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MODELS FOR THE SPREAD AND PERSISTENCE OF HANTAVIRUS INFECTION IN RODENTS WITH DIRECT AND INDIRECT TRANSMISSION

Curtis L. Wesley

Louisiana State University in Shreveport
Department of Mathematics, Shreveport, LA 71115, USA

Linda J. S. Allen

Texas Tech University
Department of Mathematics and Statistics
Lubbock, TX 79409-1042, USA

Michel Langlais

Université Victor Segalen Bordeaux 2
IMB UMR CNRS 5251 & INRIA Bordeaux Sud Ouest projet Anubis, case 36
UFR Sciences et Modelisation, 3 ter place de la Victoire, 33076 Bordeaux Cedex, France

In Honor of Professor Horst R. Thieme on the Occasion of his 60th Birthday

Abstract. Hantavirus, a zoonotic disease carried by wild rodents, is spread among rodents via direct contact and indirectly via infected rodent excreta in the soil. Spillover to humans is primarily via the indirect route through inhalation of aerosolized viral particles. Rodent-hantavirus models that include direct and indirect transmission and periodically varying demographic and epidemiological parameters are studied in this investigation. Two models are analyzed, a nonautonomous system of differential equations with time-periodic coefficients and an autonomous system, where the coefficients are taken to be the time-average. In the nonautonomous system, births, deaths, transmission rates and viral decay rates are assumed to be periodic. For both models, the basic reproduction numbers are calculated. The models are applied to two rodent populations, reservoirs for a New World and for an Old World hantavirus. The numerical examples show that periodically varying demographic and epidemiological parameters may substantially increase the basic reproduction number. Also, large variations in the viral decay rate in the environment coupled with an outbreak in rodent populations may lead to spillover infection in humans.

1. **Introduction.** Zoonotic diseases carried by wildlife are spread to humans via direct contact with infectious animals or via indirect contact with pathogens that may persist in the environment. In humans, the pathogen can be difficult to identify and hard to control when the indirect method of spread dominates. In wildlife, the indirect route may be vital to maintenance and persistence of the pathogen in the host. Seasonal variations or climatic shifts may also impact the spread and persistence of zoonotic diseases. For example, an abundance of rain and subsequent vegetative growth in a typically dry area can result in population growth and hence,

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more opportunities for contacts among infectious animals and greater likelihood for the pathogen to enter and persist in the environment.

Hantavirus, a zoonotic disease carried by wild rodents (e.g., rats and mice), is spread to humans primarily via an indirect route, through inhalation of aerosolized viral particles from infected rodent excreta in the soil [24]. Infection in humans results in a disease known either as hantavirus pulmonary syndrome (HPS) caused by a New World hantavirus (Americas), or as hemorrhagic fever with renal syndrome (HFRS), caused by an Old World hantavirus (Europe and Asia) [17, 25, 27, 28]. It is well known that rodents leave urine markings to identify their environment and for sexual advertisement [12, 20, 26]. Thus, the longevity of hantavirus viability outside of the rodent host may be crucial to its spread and persistence in rodent populations as well as spread to humans. Kallio et al. [17] studied Puumula virus (an Old World hantavirus) outside the host at different temperatures and mediums, and found that the virus can live twelve to fifteen days (and up to eighteen days) at room temperature. In addition, it was shown that Puumula virus in a wet environment persisted longer than in a dry environment. It was suggested that one of the reasons for the outbreak of hantavirus in rodents and humans in the Four Corners Region of the United States (caused by the New World Sin Nombre virus) was due to an abundance of rain preceding the outbreak [22]. Seasonal variations in population densities and antibody prevalence have been noted in several rodent species, hosts for New and Old World hantaviruses (e.g., [13, 22, 23, 27, 28]).

It is the goal of this investigation to study the effects of periodically varying demographic and epidemiological parameters and indirect transmission on the persistence of the pathogen in the wildlife host. We base our models on the rodent-hantavirus system but the models may have applications to other wildlife diseases, where indirect transmission is important. For example, indirect transmission via environmental contamination has been modeled for feline panleucopenia virus in cats [11].

In rodent-hantavirus systems, periodically varying parameters or indirect transmission have been studied in various models [3, 27, 28, 37]. The impact of a seasonal periodic carrying capacity was studied numerically in deterministic and stochastic SEIR rodent-hantavirus models, where demographic parameters were chosen for the rice rat (*Oryzomys pallustris*), carrier of the New World Bayou hantavirus [3]. However, indirect transmission was not considered in this model. Sauvage and colleagues [27, 28, 37] included direct and indirect transmission of Puumula virus (carried by bank voles, *Clethrionomys glareolus*, in Europe) with seasonal fluctuations in births and variation in the carrying capacity due to food availability. Infectious rodents were separated into two classes: newly infectious with a high transmission rate and chronically infectious with a low transmission rate. Our models are based on these latter rodent-hantavirus models. Computer simulations and numerical results were reported in Sauvage et al. [27] but an analysis of the model was not undertaken. We extend the rodent-hantavirus model of Sauvage et al. [27] (hereafter referred to as the SLP model) by including periodic variation in the transmission parameters and viral decay rate and analyze this model. We apply some recent analytical results [8, 33] to show existence of a basic reproduction number $\mathcal{R}_0$ and local stability of the disease-free state when $\mathcal{R}_0 < 1$. Then we consider the model with time-averaged coefficients, derive an explicit expression for the basic reproduction number, $\hat{\mathcal{R}}_0$, and provide a complete analysis in the case that $\hat{\mathcal{R}}_0 < 1$. In particular, we prove global stability of the disease-free equilibrium when $\hat{\mathcal{R}}_0 < 1$ and local asymptotic

stability of an endemic equilibrium when $\hat{\mathcal{R}}_0 > 1$. We apply the models to two rodent populations, one is a carrier for a New World hantavirus and the other for an Old World hantavirus. The examples illustrate the impact of indirect transmission and periodic variations on pathogen persistence in rodent populations and in the environment that may lead to spillover infection in humans.

2. **Model.** Hantavirus in the rodent population is assumed to be transmitted directly from infectious rodents or indirectly from viral-contaminated soil. The rodent population is divided into two infectious stages, newly infectious with high viral titers and chronically infectious with low viral titers. Infected rodents do not experience any increased mortality due to the disease. Once infected, they carry the disease for life; there is no immunity. Thus, the model is of SI-type.

Let S denote the density of susceptible rodents, I_n the density of newly infectious and highly contagious rodents, I_c the density of chronically infectious and moderately contagious rodents and G the proportion of viral - contaminated soil. The total rodent population density is $P = S + I_n + I_c$.

