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The role of age structure in the persistence of a chronic pathogen in a fluctuating population

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Small mammal populations exhibit large fluctuations, potentially leading to local extinction of specialist pathogens after bottlenecks. Pathogen persistence in recovering populations depends on the epidemiological characteristics of the hosts that survive the bottlenecks. Sin Nombre virus is a largely asymptomatic infection of deer mice, which creates a chronic lifelong infection. Earlier work on this virus has shown that males play a key role in pathogen persistence through a combination of longer lifespan and higher seroprevalence. Other evidence indicates that mouse age could play an equally important role, as older mice may have higher survivorship and higher contact rates. We use age structured models to examine the relationships among prevalence, age-dependent demographics, and age-dependent epidemiology.

Keywords: Sin Nombre virus; *Peromyscus maniculatus*; age structure

1. Introduction

Decades of research have addressed fluctuations in small mammal populations as consequences of density-dependent demographics or density-independent abiotic conditions [7,13,26]. These fluctuations are of great importance to the parasites and pathogens that depend on these species, which can be driven to extinction during a host population crash. Differences in the period and amplitude of host population fluctuations among small mammals could be important determinants in the diversity and abundance of their parasites.

In rodents, hantaviruses are among the most important pathogens [10], causing up to 200,000 human infections annually [20]. In one well-studied system, the Old World rodent *Myodes glareolus* (the bank vole) hosts Puumala virus and exhibits regular population cycles with periods of 3–4 years [24]. The Puumala virus causes one of the mildest human hantaviral diseases, nephropathia epidemica, which has mortality rates of $<1\%$ [25]. Among the New World rodents, *Peromyscus maniculatus* (the deer mouse) is an important host of hantavirus, most notably Sin Nombre virus (SNV). This virus causes a highly lethal disease in humans known as hantavirus cardiopulmonary syndrome (HCPS). Although human cases of HCPS are rare when compared with those by Old World strains, the syndrome is fatal in $\sim$38–60% of clinically diagnosed human cases [14,16,20].

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Early work by Terman [26] suggested that compared with other small mammal species sampled, *P. maniculatus* has relatively stable populations. Even so, both Fryxell *et al.* [13] and Mills *et al.* [19] have illustrated fluctuations of one to two orders of magnitude in *P. maniculatus* populations. In New World rodents, these fluctuations tend to be irregular and more closely tied to climatic events [19]. After the 1992 ENSO event, a population increase of *P. maniculatus* in the Southwest United States led to an outbreak of infections in humans caused by SNV [12]. The 20-fold increase of central New Mexico's rodent population was linked to the outbreak of human cases. After rodent populations decreased, so did human cases.

The hantaviruses are a unique genus in the *Bunyaviridae* family, as they are thought to be transmitted solely by their rodent hosts and not by arthropod vectors [17]. It is widely accepted that rodent to rodent transmission occurs via inhalation of aerosolized excreta or as a direct consequence of aggressive interactions [5,6], although this has yet to be confirmed conclusively. Once infected, a rodent host is assumed to remain chronically infected for life without the possibility of recovery, resulting in increased prevalence among older mice. Direct transmission may make a virus particularly susceptible to extinction during host population crashes, as only the mice themselves act as a reservoir. Indirect transmission, particularly via an environmental compartment, can provide a buffer against such extinctions [24].

In this paper, we present an age-structured, single-sex model of Sin Nombre hantavirus transmission in a demographically stationary *P. maniculatus* host population with age-dependent mortality and epidemiology [9]. We explore the role of age-dependent epidemiological parameters on the basic reproduction number R_0, prevalence, and age of infection with respect to age-specific heterogeneities in natural mortality rate at the endemic steady state. By adding exogenous population fluctuations, we test the hypothesis that long-tailed survivorship coupled with epidemiological dynamics favouring transmission of infection by older individuals enhances persistence of an infection through a population bottleneck.

