



Research article

Threshold dynamics of a time-delayed hantavirus infection model in periodic environments

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Abstract: We formulate and study a mathematical model for the propagation of hantavirus infection in the mouse population. This model includes seasonality, incubation period, direct transmission (contacts between individuals) and indirect transmission (through the environment). For the time-periodic model, the basic reproduction number R_0 is defined as the spectral radius of the next generation operator. Then, we show the virus is uniformly persistent when $R_0 > 1$ while tends to die out if $R_0 < 1$. When there is no seasonality, that is, all coefficients are constants, we obtain the explicit expression for the basic reproduction number \mathbf{R}_0 , such that if $\mathbf{R}_0 < 1$, then the virus-free equilibrium is globally asymptotically stable, but if $\mathbf{R}_0 > 1$, the endemic equilibrium is globally attractive. Numerical simulations indicate that prolonging the incubation period may be helpful in the virus control. Some sensitivity analysis of R_0 is performed.

Keywords: Hantavirus; seasonality; time delay; uniform persistence; basic reproduction number

1. Introduction

The term hantavirus represents several groups of RNA-containing viruses (that are members of the virus family of Bunyaviridae) that are carried by rodents, particularly deer mice. The virus is found in their urine and feces, but it does not make the animal sick. The hantavirus is a rare but potentially very serious disease that affects a small number of people every year. People become infected through contact with hantavirus-infected rodents or their urine and droppings. Infection with hantavirus can progress to Hantavirus Pulmonary Syndrome (HPS), which can be fatal. The Sin Nombre hantavirus, first recognized in 1993, is one of several New World hantaviruses circulating in the US. Old World hantaviruses, including Seoul virus, are found across the world and can cause Hemorrhagic Fever with Renal Syndrome (HFRS). Hantavirus does not seem to spread from human to human. The humans get the virus from the mice but have no feedback effects on the mice in the infection process. Furthermore, the transmission of the infection is horizontal, i.e., no mice are born infected [1], infection may

only be contracted in adulthood from other mice mainly through aggressive encounters, such as fights among them, or through inhalation of the aerosolized virus [2, 3, 4]. The infection and persistence of hantavirus in its rodent host has little or no effect on survival [5]. In order to have a better understanding of the spread of the disease in humans, it is necessary to understand the transmission dynamics of hantavirus in rodent populations.

Several epidemic models that have been applied to hantavirus infection in rodents are available. For instance, Abramson and Kenkre [6] and Abramson and Kenkre et al. [7] formulated a two-equation reaction diffusion model for susceptible and infected deer mice. Logistic growth is assumed with carrying capacity K . K is chosen as a control parameter of the dynamics. They analyzed the traveling waves of a model of the hantavirus infection. Allen et al. [8] developed an SI epidemic model for a host with two viral infections. The model was applied to a hantavirus and an arenavirus that infect cotton rats. The first virus is transmitted horizontally whereas the second is transmitted vertically. Considering the movement characteristics of the mice that carry the infection, Kenkre et al. [9] considered two types of mice, stationary adult mice and itinerant juvenile mice. Gedeon et al. [10] applied their model to hantavirus infection in deer mice. Their goal was to compare the relative importance of direct (from infected to healthy individuals) and indirect (by the contaminated environment) transmission in sylvan and peridomestic environments. Sauvage et al. [11] formulated a model which was applied to Puumala virus infection in bank voles. Host population was divided into two age classes, juveniles and adults. It was assumed that individuals can live in favourable or unfavourable patches. Their study showed that indirect transmission significantly increased the probability for the virus to persist in the host population. These two transmission modes also have been discussed by Wolf [12] and Wolf et al. [13]. Abramson and Kenkre [1] gave a stage-dependent model with maturation delay, in their model, a virus-free young mice variable is introduced, the adult population was subdivided into susceptibles and infectives. The spatial version of [1] was presented in [14]. Based on the model in [6], Buceta et al. [15] studied the impact of seasonality on hantavirus, they have shown that the alternation of seasons may cause outbreaks of the disease even if neither season by itself satisfies the environmental requirements for propagation of the disease. Allen et al. [16] constructed two gender-structured SEIR model, the first model is a system of ordinary differential equations, while the second model extends the first model to a system of stochastic differential equations. These models are studied mainly from the numerical simulation point of view. A spatio-temporal SEIR compartmental model was proposed in Burger et al. [17].

It has been noted that environmental conditions are directly connected to outbreaks of Hanta. For example, the Four Corners Region, where an important number of cases of HPS have occurred, has a desert climate. The largest climate variations within this region come from periods of rain and of drought [15]. The influence of the environmental conditions plays a fundamental role in the evolution of the population. Resource availability would fluctuate as seed and fruit production vary over a 3-year period [18].

As in most infectious diseases, there is a lag between exposure and infectivity, which is usually called the incubation period. Because the life expectancy of rodents is relatively short, then the incubation period cannot be neglected [16]. Since infected mice that survive the incubation period will remain infectious for the rest of their lives. Thus, the incubation period directly influences the number of infectious mice. However, explicit delay effects related to finite incubation periods have received little attention.

Motivated by the works of [10, 11, 15, 16, 17], in this paper we formulate a periodic time-delayed model by taking into account the seasonality. The model contains a time delay accounting for the incubation period of the virus.

The rest of this paper is organized as follows. In the next section, based on the work of Gedeon et al. [10] we present the model, and study its well-posedness, also we introduce the basic reproduction number R_0 . In section 3, we establish the threshold dynamics in terms of R_0 . In section 4, we study the autonomous case of the periodic model, and prove the global stability of the virus-free equilibrium and the global attractivity of the endemic equilibrium. In section 5, we perform numerical simulations to illustrate our analytic results. A brief discussion section completes the paper.

2. Model formulation

Our model was built on the framework of [10]. In [10], $S(t)$, $I(t)$ and $G(t)$ denote the susceptible, infectious adult mice at time t , and the number of contaminated sites in the environment. In our model, we add the exposed class, we let $E(t)$ denote the exposed adult mice at time t . We make the same assumptions as those in [10], that is, we assume that there is a discrete number of sites that are visited by mice. Each site is small enough to be infected by a single mouse. Also we assume that the total number of sites M is large and we represent it by a continuous variable.

We let $N(t)$ be the total population of mice, then $N(t) = S(t) + E(t) + I(t)$. The direct contact rate $c(t)$ of mice is the average number of direct contacts between mice per mouse per unit time at time t . This rate depends on a number of factors, and in particular, climatic ones, but for simplicity in this paper we assume $c(t)$ to be periodic. These contacts may involve biting and scratching and are thought to occur predominantly between sexually active males [2, 19]. Suppose the transmission probability that given an active contact between susceptible and infected mice is denoted by β , which is called a direct transmission rate.

For the indirect transmission route, we let $\bar{c}(t)$ be the number of contacts between a mouse and all the potentially contaminated sites per susceptible mouse per unit time at time t , which is also assumed to be periodic. The probability that given a contact between susceptible mouse and contaminated site is denoted by α , this is called an indirect transmission rate.

Indirect transmission is due to the fact that infected individuals can excrete viruses in their feces, vomit, urine or others. To model the process of site contamination by infected mice, let $d(t)$ be the number of contacts between the mice and the site that can lead to transmission of the infection per uncontaminated site per unit time at time t . The probability of site contamination is called the site contamination rate, which is denoted by γ , given a contact between an uncontaminated site and an infected mouse.

Assume that $B(t)$ is the recruitment rate for mice and $\mu(t)$ is the death rate of the mice. Since hantavirus is not lethal to mice, then we assume the death rates are the same for the infected and the susceptible classes [3]. The mice are infected for the rest of their lives [3, 20], so there is no recovery. We assume that the environment eliminates viruses with time at a rate $\delta(t)$, which is called the disinfection rate. Suppose that τ is the average incubation period. Then we obtain the following

system

$$\left\{ \begin{array}{l} \frac{dS(t)}{dt} = B(t) - \mu(t)S(t) - \frac{\beta_1(t)S(t)I(t)}{N(t)} - \frac{\beta_2(t)S(t)G(t)}{M}, \\ \frac{dE(t)}{dt} = \frac{\beta_1(t)S(t)I(t)}{N(t)} + \frac{\beta_2(t)S(t)G(t)}{M} - \mu(t)E(t) \\ \quad - \left[\frac{\beta_1(t-\tau)S(t-\tau)I(t-\tau)}{N(t-\tau)} + \frac{\beta_2(t-\tau)S(t-\tau)G(t-\tau)}{M} \right] e^{-\int_{t-\tau}^t \mu(r)dr}, \\ \frac{dI(t)}{dt} = \left[\frac{\beta_1(t-\tau)S(t-\tau)I(t-\tau)}{N(t-\tau)} + \frac{\beta_2(t-\tau)S(t-\tau)G(t-\tau)}{M} \right] e^{-\int_{t-\tau}^t \mu(r)dr} \\ \quad - \mu(t)I(t), \\ \frac{dG(t)}{dt} = \frac{a(t)I(t)}{N(t)}(M - G(t)) - \delta(t)G(t), \end{array} \right. \quad (2.1)$$

where $\beta_1(t) = \beta c(t)$, $\beta_2(t) = \alpha \bar{c}(t)$, $a(t) = \gamma d(t)$. All parameters are positive, continuous, and ω -periodic functions for some $\omega > 0$. It is easy to see that the equation for $E(t)$ can be rewritten as one integral equation

$$E(t) = \int_{t-\tau}^t \left[\frac{\beta_1(\xi)S(\xi)I(\xi)}{N(\xi)} + \frac{\beta_2(\xi)S(\xi)G(\xi)}{M} \right] e^{-\int_{\xi}^t \mu(r)dr} d\xi. \quad (2.2)$$

The dynamics of the mouse population is governed by the following equation

$$\frac{dN(t)}{dt} = B(t) - \mu(t)N(t). \quad (2.3)$$

It is easy to see that (2.3) has a unique positive ω -periodic solution

$$N^*(t) = \left[\int_0^t B(r) e^{\int_0^r \mu(s)ds} dr + \frac{\int_0^\omega B(r) e^{\int_0^r \mu(s)ds} dr}{e^{\int_0^\omega \mu(s)ds} - 1} \right] e^{-\int_0^t \mu(s)ds},$$

which is globally asymptotically stable.