The incident rates for newly and chronically infected rodents are $\beta_n I_n S$ and $\beta_c I_c S$, where $\beta_j \equiv \beta_j(P(t), t)$, $j = n, c$. We assume that the incidence rate is either of the form

$$\beta_j(P(t), t) = \lambda_j(t), \tag{1}$$

known as mass action incidence (or density-dependent transmission) or

$$\beta_j(P(t), t) = \frac{\lambda_j(t)}{P(t)}, \tag{2}$$

known as standard incidence (or frequency-dependent transmission), respectively. The function $\lambda_j(t)$ is a nonnegative, periodic and continuous function. Sauvage et al. [28] assumed the newly infectious rate of infection was density-dependent, whereas the chronically infectious rate of infection was frequency-dependent. Other rodent-hantavirus models have assumed one of these two forms for the incidence rate ([1, 2, 3, 4, 5, 6, 21, 28, 36]). The term $\epsilon(t)GS$ is the rate susceptible animals become infected via contact with viral-contaminated soil, frequency-dependent transmission. The transmission $\epsilon(t)$ may also be periodic. Soil contamination is normalized to a maximum of one, i.e., $0 \leq G \leq 1$. The per capita birth, death and density-dependent death rates of the rodents are $b(t)$, $m(t)$ and $k(t)$, respectively. Parameter $\tau(t)$ is the rate newly infectious rodents become chronically infectious. The expressions $\phi_n(t)(1 - G)$ and $\phi_c(t)(1 - G)$ are the per capita rates at which soil becomes contaminated by a newly or chronically infectious rodent, respectively. The parameter $d(t)$ corresponds to the decay rate of the hantavirus in the soil. In the SLP model [27], all parameters are constant, with the exception of the birth rate and density-dependent death rate. We extend our model to include periodicity for all coefficients, since seasonality may be present for all parameters. A compartmental diagram is given in Figure 1.

Based on the preceding assumptions, the rodent-hantavirus model takes the following form:

$$\begin{aligned}
\dot{S} &= b(t)P - [\beta_n(P,t)I_n + \beta_c(P,t)I_c + \epsilon(t)G]\,S - [m(t) + k(t)P]\,S \\
\dot{I}_n &= [\beta_n(P,t)I_n + \beta_c(P,t)I_c + \epsilon(t)G]\,S - [\tau(t) + m(t) + k(t)P]I_n \\
\dot{I}_c &= \tau(t)I_n - [m(t) + k(t)P]I_c \\
\dot{G} &= [\phi_n(t)I_n + \phi_c(t)I_c](1 - G) - d(t)G,
\end{aligned} \tag{3}$$

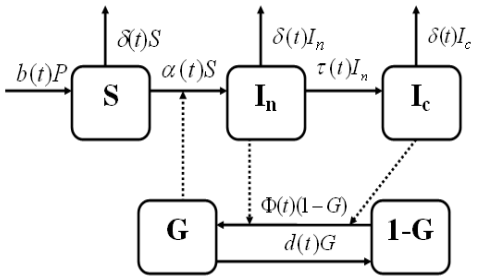

FIGURE 1. A compartmental diagram for the rodent-hantavirus model (3), where $\alpha(t) = \beta_n(P,t)I_n + \beta_c(P,t)I_c + \epsilon(t)G$, $\delta(t) = m(t)+k(t)P$ and $\Phi(t) = \phi_n(t)I_n+\phi_c(t)I_c$. Dashed arrows represent indirect transmission via ground contamination. The compartment $1-G$ represents the proportion of soil not contaminated by hantavirus.

where the total population density satisfies

$$\dot{P} = P[b(t) - m(t) - k(t)P], \quad P(0) > 0. \tag{4}$$

Initial values of S, I_n, I_c and G are nonnegative and $0 \le G(0) \le 1$. The transmission parameters $\beta_j(P,t)$ take one of the two forms, (1) or (2).

We make the following assumption regarding the time-periodic parameters.

(A1) The parameters $b(t)$, $m(t)$, $k(t)$, $\tau(t)$, $\epsilon(t)$, $d(t)$, $\lambda_j(t)$ and $\phi_j(t)$, $j = n, c$, are periodic, nonnegative (not identically zero), continuous and bounded with common minimal period $T > 0$.

Assumption (A1) allows for some of the coefficients to be positive constants but not all of them since $T > 0$.

First, we analyze the nonautonomous model (3) and show the existence of a basic reproduction number $\mathcal{R}_0$. Then we consider the special case where the coefficients in (3) are replaced by their average values, an autonomous model. For the autonomous model, an explicit formula is calculated for the basic reproduction number $\hat{\mathcal{R}}_0$ and a more complete analysis performed.

2.1. **Nonautonomous model.** We make several additional assumptions regarding the average value of the demographic parameters. Denote the average values of $b(t)$ and $m(t)$ by $\bar{b}$ and $\bar{m}$, respectively. For example, the average value of $b(t)$ is

$$\bar{b} = \frac{1}{T}\int_0^T b(t)\,dt.$$

Assume

(A2) $\bar{b} - \bar{m} > 0$.

(A3) $0 < k_{\min} < k(t) < k_{\max} < \infty$.

If assumptions (A1)-(A3) are satisfied, then it can be shown that the solution $P(t)$ to the differential equation (4) converges uniformly to a continuous, positive and bounded periodic solution of period T (Theorem 2.2, [35]). Denote this periodic solution as $\tilde{P}(t)$. The disease-free state (DFS) of model (3) is the periodic solution, where $S(t) = \tilde{P}(t)$ and the remaining states equal zero. For model (3), we show

the existence of a basic reproduction number $\mathcal{R}_0$. Only in special cases for the nonautonomous model can an explicit formula be calculated (in terms of model parameters) for the basic reproduction number [19, 33, 35].

To verify the existence of the basic reproduction number $\mathcal{R}_0$ and local stability of the DFS for model (3), we apply recent results from Bacaer and Guernaoui [8] and Wang and Zhao [33]. Existence of $\mathcal{R}_0$ and stability results for more general nonautonomous systems of differential equations can be found in [30]. First, the variables in (3) are ordered according to the infectious states and then by other states as follows: $X = (I_n, I_c, G, S)^T$. The terms in each of the differential equations are separated into new infections and other transitions, that is, $\dot{X} = \mathcal{F} - \mathcal{V}$. Computing the Jacobian matrix of $\mathcal{F}$ and $\mathcal{V}$ at the DFS, we obtain

$$D_{\mathcal{F}} = \begin{pmatrix} F(t) & \mathbf{O} \\ \mathbf{O} & 0 \end{pmatrix} \quad \text{and} \quad D_{\mathcal{V}} = \begin{pmatrix} V(t) & \mathbf{O} \\ J(t) & -M(t) \end{pmatrix}, \tag{5}$$

where matrices $\mathbf{O}$ are zero matrices, $M(t) = b(t) - m(t) - 2k(t)\tilde{P}(t)$,

$$F(t) = \begin{pmatrix} \beta_n(\tilde{P}(t), t)\tilde{P}(t) & \beta_c(\tilde{P}(t), t)\tilde{P}(t) & \epsilon(t)\tilde{P}(t) \\ 0 & 0 & 0 \\ \phi_n(t) & \phi_c(t) & 0 \end{pmatrix} \tag{6}$$

and

$$V(t) = \begin{pmatrix} \tau(t) + m(t) + k(t)\tilde{P}(t) & 0 & 0 \\ -\tau(t) & m(t) + k(t)\tilde{P}(t) & 0 \\ 0 & 0 & d(t) \end{pmatrix}. \tag{7}$$

The transmission coefficients $\beta_j(\tilde{P}(t), t) = \lambda_j(t)$ in the case of mass action incidence and $\beta_j(\tilde{P}(t), t) = \lambda_j(t)/\tilde{P}(t)$ in the case of standard incidence, $j = n, c$. Matrix $F(t)$ is periodic and nonnegative and matrix $-V(t)$ is periodic and cooperative (off-diagonal elements of $-V(t)$ are nonnegative).