2. The model

We consider a population described by a population density $N(a,t)$, which represents the sum of susceptible and infected individuals of age a at time t, given by $S(a,t)$ and $I(a,t)$, respectively. The total population at any time t is given by the integral of this density over all ages, $N(t) = \int_0^\infty N(a,t)\,\mathrm{d}a$, and similarly for the populations of susceptible and infected individuals, $S(t)$ and $I(t)$. Prevalence at time t is defined as $p(t) = I(t)/N(t)$.

Susceptible individuals are lost to death (at rate $m(a)$) or infection (at rate $\Lambda(a,t)$) (Equation (1)) and created only through births (Equation (3)). Infected individuals are lost to death and created by new infections (Equation (2)), but not by births (Equation (4)) because vertical transmission does not occur in hantavirus systems [6]. We assume that contact between individuals occurs via proportionate mixing (Equation (5)), where $\gamma(a)$ the age-specific per capita contact rate and $\sigma(a)$ the age-specific susceptibility to infection [8,15]. The probability that a contact is made by an individual of age a' is $\gamma(a')N(a',t)/\int_0^\infty \gamma(u)N(u,t)\,\mathrm{d}u$. The probability that a contact is made by an infected individual of age a' is

$$\frac{\gamma(a')N(a',t)}{\int_0^\infty \gamma(u)N(u,t)\,\mathrm{d}u}\cdot\frac{I(a',t)}{N(a',t)} = \frac{\gamma(a')I(a',t)}{\int_0^\infty \gamma(u)N(u,t)\,\mathrm{d}u}.$$

The resulting force of the infection term (Equation (5)) is of the constant contact variety [18].

$$\frac{\partial S}{\partial t} + \frac{\partial S}{\partial a} = -\Lambda(a,t)S(a,t) - m(a)S(a,t), \tag{1}$$

$$\frac{\partial I}{\partial t} + \frac{\partial I}{\partial a} = \Lambda(a,t)S(a,t) - m(a)I(a,t), \tag{2}$$

$$S(0,t) = B_S(t) = \int_0^\infty r(a,t)[S(a,t) + I(a,t)]\,\mathrm{d}a = \int_0^\infty r(a,t)N(a,t)\,\mathrm{d}a, \tag{3}$$

$$I(0,t) = B_I(t) = 0, \tag{4}$$

$$\Lambda(a,t) = \gamma(a)\sigma(a)\frac{\int_0^\infty \gamma(a')I(a',t)\,\mathrm{d}a'}{\int_0^\infty \gamma(a'')N(a'',t)\,\mathrm{d}a''}, \tag{5}$$

$$S(a,0) = S_0(a), \tag{6}$$

$$I(a,0) = I_0(a). \tag{7}$$

Although there is as yet no consensus in the literature [21,22], we assume that there is no additional mortality associated with an infection. With this assumption, the equation for the dynamics of the total population decouples from the equations for the epidemiological dynamics.

We assume a Weibull-type survivorship function described by $\ell(a) = \exp(-ca^q)$, where c is the overall mortality rate and q is the shape parameter [23]. Assuming this form of $\ell(a)$, we recover the instantaneous mortality rate $m(a)$ as $m(a) = -\ell'(a)/\ell(a)$, or $m(a) = cqa^{q-1}$. We think of q as a measure of heterogeneity in mortality rate across ages in the population, since $q = 1$ corresponds to exponential survivorship with a constant mortality rate c. For $q < 1$, the age-specific mortality rate is a decreasing function of age.