Let $C = C([-\tau, 0], \mathbb{R}^4)$, $C^+ = C([-\tau, 0], \mathbb{R}_+^4)$. Then (C, C^+) is an ordered Banach space equipped with the maximum norm and the partial order induced by the positive cone C^+ . For any given continuous function $x : [-\tau, \sigma) \rightarrow \mathbb{R}^4$ with $\sigma > 0$, we can define $x_t \in C$ as $x_t(\theta) = x(t + \theta)$, $\forall \theta \in [-\tau, 0]$ for any $t \in [0, \sigma)$.

For a given continuous ω -periodic function $g(t)$, let

$$\widehat{g} = \max_{t \in [0, \omega]} g(t), \quad \bar{g} = \min_{t \in [0, \omega]} g(t).$$

Let

$$W := C([-\tau, 0], \mathbb{R}_+^3) \times C([-\tau, 0], [0, M]).$$

In view of (2.2), we choose the initial data for system (2.1) in \mathcal{X}_{δ_0} , which is defined as

$$\begin{aligned} \mathcal{X}_{\delta_0} = \{ \phi \in W : \sum_{i=1}^3 \phi_i(s) \geq \delta_0, \forall s \in [-\tau, 0], \\ \phi_2(0) = \int_{-\tau}^0 \left[\frac{\beta_1(\xi)\phi_1(\xi)\phi_3(\xi)}{\sum_{i=1}^3 \phi_i(\xi)} + \frac{\beta_2(\xi)\phi_1(\xi)\phi_4(\xi)}{M} \right] e^{-\int_{\xi}^0 \mu(r)dr} d\xi \} \end{aligned}$$

for small $\delta_0 \in \left(0, \frac{\bar{B}}{\bar{\mu}}\right)$.

Lemma 2.1. For any $\phi \in \mathcal{X}_{\delta_0}$, system (2.1) has a unique nonnegative solution $u(t, \phi)$ with $u_0 = \phi$ for all $t \geq 0$, and solutions are ultimately bounded and uniformly bounded.

Proof. Given $\phi \in \mathcal{X}_{\delta_0}$, define $f(t, \phi) = (f_1(t, \phi), f_2(t, \phi), f_3(t, \phi), f_4(t, \phi))$ with

$$\begin{aligned} f_1(t, \phi) &= B(t) - \mu(t)\phi_1(0) - \frac{\beta_1(t)\phi_1(0)\phi_3(0)}{\sum_{i=1}^3 \phi_i(0)} - \frac{\beta_2(t)\phi_1(0)\phi_4(0)}{M}, \\ f_2(t, \phi) &= \frac{\beta_1(t)\phi_1(0)\phi_3(0)}{\sum_{i=1}^3 \phi_i(0)} + \frac{\beta_2(t)\phi_1(0)\phi_4(0)}{M} - \mu(t)\phi_2(0) \\ &\quad - \left[\frac{\beta_1(t-\tau)\phi_1(-\tau)\phi_3(-\tau)}{\sum_{i=1}^3 \phi_i(-\tau)} + \frac{\beta_2(t-\tau)\phi_1(-\tau)\phi_4(-\tau)}{M} \right] e^{-\int_{t-\tau}^t \mu(r)dr}, \\ f_3(t, \phi) &= \left[\frac{\beta_1(t-\tau)\phi_1(-\tau)\phi_3(-\tau)}{\sum_{i=1}^3 \phi_i(-\tau)} + \frac{\beta_2(t-\tau)\phi_1(-\tau)\phi_4(-\tau)}{M} \right] e^{-\int_{t-\tau}^t \mu(r)dr} - \mu(t)\phi_3(0), \\ f_4(t, \phi) &= \frac{a(t)\phi_3(0)}{\sum_{i=1}^3 \phi_i(0)}(M - \phi_4(0)) - \delta(t)\phi_4(0). \end{aligned}$$

Since $f(t, \phi)$ is continuous in $(t, \phi) \in \mathbb{R}_+ \times \mathcal{X}_{\delta_0}$, and $f(t, \phi)$ is Lipschitz in ϕ on each compact subset of \mathcal{X}_{δ_0} , it then follows that system (1) has a unique solution $u(t, \phi)$ on its maximal interval $[0, \sigma_\phi)$ of existence with $u_0 = \phi$ (see [21, Theorems 2.2.1 and 2.2.3]).

In view of the second equation of system (2.1), we have

$$\begin{aligned} \left(\frac{dE(t)}{dt} + \mu(t)E(t) \right) e^{\int_0^t \mu(s)ds} &= \left[\frac{\beta_1(t)S(t)I(t)}{N(t)} + \frac{\beta_2(t)S(t)G(t)}{M} - \left(\frac{\beta_1(t-\tau)S(t-\tau)I(t-\tau)}{N(t-\tau)} \right. \right. \\ &\quad \left. \left. + \frac{\beta_2(t-\tau)S(t-\tau)G(t-\tau)}{M} \right) e^{-\int_{t-\tau}^t \mu(r)dr} \right] e^{\int_0^t \mu(s)ds}. \end{aligned}$$

By integrating on both sides, we obtain

$$\begin{aligned} &E(t)e^{\int_0^t \mu(s)ds} - E(0) \\ &= \int_0^t \left[\frac{\beta_1(s)S(s)I(s)}{N(s)} + \frac{\beta_2(s)S(s)G(s)}{M} \right] e^{\int_0^s \mu(\rho)d\rho} ds \\ &\quad - \int_0^{t-\tau} \left[\frac{\beta_1(s-\tau)S(s-\tau)I(s-\tau)}{N(s-\tau)} + \frac{\beta_2(s-\tau)S(s-\tau)G(s-\tau)}{M} \right] e^{\int_0^{s-\tau} \mu(\rho)d\rho} ds \\ &= \int_0^t \left[\frac{\beta_1(s)S(s)I(s)}{N(s)} + \frac{\beta_2(s)S(s)G(s)}{M} \right] e^{\int_0^s \mu(\rho)d\rho} ds \\ &\quad - \int_{-\tau}^{t-\tau} \left[\frac{\beta_1(s)S(s)I(s)}{N(s)} + \frac{\beta_2(s)S(s)G(s)}{M} \right] e^{\int_0^s \mu(\rho)d\rho} ds \\ &= \int_{t-\tau}^t \left[\frac{\beta_1(s)S(s)I(s)}{N(s)} + \frac{\beta_2(s)S(s)G(s)}{M} \right] e^{\int_0^s \mu(\rho)d\rho} ds \\ &\quad - \int_{-\tau}^0 \left[\frac{\beta_1(s)S(s)I(s)}{N(s)} + \frac{\beta_2(s)S(s)G(s)}{M} \right] e^{\int_0^s \mu(\rho)d\rho} ds. \end{aligned}$$

Hence, if $E(0) = \int_{-\tau}^0 \left[\frac{\beta_1(s)S(s)I(s)}{N(s)} + \frac{\beta_2(s)S(s)G(s)}{M} \right] e^{\int_0^s \mu(\rho)d\rho} ds$ is satisfied, we then have

$$E(t) = \int_{t-\tau}^t \left[\frac{\beta_1(s)S(s)I(s)}{N(s)} + \frac{\beta_2(s)S(s)G(s)}{M} \right] e^{-\int_s^t \mu(\rho)d\rho} ds. \quad (2.4)$$

We see that $u_2(t) \geq 0$, $\forall t \in [0, m]$ whenever $u_i(t) \geq 0$ for all $i \neq 2$ and $t \in [0, m] \subseteq [0, \sigma_\phi)$. Let $\phi = (\phi_1, \phi_2, \phi_3, \phi_4) \in \mathcal{X}_{\delta_0}$ be given. If $\phi_i(0) = 0$ for some $i \in \{1, 3, 4\}$, then $f_i(t, \phi) \geq 0$. If $\phi_4(0) = M$, then $f_4(t, \phi) \leq 0$. By [22, Theorem 5.2.1] and its proof, it follows that for any $\phi \in \mathcal{X}_{\delta_0}$, $u_i(t, \phi) \geq 0$ for $i = 1, 3, 4$ for all $t \in [0, \sigma_\phi)$. By equation (2.4), we have $E(t) \geq 0$ for all $t \in [0, \sigma_\phi)$. Therefore, it

follows that for any $\phi \in \mathcal{X}_{\delta_0}$, system (2.1) has a unique nonnegative solution $u(t, \phi)$ with $u_0 = \phi$ satisfies $u(t, \phi) \in W$ for all $t \in [0, \sigma_\phi)$.