From the differential equation for $P(t)$, equation (4), and the assumptions on the coefficients it can be shown that $\exp\left(\int_0^T M(t)\,dt\right) < 1$. Let $P(t) = \tilde{P}(t)$ in (4), divide by $\tilde{P}(t)$ and integrate from 0 to T. It follows that

$$\int_0^T [b(t) - m(t) - k(t)\tilde{P}(t)]\,dt = 0 \tag{8}$$

which implies $\int_0^T M(t)\,dt = -\int_0^T k(t)\tilde{P}(t)\,dt < 0$.

The monodromy matrix $\Phi_{-V}(t)$ of the linear T-periodic system $dz/dt = -V(t)z$ also satisfies $\rho(\Phi_{-V}(T)) < 1$ (ρ is the spectral radius), since $\Phi_{-V}(T)$ has the form

$$\begin{pmatrix} e^{-\int_0^T [\tau(t)+m(t)+k(t)\tilde{P}(t)]\,dt} & 0 & 0 \\ * & e^{-\int_0^T [m(t)+k(t)\tilde{P}(t)]\,dt} & 0 \\ 0 & 0 & e^{-\int_0^T d(t)\,dt} \end{pmatrix},$$

where we have applied the identity (8) (the term $*$ in the matrix does not affect the spectral radius). Thus, the dynamics of the linearized system are determined by $dz/dt = [F(t) - V(t)]z$. The basic reproduction number exists and satisfies $\mathcal{R}_0 = 1$ (< 1, > 1) if and only if $\rho(\Phi_{F-V}(T)) = 1$ (< 1, > 1) (Theorem 2.2, p. 706, [33]). In particular, $\mathcal{R}_0 = \rho(L)$, where L is a linear integral operator, $L : C_T \to C_T$, C_T are T-periodic continuous functions, $\phi : \mathbb{R} \to \mathbb{R}^3$, and

$$(L\phi)(t) = \int_0^\infty Z(t, t-s)F(t-s)\phi(t-s)\,ds, \tag{9}$$

where $Z(t,s)$ is the 3×3 matrix solution of $dZ(t,s)/dt = -V(t)Z(t,s)$, $Z(s,s) = I =$ identity matrix [33]. Another equivalent expression to (9) was derived by Bacaer and Guernaoui [8]. The next theorem follows from the previous analysis and from Theorems 2.1 and 2.2 in Wang and Zhao (pp. 704, 706, [33]).

Theorem 2.1. *Suppose the nonautonomous system (3) satisfies conditions (A1)-(A3). Then there exists a basic reproduction number $\mathcal{R}_0 = \rho(L)$ for system (3), where the operator L is defined in (9). If $\mathcal{R}_0 < 1$, then the DFS $(\tilde{P}(t), 0, 0, 0)$ of the nonautonomous system (3) is locally asymptotically stable. If $\mathcal{R}_0 > 1$, then the DFS is unstable.*

2.2. **Autonomous model.** Assume the periodic coefficients in model (3) are replaced by their average values. That is, let $b(t)$, $m(t)$, $d(t)$, $k(t)$, $\tau(t)$, $\epsilon(t)$, $\phi_j(t)$ and $\lambda_j(t)$, $j = n, c$ be replaced by $\bar{b}$, $\bar{m}$, $\bar{d}$, $\bar{k}$, $\bar{\tau}$, $\bar{\epsilon}$, $\bar{\phi}_j$ and $\bar{\lambda}_j$, $j = n, c$, respectively, in model (3). In this case, the total population density has the form of logistic growth, $\dot{P} = P(\bar{b} - \bar{m} - \bar{k}P)$ with stable equilibrium $\bar{P} = (\bar{b} - \bar{m})/\bar{k}$. Note that $\bar{P}$ does not necessarily equal the average of the periodic solution $\tilde{P}(t)$ (see (8)). The disease-free equilibrium (DFE) for the time-averaged model (3) is

$$(\bar{S}, \bar{I}_n, \bar{I}_c, \bar{G}) = (\bar{P}, 0, 0, 0).$$

The basic reproduction number is determined by applying the next generation matrix approach [32]. The basic reproduction number for the autonomous model is denoted as $\hat{\mathcal{R}}_0$. As in the nonautonomous model, we let $\dot{X} = \mathcal{F} - \mathcal{V}$. Computing the Jacobian matrix of $\mathcal{F}$ and $\mathcal{V}$ at the DFE, we obtain matrices in the form of (5), (6) and (7). However the elements of $F(t)$, $V(t)$ and $J(t)$ are constant, since the periodic coefficients are replaced by their average values and $\tilde{P}(t)$ is replaced by $\bar{P}$. The next generation matrix is given by

$$FV^{-1} = \begin{pmatrix} \dfrac{\bar{\beta}_n\bar{P}\bar{b} + \bar{\beta}_c\bar{P}\bar{\tau}}{(\bar{\tau}+\bar{b})\bar{b}} & \dfrac{\bar{\beta}_c\bar{P}}{\bar{b}} & \dfrac{\bar{\epsilon}\bar{P}}{\bar{d}} \\ 0 & 0 & 0 \\ \dfrac{\bar{\phi}_n\bar{b} + \bar{\tau}\bar{\phi}_c}{(\bar{\tau}+\bar{b})\bar{b}} & \dfrac{\bar{\phi}_c}{\bar{b}} & 0 \end{pmatrix},$$

where $\bar{\beta}_j = \bar{\lambda}_j$ in the case of mass action incidence and $\bar{\beta}_j = \bar{\lambda}_j/\bar{P}$ in the case of standard incidence, $j = n, c$. The basic reproduction number can be calculated explicitly as the spectral radius of the next generation matrix, $\rho(FV^{-1})$:

$$\hat{\mathcal{R}}_0 = \frac{\bar{\beta}_n\bar{P}\bar{b} + \bar{\beta}_c\bar{P}\bar{\tau}}{2\bar{b}(\bar{\tau}+\bar{b})} + \frac{1}{2}\sqrt{\left(\frac{\bar{\beta}_n\bar{P}\bar{b} + \bar{\beta}_c\bar{P}\bar{\tau}}{\bar{b}(\bar{\tau}+\bar{b})}\right)^2 + \frac{4\bar{\epsilon}\bar{P}(\bar{\phi}_n\bar{b} + \bar{\tau}\bar{\phi}_c)}{\bar{b}\bar{d}(\bar{\tau}+\bar{b})}}. \tag{10}$$

A more convenient expression, equivalent to the reproduction number $\hat{\mathcal{R}}_0$ given in (10), is

$$\tilde{\mathcal{R}}_0 = \frac{\bar{\beta}_n\bar{P}\bar{b} + \bar{\beta}_c\bar{P}\bar{\tau}}{\bar{b}(\bar{\tau}+\bar{b})} + \frac{\bar{\epsilon}\bar{P}(\phi_n\bar{b} + \bar{\tau}\bar{\phi}_c)}{\bar{b}\bar{d}(\bar{\tau}+\bar{b})}. \tag{11}$$

A straightforward algebraic manipulation verifies that $\hat{\mathcal{R}}_0 < 1$ (or $\hat{\mathcal{R}}_0 > 1$ or $\hat{\mathcal{R}}_0 = 1$) if and only if $\tilde{\mathcal{R}}_0 < 1$ ($\tilde{\mathcal{R}}_0 > 1$ or $\tilde{\mathcal{R}}_0 = 1$). The following theorem follows directly from the preceding analysis and Theorem 2 in [32] (p. 39).