3. Model analysis

3.1. *Steady-state analysis*

At steady state, Equations (1–7) become a system of ordinary differential equations for the steady-state age distributions $S^*(a)$ and $I^*(a)$.

$$\frac{\mathrm{d}S^*(a)}{\mathrm{d}a} = -\Lambda^*(a)S^*(a) - m(a)S^*(a), \tag{8}$$

$$\frac{\mathrm{d}I^*(a)}{\mathrm{d}a} = \Lambda^*(a)S^*(a) - m(a)I^*(a), \tag{9}$$

$$S^*(0) = \int_0^\infty r^*(a)N^*(a)\,\mathrm{d}a, \tag{10}$$

$$\Lambda^*(a) = \gamma(a)\sigma(a)\frac{\int_0^\infty \gamma(a')I^*(a')\,\mathrm{d}a'}{\int_0^\infty \gamma(a'')N^*(a'')\,\mathrm{d}a''}. \tag{11}$$

Defining the probability that a susceptible individual remains uninfected at age a to be $W(a) = \exp\left(-\int_0^a \Lambda^*(u)\,\mathrm{d}u\right)$ and using the survivorship function above, we have solutions

$$S^*(a) = S^*(0)\ell(a)W(a), \tag{12}$$

$$I^*(a) = S^*(0)\ell(a)(1 - W(a)). \tag{13}$$

At steady state, the age distribution of the total population is given by $N^*(a) = S^*(0)\ell(a)$. If we set

$$Y = \frac{\int_0^\infty \gamma(a')I^*(a')\,\mathrm{d}a'}{\int_0^\infty \gamma(a'')N^*(a'')\,\mathrm{d}a''}$$

to be the fraction of all contacts which are made by infected individuals, we can write

$$\Lambda^*(a) = \gamma(a)\sigma(a)Y.$$

For a given Y,

$$W(a) = \exp(-Y\int_0^a \gamma(u)\sigma(u)\,\mathrm{d}u).$$

We now have an equation for Y,

$$\int_0^\infty \gamma(a')\ell(a')\exp(-Y\int_0^{a'}\gamma(u)\sigma(u)\,\mathrm{d}u)\,\mathrm{d}a' = (1-Y)\int_0^\infty \gamma(a')\ell(a')\,\mathrm{d}a',$$

involving only known functions. This equation can be solved numerically for Y, from which we can calculate $W(a)$ and $I^*(a)$. We can use these known functions to calculate the mean age of infection conditional at equilibrium [4],

$$A_i^* = \frac{\int_0^\infty a\Lambda^*(a)S^*(a)\,\mathrm{d}a}{\int_0^\infty \Lambda^*(u)S^*(u)\,\mathrm{d}u} = \frac{\int_0^\infty a\gamma(a)\sigma(a)\ell(a)W(a)\,\mathrm{d}a}{\int_0^\infty \gamma(u)\sigma(u)\ell(u)W(u)\,\mathrm{d}u}.$$

When $\gamma(a)$, $\sigma(a)$, and $m(a)$ are constant, the definition for Y becomes

$$Y = \frac{\int_0^\infty I^*(a')\,\mathrm{d}a'}{\int_0^\infty N^*(a'')\,\mathrm{d}a''} = p^*,$$

where p^* is the endemic prevalence. The equation for Y simplifies to

$$\int_0^\infty \ell(a')\mathrm{e}^{-\gamma\sigma p^* a'}\,\mathrm{d}a' = (1-p^*)\int_0^\infty \ell(a')\,\mathrm{d}a'.$$

Constant $m(a)$ corresponds to exponential survivorship, and we can write this as

$$\int_0^\infty \mathrm{e}^{-(c+\gamma\sigma p^*)a'}\,\mathrm{d}a' = (1-p^*)\int_0^\infty \mathrm{e}^{-ca'}\,\mathrm{d}a',$$

to obtain $p^* = 1 - c/\gamma\sigma$. In this case, we find that A_i^* satisfies

$$A_i^* = \frac{\int_0^\infty a\exp(-(c+\gamma\sigma p^*)a)\,\mathrm{d}a}{\int_0^\infty \exp(-(c+\gamma\sigma p^*)u)\,\mathrm{d}u} = \frac{1}{c+\gamma\sigma p^*}.$$