Note that $\frac{dN(t)}{dt} \geq \bar{B} - \widehat{\mu}N(t)$. For the system

$$\frac{dy}{dt} = \bar{B} - \widehat{\mu}y(t),$$

the equilibrium $\frac{\bar{B}}{\widehat{\mu}}$ is globally asymptotically stable. For any $0 < \delta_0 < \frac{\bar{B}}{\widehat{\mu}}$, $\frac{dy}{dt}|_{y=\delta_0} = \bar{B} - \widehat{\mu}\delta_0 > 0$. So if $y(0) \geq \delta_0$, then $y(t) \geq \delta_0$ for any $t \geq 0$. By the comparison principle,

$$N(t) \geq \delta_0 \text{ if } N(0) = \sum_{i=1}^3 \phi_i(0) \geq \delta_0.$$

This implies that $u(t, \phi) \in \mathcal{X}_{\delta_0}$ for all $t \in [0, \sigma_\phi)$. Also we have

$$\frac{dG(t)}{dt} \leq a(t)(M - G(t)) - \delta(t)G(t) = a(t)M - (a(t) + \delta(t))G(t)$$

for all $t \in [0, \sigma_\phi)$. Thus, both $N(t)$ and $G(t)$ are bounded on $[0, \sigma_\phi)$, it follows that $\sigma_\phi = \infty$ (see [21, Theorem 2.3.1]), and that all solutions are ultimately bounded. Moreover, when $N(t) > \max\{\frac{\bar{B}}{\widehat{\mu}}, \frac{\widehat{a}M}{\widehat{a}+\delta}\}$ and $G(t) > \max\{\frac{\bar{B}}{\widehat{\mu}}, \frac{\widehat{a}M}{\widehat{a}+\delta}\}$, we have

$$\frac{dN(t)}{dt} < 0 \text{ and } \frac{dG(t)}{dt} < 0.$$

This implies that all solutions are uniformly bounded. □

It is easy to see that system (2.1) has a unique virus-free periodic solution $E_0(t) = (N^*(t), 0, 0, 0)$, where $N^*(t)$ is the positive periodic solution of (2.3). Linearizing system (2.1) at its virus-free periodic solution $E_0(t) = (N^*(t), 0, 0, 0)$, we then obtain the following system of periodic linear equations for the infective variables E, I , and G

$$\begin{cases} \frac{dE(t)}{dt} = \beta_1(t)I(t) + \frac{\beta_2(t)N^*(t)}{M}G(t) - \mu(t)E(t) \\ \quad - \left[\beta_1(t-\tau)I(t-\tau) + \frac{\beta_2(t-\tau)N^*(t-\tau)}{M}G(t-\tau) \right] e^{-\int_{t-\tau}^t \mu(r)dr}, \\ \frac{dI(t)}{dt} = \left[\beta_1(t-\tau)I(t-\tau) + \frac{\beta_2(t-\tau)N^*(t-\tau)}{M}G(t-\tau) \right] e^{-\int_{t-\tau}^t \mu(r)dr} - \mu(t)I(t), \\ \frac{dG(t)}{dt} = \frac{a(t)M}{N^*(t)}I(t) - \delta(t)G(t). \end{cases} \quad (2.5)$$

Since the first equation of system (2.5) is decoupled from the second and third equations of system (2.5), it suffices to use the following system to define the basic reproduction number

$$\begin{cases} \frac{dI(t)}{dt} = \left[\beta_1(t-\tau)I(t-\tau) + \frac{\beta_2(t-\tau)N^*(t-\tau)}{M}G(t-\tau) \right] e^{-\int_{t-\tau}^t \mu(r)dr} - \mu(t)I(t), \\ \frac{dG(t)}{dt} = \frac{a(t)M}{N^*(t)}I(t) - \delta(t)G(t). \end{cases} \quad (2.6)$$

Let $F : \mathbb{R} \rightarrow \mathcal{L}(C, \mathbb{R}^2)$ be a map and $V(t)$ be a continuous 2×2 matrix function on \mathbb{R} defined as follows

$$F(t)\phi = \begin{pmatrix} [\beta_1(t-\tau)\phi_1(-\tau) + \frac{\beta_2(t-\tau)N^*(t-\tau)}{M}\phi_2(-\tau)]e^{-\int_{t-\tau}^t \mu(r)dr} \\ \frac{a(t)M}{N^*(t)}\phi_1(0) \end{pmatrix},$$

and

$$V(t) = \begin{pmatrix} \mu(t) & 0 \\ 0 & \delta(t) \end{pmatrix}.$$

Let $\Phi(t, s)$ be the evolution matrices of the linear ordinary differential system

$$\frac{dy}{dt} = -V(t)y,$$

that is

$$\frac{\partial \Phi(t, s)}{\partial t} = -V(t)\Phi(t, s), \forall t \geq s \text{ and } \Phi(s, s) = I, \forall s \in \mathbb{R},$$

where I is the 2×2 identity matrix. It then easily follows that

$$\Phi(t, s) = \begin{pmatrix} e^{-\int_s^t \mu(r)dr} & 0 \\ 0 & e^{-\int_s^t \delta(r)dr} \end{pmatrix}.$$

Let C_ω be the ordered Banach space of all continuous and ω -periodic functions from \mathbb{R} to \mathbb{R}^2 , which is equipped with the maximum norm and the positive cone $C_\omega^+ = \{v \in C_\omega : v(t) \geq 0, \forall t \in \mathbb{R}\}$. Then we can define one linear operator on C_ω by

$$[Lv](t) = \int_0^\infty \Phi(t, t-s)F(t-s)v(t-s+\cdot)ds, \forall t \in \mathbb{R}, v \in C_\omega.$$

According to [23], the basic reproduction number is defined as $R_0 = r(L)$, the spectral radius of L .

Let

$$\mathcal{Y} = C([- \tau, 0], \mathbb{R}^2), \quad \mathcal{Y}_+ = C([- \tau, 0], \mathbb{R}_+^2).$$

Then $(\mathcal{Y}, \mathcal{Y}_+)$ is an ordered Banach space.

Let $P(t)$ be the solution maps of (2.6), that is, $P(t)\phi = u_t(\phi)$, where $u(t, \phi)$ is the unique solution of (2.6) with $u_0 = \phi \in \mathcal{Y}$. Then $P := P(\omega)$ is the Poincaré map associated with (2.6). Let $r(P)$ be the spectral radius of P . By [23, Theorem 2.1], we have the following result:

Lemma 2.2. $R_0 - 1$ has the same sign as $r(P) - 1$.

The following lemma indicates that the periodic semiflow $P(t)$ is eventually strongly monotone.

Lemma 2.3. For any φ and ψ in \mathcal{Y}_+ with $\varphi > \psi$ (that is, $\varphi \geq \psi$ but $\varphi \neq \psi$), the solutions $v(t, \varphi)$ and $v(t, \psi)$ of system (2.6) with $v_0 = \varphi$ and $v_0 = \psi$, respectively, satisfy $v_i(t, \varphi) > v_i(t, \psi)$ for all $t > \tau$, $i = 1, 2$, and hence, $P(t)\varphi \gg P(t)\psi$ in \mathcal{Y}_+ for all $t > 2\tau$.

Proof. For any $\varphi, \psi \in \mathcal{Y}_+$ with $\varphi \geq \psi$, let $v(t, \varphi)$ and $v(t, \psi)$ be the unique solutions of system (3.1) satisfying $v_0 = \varphi$ and $v_0 = \psi$, respectively. By [22, Theorem 5.1.1], we have $v(t, \varphi) \geq v(t, \psi)$ for all $t \geq 0$; that is, $P(t) : \mathcal{Y}_+ \rightarrow \mathcal{Y}_+$ is monotone. Next we prove that $P(t) : \mathcal{Y}_+ \rightarrow \mathcal{Y}_+$ is eventually strongly monotone. Let $\varphi, \psi \in \mathcal{Y}_+$ satisfy $\varphi > \psi$. Denote $v(t, \varphi) = (\bar{y}_1(t), \bar{y}_2(t))$ and $v(t, \psi) = (y_1(t), y_2(t))$.

Claim 1. There exists $t_0 \in [0, \tau]$ such that $\bar{y}_1(t) > y_1(t)$ for all $t \geq t_0$.

We first prove that $\bar{y}_1(t_0) > y_1(t_0)$ for some $t_0 \in [0, \tau]$. Otherwise, we have $\bar{y}_1(t) = y_1(t), \forall t \in [0, \tau]$, and hence $\frac{d\bar{y}_1(t)}{dt} = \frac{dy_1(t)}{dt}$ for all $t \in (0, \tau)$. Thus, we have

$$\beta_1(t-\tau)[\bar{y}_1(t-\tau) - y_1(t-\tau)] + \frac{\beta_2(t-\tau)N^*(t-\tau)}{M}[\bar{y}_2(t-\tau) - y_2(t-\tau)] = 0, \forall t \in [0, \tau].$$

Since $P(t)$ is monotone, it follows that $\bar{y}_1(t - \tau) = y_1(t - \tau)$ and $\bar{y}_2(t - \tau) = y_2(t - \tau)$ for all $t \in [0, \tau]$, that is, $\varphi_1(\theta) = \psi_1(\theta)$ and $\varphi_2(\theta) = \psi_2(\theta)$ for all $\theta \in [-\tau, 0]$, a contradiction to the assumption that $\varphi > \psi$.

