], we derived and numerically computed the basic reproduction number $\mathcal{R}_0$. It is demonstrated that the global dynamics is determined by the basic reproduction number $\mathcal{R}_0$. If $\mathcal{R}_0 > 1$, then the disease is uniformly persistent and there exists at least one positive periodic solution, while the disease-free periodic solution E_0 is globally asymptotically stable and the disease dies out if $\mathcal{R}_0 < 1$. Our numerical simulations show that there is only

one positive periodic solution which is globally asymptotically stable in the case where $\mathcal{R}_0 > 1$ (see Fig. 7) and the disease dies out if $\mathcal{R}_0 < 1$ (see Fig. 6).

Numerically, 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 (see Fig. 4). 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 (see Fig. 10).

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.

The simulation results indicate that, if no additional intervention is taken, Lassa will persist and exhibit periodic fluctuation in the next few years in Nigeria. These simulations are compatible with our analytic results, and the model can be also used to study the Lassa fever transmission in other countries of West Africa such as Benin, Ghana, Guinea, Liberia, Mali, Sierra Leone, and Togo so long as the data are accessible.

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