Theorem 2.2. *Consider the autonomous system (3) with the periodic coefficients set identically equal to their positive average values. Suppose (A2) is satisfied. Then there exists a basic reproduction for system (3) given by (10). If $\hat{\mathcal{R}}_0 < 1$, then the*

DFE of the autonomous system (3) is locally asymptotically stable. If $\hat{\mathcal{R}}_0 > 1$*, then the DFE is unstable.*

Note that the fractions $1/(\bar{\tau}+\bar{b})$ and $\bar{\tau}/[\bar{b}(\bar{\tau}+\bar{b})]$ in the expressions for $\hat{\mathcal{R}}_0$ in (10) and $\tilde{\mathcal{R}}_0$ in (11) are the average infectious periods for newly and chronically infectious rodents, respectively. The fractions $1/[\bar{d}(\bar{\tau}+\bar{b})]$ and $\bar{\tau}/[\bar{b}\bar{d}(\bar{\tau}+\bar{b})]$ are the average infectious periods for the ground contamination from newly and chronically infectious rodents. The expression (11) is clearly the sum of three sources of infection from newly and chronically infectious rodents and from environmental contamination. If there is no environmental contamination, $\bar{\epsilon}=0$, then the basic reproduction number simplifies to

$$\hat{\mathcal{R}}_0|_{\bar{\epsilon}=0} = \frac{\bar{\beta}_n\bar{P}}{\bar{\tau}+\bar{b}} + \frac{\bar{\beta}_c\bar{P}\bar{\tau}}{\bar{b}(\bar{\tau}+\bar{b})} = \tilde{\mathcal{R}}_0|_{\bar{\epsilon}=0},$$

the sum of only two sources of infection from newly and chronically infectious rodents. Thus, clearly, indirect transmission, $\bar{\epsilon}>0$, increases the possibility of an outbreak

$$\hat{\mathcal{R}}_0|_{\bar{\epsilon}\neq 0} > \hat{\mathcal{R}}_0|_{\bar{\epsilon}=0}. \tag{12}$$

To study the global dynamics of the autonomous rodent system (3), we need to consider the dynamics of the limit system. That is, the autonomous system (3), where the total population size is constant, $P(t)\equiv\bar{P}$. In this case, system (3) simplifies since $S(t)=\bar{P}-I_n(t)-I_c(t)$. Solutions to the limit system are nonnegative and bounded, and the region

$$D_1=\{(S_n,I_n,I_c,G)|I_n\geq 0, I_c\geq 0, S_n=\bar{P}-I_n-I_c\geq 0, 0\leq G\leq 1\}$$

is positively invariant [34]. The following proof for global stability of the DFE for the autonomous model (3) relies on the dynamics of the limit system.

Theorem 2.3. *Consider the autonomous system (3) with the periodic coefficients set identically equal to their positive average values. Suppose (A2) is satisfied. If* $\hat{\mathcal{R}}_0<1$*, then the DFE of the autonomous system (3) is globally asymptotically stable.*

Proof. First, we consider the limit system. Define the Lyapunov function for the limit system as

$$V(I_n,I_c,G)=\bar{d}\bar{b}I_n+(\bar{\epsilon}\bar{P}\bar{\phi}_c+\bar{d}\bar{\beta}_c\bar{P})I_c+\bar{\epsilon}\bar{P}\bar{b}G.$$

Function V is nonnegative and equals zero only if $I_n=I_c=G=0$. Using the fact that $S=\bar{P}-I_n-I_c$ and differentiating with respect to t along solution trajectories for the limit system,

$$\begin{aligned}
\dot{V} &= \bar{d}\bar{b}\left[(\bar{\beta}_nI_n+\bar{\beta}_cI_c+\bar{\epsilon}G)(\bar{P}-I_n-I_c)-(\bar{\tau}+\bar{b})I_n\right]\\
&\quad +(\bar{\epsilon}\bar{P}\bar{\phi}_c+\bar{d}\bar{\beta}_c\bar{P})\left(\bar{\tau}I_n-\bar{b}I_c\right)+\bar{\epsilon}\bar{P}\bar{b}\left[(\bar{\phi}_nI_n+\bar{\phi}_cI_c)(1-G)-\bar{d}G\right]\\
&= \bar{d}\bar{b}\bar{\beta}_n\bar{P}I_n+\bar{d}\bar{\tau}\bar{\beta}_c\bar{P}I_n+\bar{\epsilon}\bar{d}\bar{b}G\bar{P}-\bar{d}\bar{b}(\bar{\tau}+\bar{b})I_n+\bar{\epsilon}\bar{P}\bar{b}\bar{\phi}_nI_n+\bar{\epsilon}\bar{P}\bar{\phi}_c\bar{\tau}I_n\\
&\quad -\bar{\epsilon}\bar{P}\bar{b}G[(\bar{\phi}_nI_n+\bar{\phi}_cI_c)+\bar{d}]-\bar{d}\bar{b}\left(\bar{\beta}_nI_n+\bar{\beta}_cI_c+\bar{\epsilon}G\right)(I_n+I_c)\\
&= \bar{d}\bar{b}(\bar{\tau}+\bar{b})(\tilde{\mathcal{R}}_0-1)I_n-\bar{d}\bar{b}\left(\bar{\beta}_nI_n+\bar{\beta}_cI_c+\bar{\epsilon}G\right)(I_n+I_c)\\
&\quad -\bar{\epsilon}\bar{P}\bar{b}G(\bar{\phi}_nI_n+\bar{\phi}_cI_c).
\end{aligned}$$

Since $\hat{\mathcal{R}}_0<1$ is equivalent to $\tilde{\mathcal{R}}_0<1$, it follows that $\dot{V}(t)\leq 0$. The Liapunov-LaSalle extension theorem [18] implies that solutions in D_1 approach the largest positively invariant subset of the set where $\dot{V}(t)=0$. Hence, solutions tend to

$\bar{I}_n = \bar{I}_c = 0$. Let $\epsilon_0 > 0$, then for t sufficiently large, $0 \leq \bar{\phi}_n I_n(t) + \bar{\phi}_c I_n(t) < \epsilon_0$. Hence, $\dot{G}(t) < \epsilon_0(1 - G(t)) - \bar{d}G(t)$. Thus, $G(t) \leq \epsilon_0/(\epsilon_0 + \bar{d})$ and since ϵ_0 is arbitrary, $G(t) \to 0$. It follows that the limit system satisfies $(S(t), I_n(t), I_c(t), G(t)) \to (\bar{P}, 0, 0, 0)$.