Let $g_1(t, y) = \left[\beta_1(t - \tau)y_1(t - \tau) + \frac{\beta_2(t - \tau)N^*(t - \tau)}{M}y_2(t - \tau) \right] e^{-\int_{t-\tau}^t \mu(r)dr} - \mu(t)y$. Since

$$\begin{aligned} \frac{d\bar{y}_1(t)}{dt} &= \left[\beta_1(t - \tau)\bar{y}_1(t - \tau) + \frac{\beta_2(t - \tau)N^*(t - \tau)}{M}\bar{y}_2(t - \tau) \right] e^{-\int_{t-\tau}^t \mu(r)dr} - \mu(t)\bar{y}_1(t) \\ &\geq \left[\beta_1(t - \tau)y_1(t - \tau) + \frac{\beta_2(t - \tau)N^*(t - \tau)}{M}y_2(t - \tau) \right] e^{-\int_{t-\tau}^t \mu(r)dr} - \mu(t)\bar{y}_1(t) = g_1(t, \bar{y}_1(t)), \end{aligned}$$

we have $\frac{d\bar{y}_1(t)}{dt} - g_1(t, \bar{y}_1(t)) \geq 0 = \frac{dy_1(t)}{dt} - g_1(t, y_1(t))$, $\forall t \geq t_0$. Since $\bar{y}_1(t_0) > y_1(t_0)$, the comparison theorem for ordinary differential equations [24, Theorem 4] implies that $\bar{y}_1(t) > y_1(t)$ for all $t \geq t_0$.

Claim 2. $\bar{y}_2(t) > y_2(t)$ for all $t > t_0$.

Let $g_2(t, y) = \frac{a(t)M}{N^*(t)}y_1(t) - \delta(t)y$. Then we have

$$\begin{aligned} \frac{d\bar{y}_2(t)}{dt} &= \frac{a(t)M}{N^*(t)}\bar{y}_1(t) - \delta(t)\bar{y}_2(t) \\ &> \frac{a(t)M}{N^*(t)}y_1(t) - \delta(t)\bar{y}_2(t) = g_2(t, \bar{y}_2(t)) \quad \forall t > t_0, \end{aligned}$$

and hence, $\frac{d\bar{y}_2(t)}{dt} - g_2(t, \bar{y}_2(t)) > 0 = \frac{dy_2(t)}{dt} - g_2(t, y_2(t))$ $\forall t > t_0$. Since $\bar{y}_2(t_0) \geq y_2(t_0)$, it follows from [24, Theorem 4] that $\bar{y}_2(t) > y_2(t)$ for all $t > t_0$.

In view of the above two claims, we obtain

$$(\bar{y}_1(t), \bar{y}_2(t)) \gg (y_1(t), y_2(t)), \quad \forall t > t_0.$$

Since $t_0 \in [0, \tau]$, it follows that $(\bar{y}_{1t}, \bar{y}_{2t}) \gg (y_{1t}, y_{2t})$, $\forall t > 2\tau$, that is, $v_t(\varphi) \gg v_t(\psi)$ for all $t > 2\tau$. This shows $P(t) : \mathcal{Y}_+ \rightarrow \mathcal{Y}_+$ is strongly monotone for any $t > 2\tau$. \square

3. Threshold dynamics

First we show that the virus will be endemic if $R_0 > 1$. Let

$$\begin{aligned} X_0 &= \{\phi = (\phi_1, \phi_2, \phi_3, \phi_4) \in \mathcal{X}_{\delta_0} : \phi_3(0) > 0, \phi_4(0) > 0\}, \\ \partial X_0 &= \mathcal{X}_{\delta_0} \setminus X_0 = \{\phi \in \mathcal{X}_{\delta_0} : \phi_3(0) = 0 \text{ or } \phi_4(0) = 0\}. \end{aligned}$$

Theorem 3.1. *Assume that $R_0 > 1$, then there exists a positive constant $\eta > 0$ such that any solution $(S(t, \phi), E(t, \phi), I(t, \phi), G(t, \phi))$ of system (2.1) with $\phi \in X_0$ satisfies*

$$\liminf_{t \rightarrow \infty} (I(t, \phi), G(t, \phi)) \geq (\eta, \eta).$$

Proof. Let $Q(t)$ be the solution maps of (2.1) on \mathcal{X}_{δ_0} , that is, $Q(t)\phi = u_t(\phi)$, $t \geq 0$, where $u(t, \phi)$ is the unique solution of (2.1) satisfying $u_0 = \phi \in \mathcal{X}_{\delta_0}$. Then $Q := Q(\omega)$ is the Poincaré map associated with (2.1).

From the third, fourth equations of system (2.1) and equation (2.2), it is easy to see that $Q(t)X_0 \subseteq X_0$ for all $t \geq 0$. Lemma 2.1 implies that $\{Q^n : \mathcal{X}_{\delta_0} \rightarrow \mathcal{X}_{\delta_0}\}_{n \geq 0}$ is point dissipative and Q^n is compact for sufficiently large n . It then follows from [25, Theorem 2.9] that Q admits a global attractor in \mathcal{X}_{δ_0} . Now we prove that Q is uniformly persistent with respect to $(X_0, \partial X_0)$.

Let $M_1 = (N_0^*, 0, 0, 0)$, where $N_0^*(\theta) = N^*(\theta)$ for all $\theta \in [-\tau, 0]$. Since $\lim_{\phi \rightarrow M_1} \|Q(t)\phi - Q(t)M_1\| = 0$ uniformly for $t \in [0, \omega]$, for any given $\varepsilon > 0$, there exists a $\eta_1 > 0$ such that for any $\phi \in X_0$ with $\|\phi - M_1\| < \eta_1$, we have $\|Q(t)\phi - Q(t)M_1\| < \varepsilon$ for all $t \in [0, \omega]$.

Claim 3. $\limsup_{n \rightarrow \infty} \|Q(n\omega)\phi - M_1\| \geq \eta_1$ for all $\phi \in X_0$.

Suppose, by contradiction, then $\limsup_{n \rightarrow \infty} \|Q(n\omega)\psi - M_1\| < \eta_1$ for some $\psi \in X_0$. Then there is an integer $N_1 \geq 1$ such that $\|Q(n\omega)\psi - M_1\| < \eta_1$ for all $n \geq N_1$. For $t \geq N_1\omega$, we have $t = n\omega + t_1$, with $n \geq N_1$, $t_1 \in [0, \omega]$ and $\|Q(t)\psi - Q(t)M_1\| = \|Q(t_1)Q(n\omega)\psi - Q(t_1)Q(n\omega)M_1\| = \|Q(t_1)Q(n\omega)\psi - Q(t_1)M_1\| < \varepsilon$ for all $t \geq N_1\omega$. Therefore, $N^*(t) - \varepsilon < S(t) < N^*(t) + \varepsilon$, $0 \leq E(t) < \varepsilon$, $0 < I(t) < \varepsilon$, $0 < G(t) < \varepsilon$ for all $t \geq N_1\omega$.

let $P_\varepsilon(t)$ be the solution maps of the following system on \mathcal{Y}_+ :

$$\begin{cases} \frac{d\check{I}(t)}{dt} = \left[\frac{\beta_1(t-\tau)(N^*(t-\tau)-\varepsilon)}{N^*(t-\tau)+3\varepsilon} \check{I}(t-\tau) + \frac{\beta_2(t-\tau)(N^*(t-\tau)-\varepsilon)}{M} \check{G}(t-\tau) \right] e^{-\int_{t-\tau}^t \mu(r)dr} \\ \quad - \mu(t)\check{I}(t), \\ \frac{d\check{G}(t)}{dt} = \frac{a(t)(M-\varepsilon)}{N^*(t)+3\varepsilon} \check{I}(t) - \delta(t)\check{G}(t). \end{cases} \quad (3.1)$$

and $P_\varepsilon := P_\varepsilon(\omega)$. Since $R_0 > 1$, then $\lim_{\varepsilon \rightarrow 0^+} r(P_\varepsilon) = r(P) > 1$. Then we can fix a sufficiently small $\varepsilon > 0$, such that $r(P_\varepsilon) > 1$, and $N^*(t) - \varepsilon > 0$, $M - \varepsilon > 0$ for all $t \geq 0$. By the arguments similar to system (2.6), it is easy to verify that $P_\varepsilon(t)$ is strongly monotone on \mathcal{Y}_+ for $t > 2\tau$. It follows from [21, Theorem 3.6.1] that the linear operator $P_\varepsilon(t)$ is compact on \mathcal{Y}_+ . Choose an integer $n_0 > 0$ such that $n_0\omega > 2\tau$. Since $P_\varepsilon^{n_0} = P_\varepsilon(n_0\omega)$, [26, Lemma 3.1] implies that $r(P_\varepsilon)$ is a simple eigenvalue of P_ε having a strongly positive eigenvector. It then follows from [27, Lemma 1] that there is a positive ω -periodic function $v^*(t) = (v_1^*(t), v_2^*(t))$ such that $u_\varepsilon^*(t) = e^{\frac{\ln r(P_\varepsilon)}{\omega} t} v^*(t)$ is a positive solution of system (3.1).