3.2. R_0

Following the method of Diekmann *et al.* [11], we can calculate R_0 using the next generation operator. We define $A(\tau, a, a')$ to be the expected infectivity of an individual who was infected τ units ago while at age a' towards a susceptible individual of age a. When,

$$(KS)(\phi) = S(a)\int_0^\infty\int_0^\infty A(\tau,a,a')\phi(a')\,\mathrm{d}a'\,\mathrm{d}\tau,$$

we use the proportionate mixing assumption $A(\tau,a,a') = f(a)g(\tau,a') = \gamma(a)\sigma(a)g(\tau+a')$. The exact forms for $f(a)$ and $g(\tau,a')$ are given in Equation (14); however, we can think of $f(a)$ as a function describing properties of a susceptible individual of age a and $g(\tau,a')$ as a

function describing the probability of contact with an individual initially infected at age a'. With $\phi(a) = S(a)f(a)$, we find

$$\begin{aligned} R_0 &= \int_0^\infty \int_0^\infty g(\tau + a')S(a')f(a')\,\mathrm{d}a'\,\mathrm{d}\tau \\ &= \int_0^\infty \left(\int_0^\infty g(\tau + a')\,\mathrm{d}\tau \right) S(a')f(a')\,\mathrm{d}a' \\ &= \int_0^\infty \left(\int_{a'}^\infty g(u)\,\mathrm{d}u \right) S(a')f(a')\,\mathrm{d}a' \\ R_0 &= \int_0^\infty \left(\int_0^\infty \frac{\gamma(a'+\tau)\ell(a'+\tau)}{\ell(a')\int_0^\infty \gamma(a)N(a)\,\mathrm{d}a}\,\mathrm{d}\tau \right) S(a')\gamma(a')\sigma(a')\,\mathrm{d}a'. \end{aligned} \tag{14}$$

We can simplify this expression (Appendix 1) to

$$R_0 = \int_0^\infty \gamma(a')\sigma(a') \left(1 - \frac{\int_0^{a'} \gamma(a)\ell(a)\,\mathrm{d}a}{\int_0^\infty \gamma(v)\ell(v)\,\mathrm{d}v} \right) \mathrm{d}a'.$$

Numerical calculations of R_0 over a range of q are given in Figure 1 for four different combinations of age dependence in $\gamma(a)$ and $\sigma(a)$.

In the case of exponential survivorship ($c = 1$) and constant parameters $\gamma(a) = \gamma$ and $\sigma(a) = \sigma$, we can simplify the expression for R_0 to obtain the standard result for the equivalent unstructured model

$$\begin{aligned} R_0 &= \int_0^\infty \gamma(a')\sigma(a') \left(1 - \frac{\int_0^{a'} \gamma(a)\ell(a)\,\mathrm{d}a}{\int_0^\infty \gamma(v)\ell(v)\,\mathrm{d}v} \right) \mathrm{d}a' \\ &= \int_0^\infty \gamma\sigma \left(1 - \frac{\int_0^{a'} \mathrm{e}^{-ca}\,\mathrm{d}a}{\int_0^\infty \mathrm{e}^{-cv}\,\mathrm{d}v} \right) \mathrm{d}a' \\ &= \frac{\gamma\sigma}{c}. \end{aligned}$$

Combining this result with the formula for p^*, we obtain the familiar relation $R_0 = 1/(1 - p^*)$ [3].

3.3. *Parameterization*

Since we are interested in the epidemiological consequences of the shape parameter in the survivorship function, to parameterize the model we must compute the scale parameter for a given mean lifespan and shape parameter [23]. The mean lifespan is $\bar{a} = \int_0^\infty \ell(a)\,\mathrm{d}a = c^{1/q}\Gamma(1/q + 1)$, which we take to be 70 days [1]. For a given mean lifespan $\bar{a}$ and shape parameter q, we choose the death rate c that satisfies $c = (\bar{a}/\Gamma(1/q + 1))^q$.

To include temporal fluctuations in the birth rate, we consider $r(a, t) = r_1(a)r_2(t)$, where $r_2(t) = 1 + (A/N^*)\sin(2\pi t/K)$. We choose $r_2(t)$ to be K-year periodic with varying amplitudes (Table 1).