The set D_1 [containing $(\bar{P}, 0, 0, 0)$] is the attractive region for the limit system. Since $P(t) \to \bar{P}$ for system (3), the $\omega-$limit set of (3) is contained in D_1. Thus, it follows from the theory of asymptotically autonomous systems, Theorem 4.1 in [29], that if $\hat{\mathcal{R}}_0 < 1$, then the $\omega-$limit set of (3) is the DFE. □

We now show that there exists a unique positive EE of system (3). Setting the differential equation $\dot{I}_c$ equal to zero and substituting the values of the population at the EE, where $\bar{P} = S^* + I_n^* + I_c^*$, the endemic values for I_c^*, G^* and S^* can be expressed in terms of I_n^*:

$$I_c^* = \frac{\bar{\tau}}{\bar{b}} I_n^*, \tag{13}$$

$$G^* = \frac{\bar{\phi}_n I_n^* + \bar{\phi}_c I_c^*}{\bar{\phi}_n I_n^* + \bar{\phi}_c I_c^* + \bar{d}} \tag{14}$$

and

$$S^* = \bar{b}\bar{P}\left[\bar{\beta}_n I_n^* + \bar{\beta}_c I_c^* + \bar{\epsilon} G^* + \bar{b}\right]^{-1}, \tag{15}$$

where

$$I_n^* = \frac{-\gamma + \sqrt{\gamma^2 - 4\alpha\xi}}{2\alpha}; \tag{16}$$

$$\begin{aligned}
\alpha &= \left(\bar{\beta}_n + \frac{\bar{\beta}_c\bar{\tau}}{\bar{b}}\right)\left(1 + \frac{\bar{\tau}}{\bar{b}}\right)\left(\bar{\phi}_n + \frac{\bar{\phi}_c\bar{\tau}}{\bar{b}}\right) \\
\gamma &= \left[(\bar{b} + \bar{\epsilon})\left(1 + \frac{\bar{\tau}}{\bar{b}}\right) - \left(\bar{\beta}_n + \frac{\bar{\beta}_c\bar{\tau}}{\bar{b}}\right)\bar{P}\right]\left[\bar{\phi}_n + \frac{\bar{\phi}_c\bar{\tau}}{\bar{b}}\right] \\
&\quad + \left(\bar{\beta}_n + \frac{\bar{\beta}_c\bar{\tau}}{\bar{b}}\right)\left(1 + \frac{\bar{\tau}}{\bar{b}}\right)\bar{d} \\
\xi &= -\left(\bar{\beta}_n + \frac{\bar{\beta}_c\bar{\tau}}{\bar{b}}\right)\bar{d}\bar{P} - \left(\bar{\phi}_n + \frac{\bar{\phi}_c\bar{\tau}}{\bar{b}}\right)\bar{\epsilon}\bar{P} + \left(\bar{b} + \bar{\tau}\right)\bar{d}.
\end{aligned} \tag{17}$$

If $I_n^* = 0$, then $I_c^* = 0$, $G^* = 0$ and $S^* = \bar{P}$ by (13), (14) and (15) which yields the DFE.

The EE is defined uniquely by the preceding formulas. Since the value α is positive, there is a unique positive solution for I_n^* if and only if $\xi < 0$. Note that $\xi < 0$ in (17) if and only if

$$\frac{\bar{\beta}_n\bar{P}}{(\bar{\tau} + \bar{b})} + \frac{\bar{\beta}_c\bar{P}\bar{\tau}}{\bar{b}(\bar{\tau} + \bar{b})} + \frac{\bar{\epsilon}\phi_n\bar{P}}{\bar{d}(\bar{\tau} + \bar{b})} + \frac{\bar{\epsilon}\bar{\phi}_c\bar{\tau}\bar{P}}{\bar{b}\bar{d}(\bar{\tau} + \bar{b})} > 1.$$

This latter inequality is equivalent to $\tilde{\mathcal{R}}_0 > 1$ (and $\hat{\mathcal{R}}_0 > 1$). Consequently, if $I_n^* > 0$ ($\hat{\mathcal{R}}_0 > 1$), the expressions in (13), (14) and (15) imply the EE is positive and unique. Hence, we have shown that there is a unique positive EE to system (3) if and only if $\hat{\mathcal{R}}_0 > 1$. The next result verifies that this unique EE is locally asymptotically stable.

Theorem 2.4. *Consider the autonomous system (3) with the periodic coefficients set identically equal to their positive average values. Suppose (A2) is satisfied. If*

$\hat{\mathcal{R}}_0 > 1$, then the autonomous system (3) has a unique positive locally asymptotically stable EE given by (13), (14), (15) and (16).

Proof. To show local asymptotic stability, we rewrite system (3) in an equivalent form:

$$\begin{aligned} \dot{P} &= P(\bar{b} - \bar{m} - \bar{k}P) \\ \dot{I}_n &= (\bar{\beta}_n I_n + \bar{\beta}_c I_c + \bar{\epsilon}G)(P - I_n - I_c) - (\bar{\tau} + \bar{m} + \bar{k}P)I_n \\ \dot{I}_c &= \bar{\tau} I_n - (\bar{m} + \bar{k}P)I_c \\ \dot{G} &= (\bar{\phi}_n I_n + \bar{\phi}_c I_c)(1 - G) - \bar{d}G. \end{aligned} \tag{18}$$

The Jacobian matrix J of system (18) evaluated at the EE is equal to

$$\left(\begin{array}{c|c|c|c} -(\bar{b}-\bar{m}) & 0 & 0 & 0 \\ \hline & \bar{\beta}_n(\bar{P} - I_n^* - I_c^*) - \bar{\beta}_n I_n^* & \bar{\beta}_c(\bar{P} - I_n^* - I_c^*) & \bar{\epsilon}(\bar{P} - I_n^* - I_c^*) \\ * & -\bar{\beta}_c I_c^* - \bar{\epsilon}G^* - \bar{\tau} - \bar{b} & -\bar{\beta}_n I_n^* - \bar{\beta}_c I_c^* - \bar{\epsilon}G^* & \\ \hline & \bar{\tau} & -\bar{b} & 0 \\ \hline * & \bar{\phi}_n(1 - G^*) & \bar{\phi}_c(1 - G^*) & -\bar{\phi}_n I_n^* - \bar{\phi}_c I_c^* - \bar{d} \end{array}\right)$$

where $*$ denotes matrix entries that are not needed for the stability analysis.