For all $t \geq N_1\omega + \tau$, by system (2.1), we have

$$\begin{cases} \frac{dI(t)}{dt} \geq \left[\frac{\beta_1(t-\tau)(N^*(t-\tau)-\varepsilon)}{N^*(t-\tau)+3\varepsilon} I(t-\tau) + \frac{\beta_2(t-\tau)(N^*(t-\tau)-\varepsilon)}{M} G(t-\tau) \right] e^{-\int_{t-\tau}^t \mu(r)dr} \\ \quad - \mu(t)I(t), \\ \frac{dG(t)}{dt} \geq \frac{a(t)(M-\varepsilon)}{N^*(t)+3\varepsilon} I(t) - \delta(t)G(t). \end{cases}$$

Since $I(t, \psi) > 0$, $G(t, \psi) > 0$ for all $t \geq 0$, we can choose a sufficiently small $k > 0$ such that

$$I(t, \psi), G(t, \psi) \geq ku_\varepsilon^*(t), \forall t \in [N_1\omega + \tau, N_1\omega + 2\tau].$$

By [22, Theorem 5.1.1] it follows that $I(t, \psi), G(t, \psi) \geq ku_\varepsilon^*(t)$, $\forall t \geq N_1\omega + 2\tau$. Thus we have $I(t, \psi) \rightarrow \infty$, $G(t, \psi) \rightarrow \infty$, a contradiction.

Define

$$M_\partial := \{\phi \in \partial X_0 : Q^n(\phi) \in \partial X_0, \forall n \geq 0\}.$$

For any given $\psi \in \partial X_0$, we have $\psi_3(0) = 0$ or $\psi_4(0) = 0$.

If $\psi_3(0) = 0$, we have the following two cases.

Case 1. $I(t, \psi) = 0$ for all $t \geq 0$.

From the third equation of (2.1), we have $G(t - \tau, \psi) = 0$ for all $t \geq \tau$. Then from equation (2.2), we get $E(t, \psi) = 0$ for all $t \geq \tau$. In this case, $Q^n(\psi) \rightarrow M_1$ as $n \rightarrow \infty$.

Case 2. $I(t_2, \psi) > 0$ for some $t_2 > 0$.

From the third and fourth equations of (2.1), we have $I(t, \psi) > 0$ and $G(t, \psi) > 0$ for all $t \geq t_2$. Thus $Q^n(\psi) \in X_0$ for $n\omega > t_2$.

For the case $\psi_4(0) = 0$, we can do similar analysis. Finally, we see that for any $\psi \in M_\partial$, $Q^n(\psi) \rightarrow M_1$ as $n \rightarrow \infty$. Thus $\omega(\psi) = M_1$ for any $\psi \in M_\partial$, and M_1 can not form a cycle in ∂X_0 .

By Claim 3, we see that M_1 is an isolated invariant set for Q in X , and $W^s(M_1) \cap X_0 = \emptyset$, where $W^s(M_1)$ is the stable set of M_1 for Q . By the acyclicity theorem on uniform persistence for maps (see [28, Theorem 1.3.1 and Remark 1.3.1]), it follows that $Q : X \rightarrow X$ is uniformly persistent with respect to X_0 . Thus, [28, Theorem 3.1.1] implies that the periodic semiflow $Q(t) : X \rightarrow X$ is also uniformly persistent with respect to X_0 .

It remains to prove the practical uniform persistence. By [25, Theorem 4.5], with $\rho(x) = d(x, \partial X_0)$, it then follows that $Q : X_0 \rightarrow X_0$ has a compact global attractor A_0 . For any $\phi \in A_0$, we have $\phi_i(0) > 0$ for all $i = 3, 4$. Let $B_0 = \cup_{t \in [0, \omega]} Q(t)A_0$. Then $\psi_i(0) > 0$, $i = 3, 4$, for all $\psi \in B_0$. It is easy to see that $\lim_{t \rightarrow \infty} d(Q(t)\phi, B_0) = 0$ for all $\phi \in X_0$. Let $X_+ = C([-\tau, 0], \mathbb{R}_+^4)$, and define a continuous function $p : X_+ \rightarrow \mathbb{R}_+$ by

$$p(\phi) = \min\{\phi_3(0), \phi_4(0)\}, \forall \phi \in X_+.$$

Clearly, $p(\phi) > 0$ for all $\phi \in B_0$. Since B_0 is a compact subset of X_+ , we have $\inf_{\phi \in B_0} p(\phi) = \min_{\phi \in B_0} p(\phi) > 0$. By the attractiveness of B_0 , it then follows that there exists $\eta > 0$ such that

$$\liminf_{t \rightarrow \infty} \min(I(t, \phi), G(t, \phi)) = \liminf_{t \rightarrow \infty} p(Q(t)\phi) \geq \eta, \forall \phi \in X_0.$$

This completes the proof. \square

The following theorem shows that the virus will be cleared from the population if $R_0 < 1$.

Theorem 3.2. *If $R_0 < 1$, then the virus-free periodic solution $E_0(t) = (N^*(t), 0, 0, 0)$ is globally attractive for system (2.1) in X_{δ_0} .*

Proof. By the aforementioned analysis for (2.3), we know that (2.3) has a positive ω -periodic solution $N^*(t)$ which is globally asymptotically stable. It then follows that for any $\epsilon > 0$, we can choose a sufficiently large integer $n_1 > 0$ such that $n_1\omega > \tau$ and $N^*(t) - \epsilon < N(t) = S(t) + E(t) + I(t) < N^*(t) + \epsilon$ for $t > n_1\omega - \tau$. Thus, for $t > n_1\omega$, we have

$$\begin{cases} \frac{dI(t)}{dt} \leq \left[\beta_1(t - \tau)I(t - \tau) + \frac{\beta_2(t - \tau)(N^*(t - \tau) + \epsilon)}{M}G(t - \tau) \right] e^{-\int_{t-\tau}^t \mu(r)dr} - \mu(t)I(t), \\ \frac{dG(t)}{dt} \leq \frac{a(t)M}{N^*(t) - \epsilon}I(t) - \delta(t)G(t). \end{cases}$$

It then suffices to show that positive solutions of the auxiliary system

$$\begin{cases} \frac{d\tilde{I}(t)}{dt} = \left[\beta_1(t - \tau)\tilde{I}(t - \tau) + \frac{\beta_2(t - \tau)(N^*(t - \tau) + \epsilon)}{M}\tilde{G}(t - \tau) \right] e^{-\int_{t-\tau}^t \mu(r)dr} \\ \quad - \mu(t)\tilde{I}(t), \\ \frac{d\tilde{G}(t)}{dt} = \frac{a(t)M}{N^*(t) - \epsilon}\tilde{I}(t) - \delta(t)\tilde{G}(t) \end{cases} \quad (3.2)$$

tend to zero when t tends to infinity. Let $P_\epsilon(t)$ be the solution maps of system (3.2) on \mathcal{Y} , and $P_\epsilon := P_\epsilon(\omega)$. Since $R_0 < 1$, then by Lemma 2.2, we have $\lim_{\epsilon \rightarrow 0^+} r(P_\epsilon) = r(P) < 1$. Thus we can fix $\epsilon > 0$ small enough such that $r(P_\epsilon) < 1$. According to [27, Lemma 1], there is a positive ω -periodic function $\varsigma(t) = (\varsigma_1(t), \varsigma_2(t))$, such that $u_\epsilon(t) = e^{\frac{\ln r(P_\epsilon)}{\omega}t} \varsigma(t)$ is a positive solution of system (3.2).

Let $l > 0$ large enough, such that $(I(t), G(t)) \leq lu_\epsilon(t)$ for $t \in [n_1\omega, n_1\omega + \tau]$. Then [22, Theorem 5.1.1] implies that $(I(t), G(t)) \leq lu_\epsilon(t)$ for all $t \geq n_1\omega + \tau$. Hence, $I(t) \rightarrow 0, G(t) \rightarrow 0$ as $t \rightarrow \infty$. It then follows from the theory of asymptotically periodic semiflow (see [28, Theorem 3.2.1]) that

$$\lim_{t \rightarrow \infty} (S(t) - N^*(t)) = 0, \quad \lim_{t \rightarrow \infty} E(t) = 0.$$

This completes the proof. \square

4. Autonomous case of system (2.1)

In this section, we study the corresponding autonomous system of system (2.1), that is, we suppose that all coefficients in system (2.1) are time independent and positive. In this case, system (2.1) becomes

$$\begin{cases} \frac{dS(t)}{dt} = B - \mu S(t) - \frac{\beta_1 S(t)I(t)}{N(t)} - \frac{\beta_2 S(t)G(t)}{M}, \\ \frac{dE(t)}{dt} = \frac{\beta_1 S(t)I(t)}{N(t)} + \frac{\beta_2 S(t)G(t)}{M} - \mu E(t) \\ \quad - \left[\frac{\beta_1 S(t-\tau)I(t-\tau)}{N(t-\tau)} + \frac{\beta_2 S(t-\tau)G(t-\tau)}{M} \right] e^{-\mu\tau}, \\ \frac{dI(t)}{dt} = \left[\frac{\beta_1 S(t-\tau)I(t-\tau)}{N(t-\tau)} + \frac{\beta_2 S(t-\tau)G(t-\tau)}{M} \right] e^{-\mu\tau} - \mu I(t), \\ \frac{dG(t)}{dt} = \frac{aI(t)}{N(t)}(M - G(t)) - \delta G(t). \end{cases} \quad (4.1)$$

For system (4.1), there is always the virus-free equilibrium $P_0 = (N^*, 0, 0, 0)$ with $N^* = \frac{B}{\mu}$.