Our goal is to study the interaction between long-tailed survivorship ($q < 1$) and linearly increasing functions $\gamma(a)$ or $\sigma(a)$, indicating increasing contact rates or susceptibility with age. To normalize, we fix baseline values $\gamma(a) = \gamma_m(q)$ and $\sigma(a) = \sigma_m(q)$ such that prevalence at the endemic steady state is $p^* = 0.20$ in the case when $\gamma(a)$ and $\sigma(a)$ are constant.

Table 1. Parameters for age-structured model, with description, baseline values or constraints, and references when available. Demographic parameters are denoted by Roman characters and epidemiological parameters are denoted by Greek characters.

Parameter	Description	Baseline values	References
$r_1(a) = \begin{cases} 0, a \le 50 \\ r_1, 50 < a \end{cases}$	Birth rate in offspring per day	r_1 chosen so that population is stationary	
$r_2(t) = 1 + (A/N^*)\sin(2\pi t/K)$	Birth rate forcing function with amplitude A and frequency K	$A = 1, 3$, and 7; $K = 1$ year	
$\bar{a}$	Mean lifespan	70 days	[1]
c	Survivorship function scale parameter	Chosen so that mean lifespan $\bar{a} = 70$ days	
q	Survivorship function shape parameter	$q \in [0.5, 1]$	
$\gamma(a)$	Contact rate	See Table 2	[1,2]
$\sigma(a)$	Susceptibility	See Table 2	[1]

To compare with cases with non-constant $\gamma(a)$, we let $\gamma(a) = \gamma_m/2 + (\gamma_s/\bar{a})a$ and find γ_s such that $\int_0^\infty \gamma(a)\ell(a)\,\mathrm{d}a = \gamma_m(q)$ for each q. For cases with non-constant $\sigma(a)$, we let $\sigma(a) = 1/2 + (\sigma_s/\bar{a})a$ and find σ_s such that $\int_0^\infty \sigma(a)\ell(a)\,\mathrm{d}a = 1$ for each q. Thus, we are comparing among cases with the same mean lifespan, the same average contact rate, and the same average susceptibility.

4. Results

4.1. *Static demography*

Our first result lies in the parameterization itself. We see that with no age-dependence in contact rate or susceptibility (Table 2, row one), the baseline contact rate γ_m for long-tailed survivorship is roughly a third of that for exponential survivorship. Thus, with respect to our normalization, we see that attaining a prevalence of $p^* = 0.20$ with exponential survivorship requires a much larger baseline contact rate when compared with long-tailed survivorship. Similar trends hold for

Table 2. Slope and intercept for contact and susceptibility parameters used in analytical and numerical solutions for the four combinations explored.

			Normalized parameter coefficients for a given q					
Age dependence	Form of parameter	q	0.5	0.6	0.7	0.8	0.9	1.0
None	$\gamma(a) = \gamma_m$	γ_m	0.00677	0.00947	0.01197	0.01419	0.01615	0.01786
	$\sigma(a) = \sigma_m$	σ_m	1	1	1	1	1	1
Contact rate	$\gamma(a) = \gamma_m/2 + (\gamma_s/70)a$	γ_m	0.00677	0.00947	0.01197	0.01419	0.01615	0.01786
		γ_s	0.00113	0.00232	0.00381	0.00548	0.00721	0.00893
	$\sigma(a) = \sigma_m$	σ_m	1	1	1	1	1	1
Susceptibility	$\gamma(a) = \gamma_m$	γ_m	0.00677	0.00947	0.01197	0.01419	0.01615	0.01786
	$\sigma(a) = 1/2 + (\sigma_s/70)a$	σ_s	0.16667	0.24445	0.31860	0.38627	0.44666	0.5
Both	$\gamma(a) = \gamma_m/2 + (\gamma_s/70)a$	γ_m	0.00677	0.00947	0.01197	0.01419	0.01615	0.01786
		γ_s	0.00113	0.00232	0.00381	0.00548	0.00721	0.00893
	$\sigma(a) = 1/2 + (\sigma_s/70)a$	σ_s	0.16667	0.24445	0.31860	0.38627	0.44666	0.5