Applying the identity

$$\bar{P} - I_n^* - I_c^* = \frac{(\bar{\tau} + \bar{b})I_n^*}{\bar{\beta}_n I_n^* + \bar{\beta}_c I_c^* + \bar{\epsilon}G^*},$$

the second, third and fourth entries of the second row of J can be rewritten. Then applying a similarity transformation with diagonal matrix $B = \mathrm{diag}(\bar{P}, I_n^*, I_c^*, G^*)$, a matrix $\hat{J} = B^{-1}JB$ similar to J is equal to

$$\left(\begin{array}{c|c|c|c} -(\bar{b}-\bar{m}) & 0 & 0 & 0 \\ \hline & \dfrac{(\bar{\tau}+\bar{b})\bar{\beta}_n I_n^*}{\bar{\beta}_n I_n^* + \bar{\beta}_c I_c^* + \bar{\epsilon}G^*} & \dfrac{(\bar{\tau}+\bar{b})\bar{\beta}_c I_c^*}{\bar{\beta}_n I_n^* + \bar{\beta}_c I_c^* + \bar{\epsilon}G^*} & \\ * & -\bar{\beta}_n I_n^* - \bar{\beta}_c I_c^* & -(\bar{\tau}/\bar{b})(\bar{\beta}_n I_n^* + \bar{\beta}_c I_c^*) & \dfrac{\bar{\epsilon}(\bar{\tau}+\bar{b})G^*}{\bar{\beta}_n I_n^* + \bar{\beta}_c I_c^* + \bar{\epsilon}G^*} \\ & -\bar{\epsilon}G^* - \bar{\tau} - \bar{b} & -(\bar{\tau}/\bar{b})\bar{\epsilon}G^* & \\ \hline & \bar{b} & -\bar{b} & 0 \\ \hline * & \bar{\phi}_n I_n^*(1-G^*)G^{*-1} & \bar{\phi}_c I_c^*(1-G^*)G^{*-1} & -\bar{\phi}_n I_n^* - \bar{\phi}_c I_c^* - \bar{d} \end{array}\right).$$

Finally, making the substitution for G^*, equation (14), in the second and third entries of the last row of matrix $\hat{J}$, these two entries simplify to

$$\frac{\bar{\phi}_n \bar{d} I_n^*}{\bar{\phi}_n I_n^* + \bar{\phi}_c I_c^*} \quad \text{and} \quad \frac{\bar{\phi}_c \bar{d} I_c^*}{\bar{\phi}_n I_n^* + \bar{\phi}_c I_c^*},$$

respectively.

Matrix $\hat{J}$ can be expressed in block matrix form as

$$\hat{J} = \begin{pmatrix} -(\bar{b} - \bar{m}) & \mathbf{O} \\ \mathbf{S_1} & \mathbf{S_2} \end{pmatrix},$$

where $\mathbf{O}$ is the zero matrix. The eigenvalues of $\hat{J}$ are the same as those of J. One eigenvalue is negative, $-(\bar{b} - \bar{m}) < 0$, and the remaining eigenvalues can be found from matrix $\mathbf{S_2}$. We apply the Routh-Hurwitz criteria to show that the eigenvalues of $\mathbf{S_2}$ are negative or have negative real parts. Given the characteristic equation

$$\lambda^3 + a_1\lambda^2 + a_2\lambda + a_3 = 0,$$

the Routh-Hurwitz criteria requires that $a_1 > 0$, $a_3 > 0$ and $a_1a_2 - a_3 > 0$. A computer algebra system can be used to show that each of the terms a_1, a_3 and $a_1a_2 - a_3$ consist of a sum of positive terms (see the Appendix for details). Since the Routh-Hurwitz criteria are satisfied, the EE of (3) is locally asympotically stable. □

3. **Numerical examples.** We apply model (3) to an Old and a New World hantavirus. In the first example, we study Puumala virus carried by bank voles in northern Europe. In the second example, we concentrate on the number of human HPS cases in an outbreak that occurred in Chile from infection with Andes virus, carried by the long-tailed rice rat. Time is measured in years.

3.1. **Old world hantavirus.** Parameter values in the SLP model [27] were chosen so that the model behavior mimics the observed dynamical patterns of Puumala virus infection in bank voles (*Clethrionomys glareolus*) in northern Europe. Puumula virus infection in humans results in nephropathia epidemica, a type of HFRS. The newly infectious stage has a density-dependent incidence rate whereas the chronically infectious stage has a frequency-dependent rate, $\beta_n(P(t), t) = \lambda_n(t)$ and $\beta_c(P(t), t) = \lambda_c(t)/P(t)$ [27]. Here, we differ from the SLP model, where λ_c and λ_n were assumed constant, and investigate the effect of periodic transmission rates. Let

$$\lambda_j(t) = \bar{\lambda}_j[1 + 0.5\sin(2\pi(t - 0.15))],\ j = n, c, \tag{19}$$

where the constant values $\bar{\lambda}_j$ are the values assumed in the SLP model, $\bar{\lambda}_n = 0.9$ and $\bar{\lambda}_c = 5$.

The birth and density-dependent death rates are the same as those given for the SLP model. The births $b(t)$ follow an annual cyclical pattern given by

$$b(t) = 7.5[|\sin(2\pi(t - 0.15))| + \sin(2\pi(t - 0.15))]. \tag{20}$$

Implicit in the birth function $b(t)$ is a six month breeding period from October to March and a nonbreeding period during the remaining six months. The density-dependent death rate is periodic but not seasonal (period of three years) given by

$$k(t) = \frac{\bar{b} - \bar{m}}{6[10 + (\cos(2\pi(t + 0.35)/3))^2 - 8\sin(2\pi(t + 0.35)/3)]}, \tag{21}$$

corresponding to rodent population densities in northern Europe, where $\bar{b} = 15/\pi$ is the average birth rate and $\bar{m} = 2.5 = m(t)$ is the average density-independent death rate. The average value $\bar{k} = 0.0596$. This gives a value of $\bar{P} = (\bar{b} - \bar{m})/\bar{k} = 38.2$ for the equilibrium total population size in the autonomous model.

The remaining parameter values are positive constants. They agree with the parameter values in the SLP model. The average duration of viable Puumala virus outside the host is approximately 12 days ($d(t) \equiv 30$, $(1/d(t)) \times 365$ days ≈ 12 days) [17]. The duration of the newly infectious stage is $1/\tau(t) \equiv 1/12 =$ one month [10]. On average, rodents frequent every point of the area at least once every 73 days per year, $\epsilon(t) \equiv 365/73 = 5/(\text{ha}\times\text{year})$ [27]. Newly infectious rodents shed virus with greater titer than chronically infectious rodents, $0.1 \equiv \phi_c(t) \leq \phi_n(t) \equiv 0.5$. The rodent-hantavirus model is scaled to the spatial size of one hectare so that the variables have units of rodents per hectare. The parameter values are summarized in Table 1 and in equations (19), (20) and (21).

TABLE 1. Baseline parameter values and functional forms for the rodent-hantavirus models; $\lambda_j(t)$, $j = n, c$, are defined in (19).

Parameter	Value	Parameter	Value
$m(t)$	2.5	$\beta_n(P(t), t)$	$\lambda_n(t)$
$\tau(t)$	12	$\beta_c(P(t), t)$	$\lambda_c(t)/P(t)$
$d(t)$	30	$\phi_n(t)$	0.5
$\epsilon(t)$	5	$\phi_c(t)$	0.1

A practical method for calculating the basic reproduction number for the nonautonomous system is based on the linear periodic system

$$\frac{dw}{dt} = \left[\frac{F(t)}{\lambda} - V(t)\right] w,$$

$\lambda \in (0, \infty)$ [7, 33]. If $W(t, s, \lambda)$, $t \geq s$ is the monodromy matrix for this system, it follows that $\mathcal{R}_0 = \lambda_0$ is the unique solution of $\rho(W(T, 0, \lambda_0)) = 1$. To calculate the value of $\mathcal{R}_0$, first ensure $P(t)$ is close to the periodic solution $\tilde{P}(t)$, then numerically approximate the 3×3 Floquet matrix for $T = 3$ and fixed λ. Since $\rho(W(T, 0, \lambda))$ is a nonincreasing function of λ, the value of $\lambda_0 = \mathcal{R}_0$ is obtained by successively decreasing λ until $\rho(W(T, 0, \lambda_0))$ is sufficiently close to one. The basic reproduction number for the nonautonomous model is $\mathcal{R}_0 = 4.9$. If there is no indirect transmission, $\epsilon = 0$, then $\mathcal{R}_0|_{\epsilon=0} = 4.8$.