Let

$$F_1 = \begin{pmatrix} \beta_1 e^{-\mu\tau} & \frac{\beta_2 N^* e^{-\mu\tau}}{M} \\ 0 & 0 \end{pmatrix}, \quad F_2 = \begin{pmatrix} 0 & 0 \\ \frac{aM}{N^*} & 0 \end{pmatrix} \quad \text{and} \quad V = \begin{pmatrix} \mu & 0 \\ 0 & \delta \end{pmatrix}.$$

It then follows that $F(\phi) = F_1\phi(-\tau) + F_2\phi(0)$. By [23, Corollary 2.1], we can define the basic reproduction number for system (4.1) as $\mathbf{R}_0 = r(\hat{F}V^{-1})$, where $\hat{F} = F_1 + F_2$. It then easily follows that

$$\hat{F}V^{-1} = \begin{pmatrix} \frac{\beta_1 e^{-\mu\tau}}{\mu} & \frac{\beta_2 N^* e^{-\mu\tau}}{\delta M} \\ \frac{aM}{\mu N^*} & 0 \end{pmatrix}$$

and

$$\mathbf{R}_0 = \frac{1}{2} \left(C_1 + \sqrt{C_1^2 + 4C_0} \right),$$

where $C_0 = \frac{a\beta_2 e^{-\mu\tau}}{\mu\delta}$, $C_1 = \frac{\beta_1 e^{-\mu\tau}}{\mu}$. We define $\Theta = \frac{\beta_1 \delta + \beta_2 a}{\mu\delta} e^{-\mu\tau}$, it is easy to verify that $\mathbf{R}_0 - 1$ has the same sign as $\Theta - 1$.

Now consider endemic equilibria with $I = I^* > 0$. Let the right-hand sides be zero, then system (4.1) admits another equilibrium: $P^* = (S^*, E^*, I^*, G^*)$, where

$$S^* = N^* - e^{\mu\tau} I^*,$$

$$E^* = (e^{\mu\tau} - 1)I^*,$$

$$G^* = \frac{aMI^*}{aI^* + \delta N^*},$$

and I^* is a positive real root of equation $g_1(I) = g_2(I)$, where

$$g_1(I) = \frac{\beta_1}{N^*} + \frac{\beta_2 a}{aI + \delta N^*}, \quad g_2(I) = \frac{\mu e^{\mu\tau}}{N^* - e^{\mu\tau} I}.$$

Note that $g_1(0) = \frac{\beta_1}{N^*} + \frac{\beta_2 a}{\delta N^*}$, $g_1(I)$ is decreasing with respect to $I > 0$ and $\lim_{I \rightarrow +\infty} g_1(I) = \frac{\beta_1}{N^*}$. Also $g_2(0) = \frac{\mu e^{\mu\tau}}{N^*}$, $g_2'(I) > 0$ for $I \in (0, N^* e^{-\mu\tau})$, and $\lim_{x \rightarrow (N^* e^{-\mu\tau})^-} g_2(x) = +\infty$. Then $g_1(I) = g_2(I)$ has a unique positive root in $(0, N^* e^{-\mu\tau})$ if and only if $g_1(0) > g_2(0)$, which is equivalent to $\mathbf{R}_0 > 1$. Therefore, if $\mathbf{R}_0 > 1$, system (4.1) has a unique endemic equilibrium P^* .

Define

$$\Omega_{\delta_0} = \{ \phi \in W : \sum_{i=1}^3 \phi_i(s) \geq \delta_0, \forall s \in [-\tau, 0],$$

$$\phi_2(0) = \int_{-\tau}^0 \left[\frac{\beta_1 \phi_1(\xi) \phi_3(\xi)}{\sum_{i=1}^3 \phi_i(\xi)} + \frac{\beta_2 \phi_1(\xi) \phi_4(\xi)}{M} \right] e^{\mu\xi} d\xi \}.$$

The following theorem provides the global stability of the virus-free equilibrium.

Theorem 4.1. *If $\mathbf{R}_0 < 1$, then the virus-free equilibrium P_0 is globally asymptotically stable for system (4.1) in Ω_{δ_0} , and is unstable if $\mathbf{R}_0 > 1$.*

Proof. Linearizing system (4.1) at the virus-free equilibrium P_0 , we obtain the characteristic equation

$$(\lambda + \mu)^2 g(\lambda, \tau) = 0,$$

with

$$g(\lambda, \tau) = \lambda^2 + (\mu + \delta)\lambda - e^{-\mu\tau} e^{-\lambda\tau} (\beta_1 \lambda + \beta_1 \delta + \beta_2 a) + \mu\delta.$$

It is clear that the local stability of P_0 is determined by the roots of $g(\lambda, \tau) = 0$. If $\tau = 0$, then $g(\lambda, 0) = \lambda^2 + (\mu + \delta - \beta_1)\lambda + \mu\delta - (\beta_1 \delta + \beta_2 a)$. If $\mathbf{R}_0 < 1$, then $\Theta = \frac{\beta_1 \delta + \beta_2 a}{\mu\delta} < 1$, which implies that $\mu + \delta - \beta_1 > 0$ and $\mu\delta - (\beta_1 \delta + \beta_2 a) > 0$. Then by the Routh-Hurwitz criterion, all the roots of $g(\lambda, 0) = 0$ have negative real parts, while if $\mathbf{R}_0 > 1$, then $\mu\delta - (\beta_1 \delta + \beta_2 a) < 0$, and $g(\lambda, 0) = 0$ has one positive real root. That is, for $\tau = 0$, P_0 is locally asymptotically stable for $\mathbf{R}_0 < 1$, and is unstable if $\mathbf{R}_0 > 1$.

Next we will show that $g(\lambda, \tau) = 0$ has no pure imaginary roots if $\mathbf{R}_0 < 1$. Obviously, $i\rho$ ($\rho \in \mathbb{R}$) is a root of $g(\lambda, \tau) = 0$ if and only if ρ satisfies

$$-\rho^2 + (\mu + \delta)\rho i - e^{-\mu\tau} (\cos \rho\tau - i \sin \rho\tau) (\beta_1 \rho i + \beta_1 \delta + \beta_2 a) + \mu\delta = 0.$$

Separating the real and the imaginary parts, we have

$$\begin{cases} \mu\delta - \rho^2 = \beta_1 e^{-\mu\tau} \rho \sin \rho\tau + (\beta_1 \delta + \beta_2 a) e^{-\mu\tau} \cos \rho\tau, \\ (\mu + \delta)\rho = \beta_1 e^{-\mu\tau} \rho \cos \rho\tau - (\beta_1 \delta + \beta_2 a) e^{-\mu\tau} \sin \rho\tau. \end{cases}$$

Squaring the two equations and adding them gives

$$z^2 + (\mu^2 + \delta^2 - \beta_1^2 e^{-2\mu\tau})z + \mu^2 \delta^2 (1 - \Theta^2) = 0, \quad (4.2)$$

where $z = \rho^2$. If $\mathbf{R}_0 < 1$, we have $\beta_1 e^{-\mu\tau} < \mu$, hence, (4.2) has no nonnegative root, which implies that $g(\lambda, \tau) = 0$ has no zero root and pure imaginary roots. Therefore, P_0 is locally asymptotically stable for all $\tau \geq 0$ if $\mathbf{R}_0 < 1$. Together with Theorem 3.2, we can show that P_0 is globally asymptotically stable in Ω_{δ_0} when $\mathbf{R}_0 < 1$.

□

We let

$$S^\infty = \limsup_{t \rightarrow \infty} S(t), \quad S_\infty = \liminf_{t \rightarrow \infty} S(t).$$

We can define $I^\infty, I_\infty, G^\infty, G_\infty$ in a similar way. Now we will use the method of fluctuations (see, e.g., [29]) to show the global attractivity of the endemic equilibrium P^* . To do this, we need the following assumption:

$$(H) (e^{-\mu\tau}a - \delta)\beta_2a > \beta_1(a + \delta)^2.$$

The condition (H) is technically needed in the arguments supporting the global attractivity of the endemic equilibrium P^* for system (4.1).