Figure 2 is a graph of the solutions for the variables over time (years 1-7) for the nonautonomous model (3). Solutions appear to converge to a periodic solution of period 3 years, the common period T of $b(t)$, $k(t)$, and $\lambda_j(t)$, $j = n, c$. To show the existence of a periodic solution is not easy. However, for periodic coefficients with small amplitude that differ slightly from the average parameter values associated with the autonomous system, it can be shown that there exists a unique periodic solution (by applying a Theorem due to Poincaré, [16], p. 415). For example, Poincaré's theorem applies when the periodic parameters have a form such as

$$f(t) = \bar{f} + \alpha \hat{f}(t),$$

where $\alpha > 0$ is sufficiently small, $\bar{f} > 0$ is the average value of $f(t)$, and $f(t)$ satisfies (A1). If stochastic effects are included, solution values may oscillate to very low values, resulting in disease extinction (see [14, 15]).

Solutions to the autonomous model (3) (graph not shown) tend to a constant endemic equilibrium (Theorem 2.4, equations (13)-(16)). The stable EE for the rodent model (3) is

$$(S^*, I_n^*, I_c^*, G^*) = (12.6, 7.3, 18.3, 0.15)$$

in units of rodents per hectare. In this autonomous case, $\hat{\mathcal{R}}_0 = 2.9$. If there is no indirect transmission, $\epsilon = 0$, then $\hat{\mathcal{R}}_0|_{\epsilon=0} = 2.8$.

The two reproduction numbers for the autonomous and nonautonomous models differ significantly, $\mathcal{R}_0 = 4.9$ versus $\hat{\mathcal{R}}_0 = 2.9$. They also differ in the case that the direct transmission rates are constant, $\lambda_j(t) = \bar{\lambda}_j$, $j = n, c$, as in the SLP model, $\mathcal{R}_0 = 4.3$ versus $\hat{\mathcal{R}}_0 = 2.9$. Thus, the basic reproduction number for the

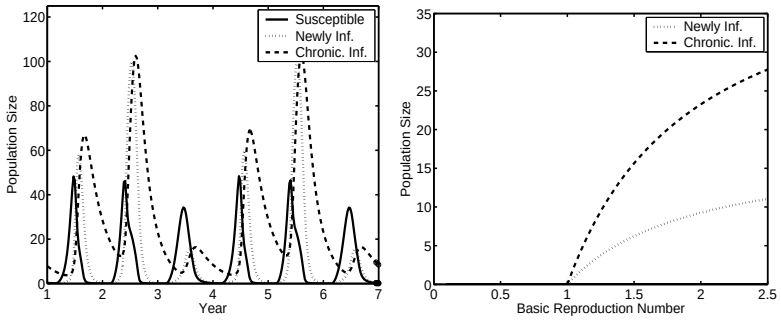

FIGURE 2. Solution of the nonautonomous model with periodic transmission rates, equation (19), birth function, equation (20), and density-dependent death rate, equation (21) (years 1 to 7). The left graph is the number of rodents that are susceptible, newly infectious and chronically infectious. The right graph is the autonomous model with $\bar{P} = 38.2$; the stable equilibrium values I_n and I_c as a function of the basic reproduction number $\hat{\mathcal{R}}_0(p)$, which depends on the transmission rates $(\beta_n, \beta_c, \epsilon) = (\beta_n^*, \beta_c^*, \epsilon^*)p$, where β_n^*, β_c^* and ϵ^* are the baseline parameter values in Table 1 ($p > 0$).

autonomous model with the time-averaged coefficients does not reflect the true basic reproduction number. For this model, the autonomous model produces an underestimate of the true value. Wang and Zhao [33] provide examples where $\hat{\mathcal{R}}_0$ is an underestimate or an overestimate of the true value $\mathcal{R}_0$. Viral persistence in the rodent host, as measured by $\mathcal{R}_0$, is not so much affected by indirect transmission as it is by the periodicity in the demographic parameters. Periodic demographics coupled with periodic transmission and mass action incidence can lead to marked differences in the two reproduction numbers, $\mathcal{R}_0$ versus $\hat{\mathcal{R}}_0$ [35]. Whether $\mathcal{R}_0$ exceeds $\hat{\mathcal{R}}_0$ will most likely depend on many factors, including the amplitude of the periodic functions and whether the peak values for transmission and population density coincide.

A bifurcation diagram for the autonomous rodent-hantavirus model (3) is graphed in Figure 2. The stable equilibrium values for the number of newly and chronically infectious rodents are graphed as a function of $\hat{\mathcal{R}}_0(p)$ which depends on the transmission rates $(\beta_n, \beta_c, \epsilon) = (\beta_n^*, \beta_c^*, \epsilon^*)p$, where β_n^*, β_c^* and ϵ^* are the baseline parameter values in Table 1 ($p > 0$). For the baseline values ($p = 1$), $\hat{\mathcal{R}}_0(1) = 2.9$. A transcritical bifurcation occurs at $\hat{\mathcal{R}}_0 = 1$.

3.2. **New world hantavirus.** The rodent reservoir for New World hantaviruses exhibit less seasonal variation in birth rate, death rate and overall contact behavior than Old World hantaviruses but the viral decay rate varies according to wet and dry seasons [17]. Thus, in a model for a New World hantavirus, we assume seasonal periodicity in the viral decay rate but not in the birth rate, death rate or transmission rates. We focus on the indirect impact on humans, using data for human cases due to Andes virus, a hantavirus carried by the long-tailed rice rat (*Oligoryzomys longicaudatus*) that is found in Chile and Argentina. The Andes virus was the cause of the HPS outbreak in southern Chile, recorded from July 1997 through January

1998. During this period, there were 25 confirmed cases of HPS. Prior to July 1997, small sporadic cases of HPS occurred throughout the year [31].

We choose parameter values for illustration purposes and focus on the seasonal viral decay rate outside the host and the impact on humans. For the rodent population, we assume the rodent birth rate is constant $b(t) \equiv \bar{b} = 10$ and the density-dependent death rate is constant, $k(t) = 0.075$. Suppose the seasonal viral decay rate has the form

$$d(t) = 375 + 355\cos(2\pi t),$$

where $\bar{d} = 375$. The survival of the virus in the environment varies between 12 hours and 18 days. These periodic fluctuations in hantavirus persistence correspond to seasonal dry and wet conditions in the environment, with wet conditions supporting hantavirus survival [17]. Other parameter values are set equal to the average (or the constant value) of the parameters given for the Old World hantavirus example, (see Table 1). The total population size approaches a constant, $P(t) \to \bar{P} = 100$.

The basic reproduction number for the nonautonomous system is found by applying the numerical method with $T = 1$. Thus, $\mathcal{R}_0 = 4.4$. An epizootic occurs in the rodent population. This basic reproduction number $\mathcal{R}_0$ does not differ significantly from the autonomous model with time-averaged viral decay rate, $\bar{d}$, $\hat{\mathcal{R}}_0 = 4.4$. In this example, unlike the Old World hantavirus example, the birth and death rates are not periodic which may be the reason for the small difference in the two reproduction numbers.

In Figure 3 (A), the rodent population is constant year round, with only slight variation in numbers of susceptible, newly and chronically infectious rodents occurring in the months of May through August. This small change in rodent susceptibility would go undetected, however, the corresponding change in the proportion of viral contaminated soil is highly significant. The ground contamination is periodic, a ten-fold increase from less than 0.05 in January to 0.5 in June. The left graph of Figure 3 (B) displays the bar graph of the actual number of human HPS cases in southern Chile during 1997. Figure 3 (B) also shows the average annual precipitation values near Valdivia, a representative city in southern Chile [9]. The largest number of human cases. This example shows that indirect transmission has a weak impact on rodents but may have a strong impact on humans, especially if human exposure occurs during peak times in ground contamination.

4. **Discussion.** Very few human cases of hantavirus pulmonary syndrome or hemorrhagic fever with renal syndrome are contracted through direct contact with the rodent host. Indirect transmission via ground contamination, measured by the parameter ϵ, increases the basic reproduction number, $\mathcal{R}_0$ (e.g., equation (12)), in the rodent population which may allow for pathogen persistence during times of low rodent densities. In [27] and [28], the persistence of Puumula virus (virus that causes nephropathia epidemica in humans) outside the host is an important assumption. Prolonged viral persistence during wet seasons coupled with rodent outbreaks may increase the likelihood of human exposure to the virus. Indeed, Puumula virus can survive for long periods of time outside of the host [17]. For other hantaviruses, few studies have focused on the longevity of hantavirus outside the host. Many questions about indirect transmission are still unanswered. The data from Chile, given in Figure 3, provide motivation for more research on indirect transmission of hantaviruses in wet and dry environments. The Old and New World hantavirus

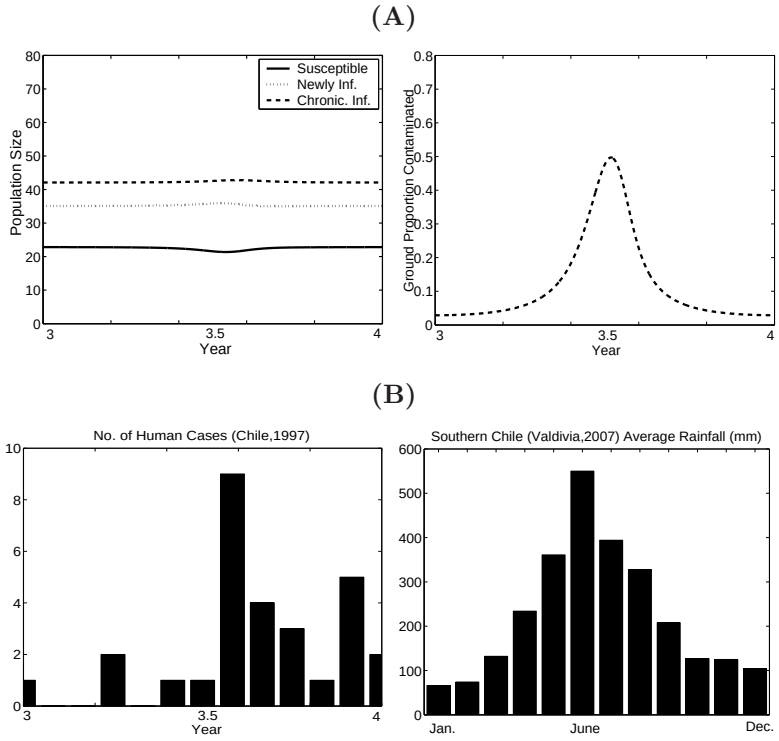

FIGURE 3. (A) Solution of model (3) with seasonal viral decay rate, constant birth rate, constant transmission rates, and constant carrying capacity (year 3-4). The left graph is the number of rodents that are susceptible, newly infectious and chronically infectious. The right graph is the proportion of virus present in the forest environment due to rodents. (B) The left graph is a bar graph of the number of human cases of HPS in Chile in 1997. The right graph gives the 2007 average precipitation values for Valdivia, Chile.

examples illustrate the significant impact that indirect transmission and periodically varying demographic and epidemiological parameters may have on infection in rodents and humans. Periodicity in demographic and epidemiological parameters may lead to greater hantavirus persistence in wild rodent populations, and indirect transmission and periodicity in the viral decay rate may lead to spillover infection in humans.

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Appendix. The following program, written for Maple, checks the three conditions in the Routh-Hurwitz criteria to show local asymptotic stability of the EE. That is,

the program checks the conditions on the coefficients of the characteristic polynomial of matrix $\mathbf{S_2}$ (see proof of Theorem 2.4). An equivalent program to check these conditions can be written for other computer algebra systems, such as Mathematica. Program comments are shown in brackets for reader's convenience.

```
with(linalg):
{The values of the EE and the parameters are assumed positive.}
assume(beta[n]>0,beta[c]>0,epsilon>0,tau>0,b>0,phi[n]>0,phi[c]>0,
I[n]>0,I[c]>0,G>0,d>0);
{Define the 3 by 3 matrix S2.}
S2:=matrix([[-beta[n]*I[n]-beta[c]*I[c]-epsilon*G-(tau+b)*
(beta[n]*I[n])/(beta[n]*I[n]+beta[c]*I[c]+epsilon*G)-tau-b,
-tau/b*(beta[n]*I[n]+beta[c]*I[c]+epsilon*G)+(tau+b)*(beta[c]
*I[c])/(beta[n]*I[n]+beta[c]*I[c]+epsilon*G),(tau+b)*(epsilon*G)
/(beta[n]*I[n]+beta[c]*I[c]+epsilon*G)],[b,-b,0],[phi[n]*I[n]
*d/(phi[n]*I[n]+phi[c]*I[c]),phi[c]*I[c]*d/(phi[n]*I[n]+phi[c]
*I[c]),-phi[n]*I[n]-phi[c]*I[c]-d]]);
{Compute the characteristic polynomial of S2.}
f:=collect(charpoly(S2,lambda),lambda):
a0:=simplify(coeff(f,lambda,3)):
{Divide by a0, the coefficient of x^3, if not equal to one, so that
the characteristic polynomial has the form x^3+a1x^2+a2x+a3.
Then the Routh-Hurwitz criteria is checked: a1>0,a3>0,a1a2>a3.}
a1:=coeff(f,lambda,2)/a0:is(a1>0);
a2:=coeff(f,lambda,1)/a0:is(a2>0);
a3:=coeff(f,lambda,0)/a0:is(a3>0);
is(a1*a2>a3);
```

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E-mail address: curtis.wesley@lsus.edu
E-mail address: linda.j.allen@ttu.edu
E-mail address: michel.langlais@u-bordeaux2.fr