Theorem 4.2. *Let (H) hold. If $R_0 > 1$, then (4.1) has a unique endemic equilibrium $P^* = (S^*, E^*, I^*, G^*)$ such that $\lim_{t \rightarrow \infty} u(t, \phi) = P^*$ for any $\phi \in \Omega_{\delta_0}$ with $\phi_3(0) > 0$ and $\phi_4(0) > 0$.*

Proof. The whole mouse population satisfies the following equation:

$$\frac{dN(t)}{dt} = B - \mu N(t).$$

Then N^* is globally asymptotically stable. Hence, we have the following limiting system:

$$\left\{ \begin{array}{l} \frac{dS(t)}{dt} = B - \mu S(t) - \tilde{\beta}_1 S(t)I(t) - \tilde{\beta}_2 S(t)G(t), \\ \frac{dE(t)}{dt} = \tilde{\beta}_1 S(t)I(t) + \tilde{\beta}_2 S(t)G(t) - \mu E(t) \\ \quad - [\tilde{\beta}_1 S(t - \tau)I(t - \tau) + \tilde{\beta}_2 S(t - \tau)G(t - \tau)]e^{-\mu\tau}, \\ \frac{dI(t)}{dt} = [\tilde{\beta}_1 S(t - \tau)I(t - \tau) + \tilde{\beta}_2 S(t - \tau)G(t - \tau)]e^{-\mu\tau} - \mu I(t), \\ \frac{dG(t)}{dt} = \tilde{a}I(t)(M - G(t)) - \delta G(t), \end{array} \right. \quad (4.3)$$

where $\tilde{\beta}_1 = \frac{\beta_1}{N^*}$, $\tilde{\beta}_2 = \frac{\beta_2}{M}$, $\tilde{a} = \frac{a}{N^*}$. Since the second equation of system (4.3) is decoupled from the other three equations of system (4.3), we then consider the following system:

$$\left\{ \begin{array}{l} \frac{dS(t)}{dt} = B - \mu S(t) - \tilde{\beta}_1 S(t)I(t) - \tilde{\beta}_2 S(t)G(t), \\ \frac{dI(t)}{dt} = [\tilde{\beta}_1 S(t - \tau)I(t - \tau) + \tilde{\beta}_2 S(t - \tau)G(t - \tau)]e^{-\mu\tau} - \mu I(t), \\ \frac{dG(t)}{dt} = \tilde{a}I(t)(M - G(t)) - \delta G(t). \end{array} \right. \quad (4.4)$$

From the proof of Lemma 2.1, we can show that

$$\Gamma = C \left([-\tau, 0], \left[0, \frac{B}{\mu} \right] \times [0, M] \right)$$

is positively invariant for system (4.4). By the arguments similar to those in Theorem 3.1, it is easy to verify that system (4.4) is uniformly persistent in the sense that there exists a $\eta_2 > 0$ such that for

any given $\psi = (\psi_1, \psi_2, \psi_3) \in \Gamma$ with $\psi_2(0) > 0$, $\psi_3(0) > 0$, the solution $(S(t, \psi), I(t, \psi), G(t, \psi))$ of (4.4) satisfies $\liminf_{t \rightarrow \infty} (I(t, \psi), G(t, \psi)) \geq (\eta_2, \eta_2)$.

For any given $\psi \in \Gamma$ with $\psi_2(0) > 0$, $\psi_3(0) > 0$, let $(S(t), I(t), G(t)) = (S(t, \psi), I(t, \psi), G(t, \psi))$. It is clear that $S^\infty \geq S_\infty$, $\frac{B}{\mu} \geq I^\infty \geq I_\infty \geq \eta_2 > 0$, $G^\infty \geq G_\infty \geq \eta_2 > 0$. Moreover, there exist sequences t_n^i and σ_n^i , $i = 1, 2, 3$, such that

$$\begin{aligned} \lim_{n \rightarrow \infty} S(t_n^1) &= S^\infty, S'(t_n^1) = 0, \lim_{n \rightarrow \infty} S(\sigma_n^1) = S_\infty, S'(\sigma_n^1) = 0, \forall n \geq 1; \\ \lim_{n \rightarrow \infty} I(t_n^2) &= I^\infty, I'(t_n^2) = 0, \lim_{n \rightarrow \infty} I(\sigma_n^2) = I_\infty, I'(\sigma_n^2) = 0, \forall n \geq 1; \\ \lim_{n \rightarrow \infty} G(t_n^3) &= G^\infty, G'(t_n^3) = 0, \lim_{n \rightarrow \infty} G(\sigma_n^3) = G_\infty, G'(\sigma_n^3) = 0, \forall n \geq 1. \end{aligned}$$

It then follows from the first equation of (4.4), we have

$$B - \mu S^\infty - \tilde{\beta}_1 S^\infty I_\infty - \tilde{\beta}_2 S^\infty G_\infty \geq 0 \geq B - \mu S_\infty - \tilde{\beta}_1 S_\infty I^\infty - \tilde{\beta}_2 S_\infty G^\infty,$$

and

$$B - \mu S_\infty - \tilde{\beta}_1 S_\infty I_\infty - \tilde{\beta}_2 S_\infty G_\infty \geq 0 \geq B - \mu S_\infty - \tilde{\beta}_1 S_\infty I^\infty - \tilde{\beta}_2 S_\infty G^\infty,$$

we see that

$$\frac{B}{\mu + \tilde{\beta}_1 I_\infty + \tilde{\beta}_2 G_\infty} \geq S^\infty \geq S_\infty \geq \frac{B}{\mu + \tilde{\beta}_1 I^\infty + \tilde{\beta}_2 G^\infty}. \quad (4.5)$$

By the second and third equations of (4.4), by a similar argument, it then follows that

$$\frac{(\tilde{\beta}_1 S^\infty I^\infty + \tilde{\beta}_2 S^\infty G^\infty)e^{-\mu\tau}}{\mu} \geq I^\infty \geq I_\infty \geq \frac{(\tilde{\beta}_1 S_\infty I_\infty + \tilde{\beta}_2 S_\infty G_\infty)e^{-\mu\tau}}{\mu}, \quad (4.6)$$

and

$$\frac{\tilde{a}MI^\infty}{\tilde{a}I^\infty + \delta} \geq G^\infty \geq G_\infty \geq \frac{\tilde{a}MI_\infty}{\tilde{a}I_\infty + \delta}. \quad (4.7)$$

Using (4.5) and (4.6), we get

$$\frac{(\tilde{\beta}_1 I^\infty + \tilde{\beta}_2 G^\infty)Be^{-\mu\tau}}{\mu(\mu + \tilde{\beta}_1 I_\infty + \tilde{\beta}_2 G_\infty)} \geq I^\infty \geq I_\infty \geq \frac{(\tilde{\beta}_1 I_\infty + \tilde{\beta}_2 G_\infty)Be^{-\mu\tau}}{\mu(\mu + \tilde{\beta}_1 I^\infty + \tilde{\beta}_2 G^\infty)}. \quad (4.8)$$

Then (4.7) and (4.8) imply that

$$\begin{aligned} \frac{Be^{-\mu\tau}}{\mu} \left(\tilde{\beta}_1 + \frac{\tilde{\beta}_2 \tilde{a}M}{\tilde{a}I^\infty + \delta} \right) &\geq \mu + \tilde{\beta}_1 I_\infty + \frac{\tilde{\beta}_2 \tilde{a}MI_\infty}{\tilde{a}I_\infty + \delta}, \\ \frac{Be^{-\mu\tau}}{\mu} \left(\tilde{\beta}_1 + \frac{\tilde{\beta}_2 \tilde{a}M}{\tilde{a}I_\infty + \delta} \right) &\leq \mu + \tilde{\beta}_1 I^\infty + \frac{\tilde{\beta}_2 \tilde{a}MI^\infty}{\tilde{a}I^\infty + \delta}. \end{aligned}$$

Simplifying the above two inequalities, we get

$$\tilde{\beta}_1(\tilde{a}I^\infty + \delta)(\tilde{a}I_\infty + \delta)(I^\infty - I_\infty) \geq \tilde{\beta}_2 \tilde{a}M \left(\frac{Be^{-\mu\tau}}{\mu} \tilde{a} - \delta \right) (I^\infty - I_\infty).$$

Since $\tilde{\beta}_1(\tilde{a}I^\infty + \delta)(\tilde{a}I_\infty + \delta) \leq \tilde{\beta}_1(\tilde{a}\frac{B}{\mu} + \delta)^2$, then if condition (H) holds, we have $I^\infty = I_\infty$. By (4.5) and (4.7), we get $S^\infty = S_\infty$ and $G^\infty = G_\infty$. Then we have $\lim_{t \rightarrow \infty} (S(t), I(t), G(t)) = (S^*, I^*, G^*)$ for any $\psi \in \Gamma$ with $\psi_2(0) > 0$ and $\psi_3(0) > 0$. By the theory of chain transitive sets [28], we can lift the global attractivity for system (4.4) to system (4.1). It follows that $\lim_{t \rightarrow \infty} u(t, \phi) = P^*$, for any $\phi \in \Omega_{\delta_0}$ with $\phi_3(0) > 0$ and $\phi_4(0) > 0$.

□

5. Numerical simulations

In this section, we give numerical simulations that support the theory presented in the previous sections. To compute the basic reproduction number R_0 numerically, we first write the operator L into the integral form in [30]. For $v \in C_\omega$, we get

$$\begin{aligned}
 [Lv](t) &= \int_0^\infty \Phi(t, t-s)F(t-s)v(t-s+\cdot)ds \\
 &= \int_0^\infty \Phi(t, t-s) \\
 &\quad \times \left(\begin{array}{c} [\beta_1(t-s-\tau)v_1(t-s-\tau) + \frac{\beta_2(t-s-\tau)N^*(t-s-\tau)}{M}v_2(t-s-\tau)]e^{-\int_{t-s-\tau}^{t-s}\mu(r)dr} \\ \frac{a(t-s)M}{N^*(t-s)}v_1(t-s) \end{array} \right) ds \\
 &= \int_0^\infty \left(\begin{array}{c} [\beta_1(t-s-\tau)v_1(t-s-\tau) + \frac{\beta_2(t-s-\tau)N^*(t-s-\tau)}{M}v_2(t-s-\tau)]e^{-\int_{t-s-\tau}^t\mu(r)dr} \\ \frac{a(t-s)M}{N^*(t-s)}e^{-\int_{t-s}^t\delta(r)dr}v_1(t-s) \end{array} \right) ds \\
 &= \left(\begin{array}{c} \int_\tau^\infty [\beta_1(t-s)v_1(t-s) + \frac{\beta_2(t-s)N^*(t-s)}{M}v_2(t-s)]e^{-\int_{t-s}^t\mu(r)dr} ds \\ \int_0^\infty \frac{a(t-s)M}{N^*(t-s)}e^{-\int_{t-s}^t\delta(r)dr}v_1(t-s)ds \end{array} \right) \\
 &= \int_0^\infty K(t, s)v(t-s)ds,
 \end{aligned}$$

where

$$K(t, s) = \left(\begin{array}{cc} \beta_1(t-s)e^{-\int_{t-s}^t\mu(r)dr} & \frac{\beta_2(t-s)N^*(t-s)}{M}e^{-\int_{t-s}^t\mu(r)dr} \\ \frac{a(t-s)M}{N^*(t-s)}e^{-\int_{t-s}^t\delta(r)dr} & 0 \end{array} \right) \text{ if } s \geq \tau,$$

and

$$K(t, s) = \left(\begin{array}{cc} 0 & 0 \\ \frac{a(t-s)M}{N^*(t-s)}e^{-\int_{t-s}^t\delta(r)dr} & 0 \end{array} \right) \text{ if } s < \tau.$$

By the ω -periodicity of v , we obtain

$$[Lv](t) = \int_0^\omega G(t, s)v(t-s)ds,$$

where $G(t, s) = \sum_{n=0}^\infty K(t, s+n\omega)$. Consequently, we can use the numerical method in [30] to compute R_0 .

5.1. Long term behavior

The time unit is taken as month. Baseline parameters are $\mu = 0.246$, $\beta = 0.0024$, $\alpha = 0.0016$, $\gamma = 0.5$, $d = 60$, $\delta = 9.21$, $M = 50$. These parameters values are taken from [10]. To reflect the seasonality, we suppose that the birth rate of mice is $B(t) = 5.85(1 + 0.8 \sin(\pi t/6))$, the direct contact rate and the indirect contact rate are equal, that is, $c(t) = \bar{c}(t) = 60(1 + 0.8 \sin(\pi t/6))$. Since the incubation period is about one week, then we take $\tau = \frac{1}{3}$.

With this set of parameters, we have $R_0 = 1.3586 > 1$, the virus will be endemic and the infection is persistent in the mouse population (see Figure 1(a)). If we can increase the incubation period to $\tau = 2$, then $R_0 = 0.9876 < 1$. In this case, the long-term behavior of the infectious mice is shown in

Figure 1(b), which implies that the virus will be eradicated from the mouse population. These results are coincident with Theorems 3.1 and 3.2.

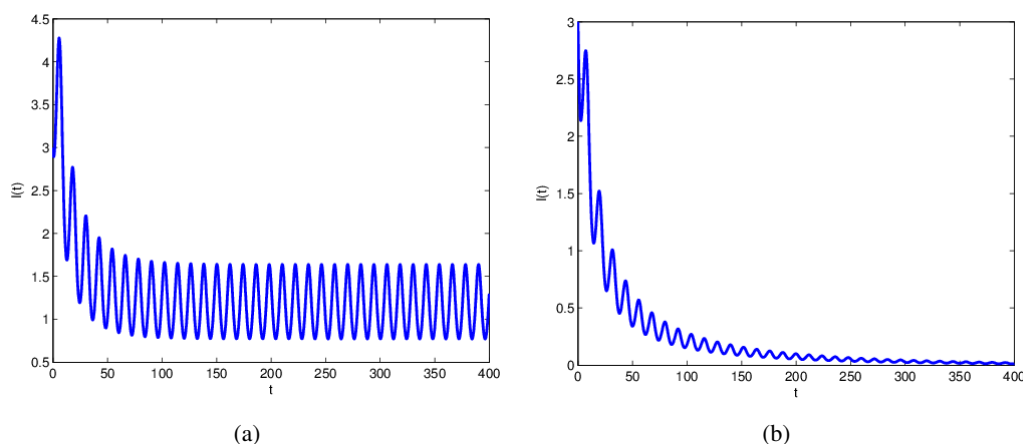


Figure 1. Long-term behavior of the infectious mouse population (a) $R_0 > 1$ and (b) $R_0 < 1$.

5.2. Effects of parameters on R_0

First, we discuss the influence of the incubation period. Let τ varies and keep other parameters as above. Our numerical computations demonstrate that R_0 is a decreasing function (see Figure 2). Hence, we may try to prolong the incubation period via medical drugs or control measures to control hantavirus infection. For example, to eradicate the virus, we should keep $\tau > 1.923$.

The dependence of \mathbf{R}_0 on τ is also illustrated in Figure 2. One can observe that for each fixed τ , \mathbf{R}_0 is greater than or equal to R_0 . Thus, the autonomous model may overestimate the value of R_0 .

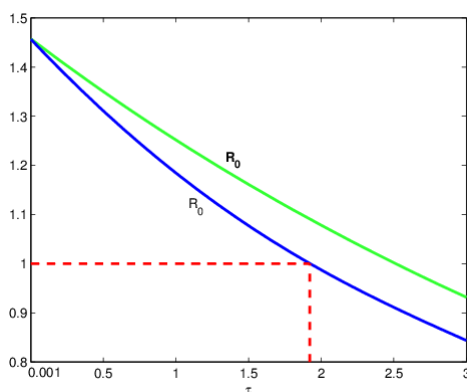


Figure 2. The graph of the basic reproduction numbers R_0 and \mathbf{R}_0 when τ varies.

Since contact rate plays a very important role in the spread of hantavirus. To explore the influence of direct contact rate and indirect contact rate on hantavirus transmission, we replace $c(t)$ with $\hat{c}(t) = (1-k)c(t)$ and $\bar{c}(t)$ with $\hat{\bar{c}}(t) = (1-l)\bar{c}(t)$ in our model. Then, Figure 3 shows R_0 is a decreasing function with respect to k and l . Moreover, Figure 3(a) shows that the virus will be endemic even if $k = 1$ (that is, $\hat{c}(t) = 0$) for $l = 0$, Figure 3(b) shows that if we keep $l > 0.63$, then the virus can be eradicated for

$k = 0$. For the parameters we have chosen, R_0 is more sensitive to the indirect transmission than the direct transmission. Thus, indirect transmission can not be neglected.

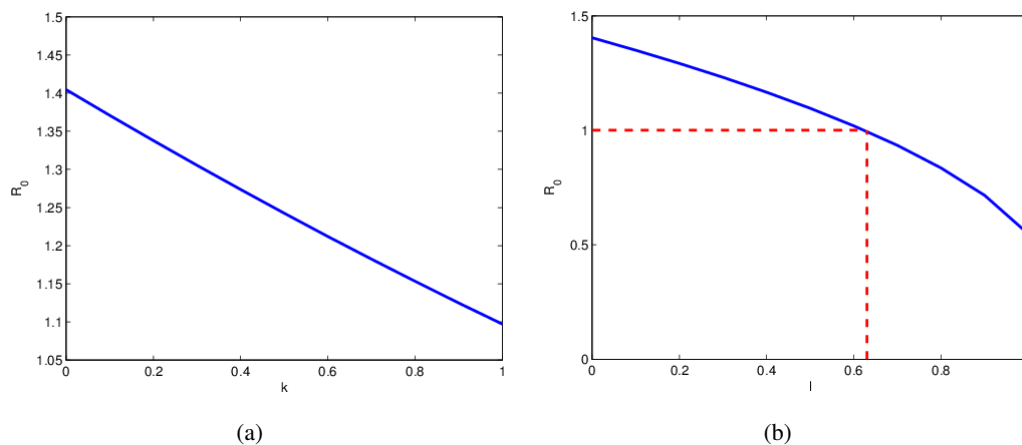


Figure 3. R_0 vs k and l . (a) Relationship between R_0 and k . (b) Relationship between R_0 and l .

6. Discussion

In this paper, we formulate and analyze a compartmental model for hantavirus infection that incorporating the seasonality, incubation period of the mice, direct and indirect transmission. Using the theory developed in [23], we first introduce the basic reproduction number R_0 for the model. Then we show that R_0 is a threshold parameter for the persistence and extinction of the virus. More precisely, the virus will be endemic when $R_0 > 1$, and the virus will be cleared if $R_0 < 1$. For the corresponding autonomous system, we obtain an explicit expression of \mathbf{R}_0 and establish a threshold result on the global stability in terms of \mathbf{R}_0 .

Numerical simulations are performed to illustrate our analytic results. Figure 2 shows that an increase of the incubation period could reduce R_0 , which implies that the virus infection can be relieved by prolonging the length of the incubation period. Moreover, our numerical results show that completely abolishing direct transmission would not eradicate virus (see Figure 3(a)), indirect transmission may play an important role in the virus transmission. On the other hand, Figure 3(b) shows that lowering the indirect transmission to 37% of the original value would lead to eradication of the virus. Hence, outdoor disinfection is very important to control the transmission of hantavirus.

In this paper, we ignore the age-structure of the mouse population, since juvenile mice must leave to find and establish their own home ranges, while the adults do not move, so it should be more reasonable to consider two types of mice: the adult and juvenile mice as noted in [9]. Also the diffusion of the juvenile mice plays an important role in hantavirus infection. We leave these problems for further investigation.

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Conflict of interest

The author declares there is no conflict of interest.

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