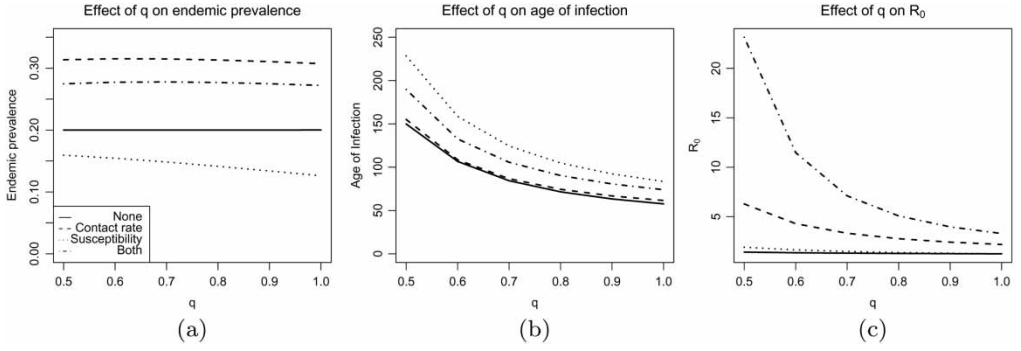

Figure 1. Effects of age-specific contact and susceptibility on endemic prevalence, age of infection, and R_0, with respect to the shape parameter of the survivorship function. (a) Endemic prevalence, (b) age of infection, and (c) R_0.

the slopes γ_s and σ_s, which suggests that to maintain baseline prevalence, the contact rate and susceptibility must increase faster with age when survivorship is exponential.

With static demographic parameters, we are able to study the behaviour of the steady-state solutions of Equations (8)–(11). We compute R_0 given by the formula in Equation (14) for a constant contact rate and susceptibility for each parameter held fixed while the other increases linearly with age, and lastly for both parameters increasing with age.

Endemic prevalence is reduced when susceptibility is age-dependent (Figure 1(a)) and the magnitude of the reduction increases as the shape parameter increases ($q \to 1$). When the contact rate is an increasing function of age, endemic prevalence is greater than in the constant case, but there is little effect of the shape parameter q (Figure 1(b)).

While endemic prevalence was largely unchanged with respect to increases in q, a striking relationship exists between mean age of infection and survivorship (Figure 1(b)). The mean age of infection decreases dramatically with increasing q, taking on a minimum with exponential survivorship. Age-dependent susceptibility as a function of age greatly increases the mean age of infection, whereas the age-dependent contact rate has little effect on the mean age of infection. This relationship may shed light on the prevalence values for each treatment. Age-dependent susceptibility reduces endemic prevalence and increases the mean age of infection; however, the age-dependent contact rate increases prevalence while leaving the mean age of infection largely unchanged.

The basic reproduction number R_0 (Figure 1(c)) is largely unchanged in the case of age-dependent susceptibility. In contrast, the age-dependent contact rate dramatically increases R_0 for long-tailed survivorship. Although the effect of interactions between susceptibility and contact rate were not surprising in the relationships between prevalence (Figure 1(a)) and mean age of infection (Figure 1(b)) with q, the interaction between susceptibility and contact rate results in a large increase in R_0 (Figure 1(c)). While the interaction of age-dependent contact and susceptibility resulted in R_0's that were greater for all q's, the effect was most significant for long-tailed survivorship. This suggests the role of older individuals as a core group to the transmission of infection.

4.2. *Variable demography*

With a periodic birth rate, we lose the luxury of using steady-state solutions for any calculations and resort to numerical approximations. We quantify the effects of variable period and amplitude population oscillations by computing the mean prevalence and age of infection over one period of the oscillation.

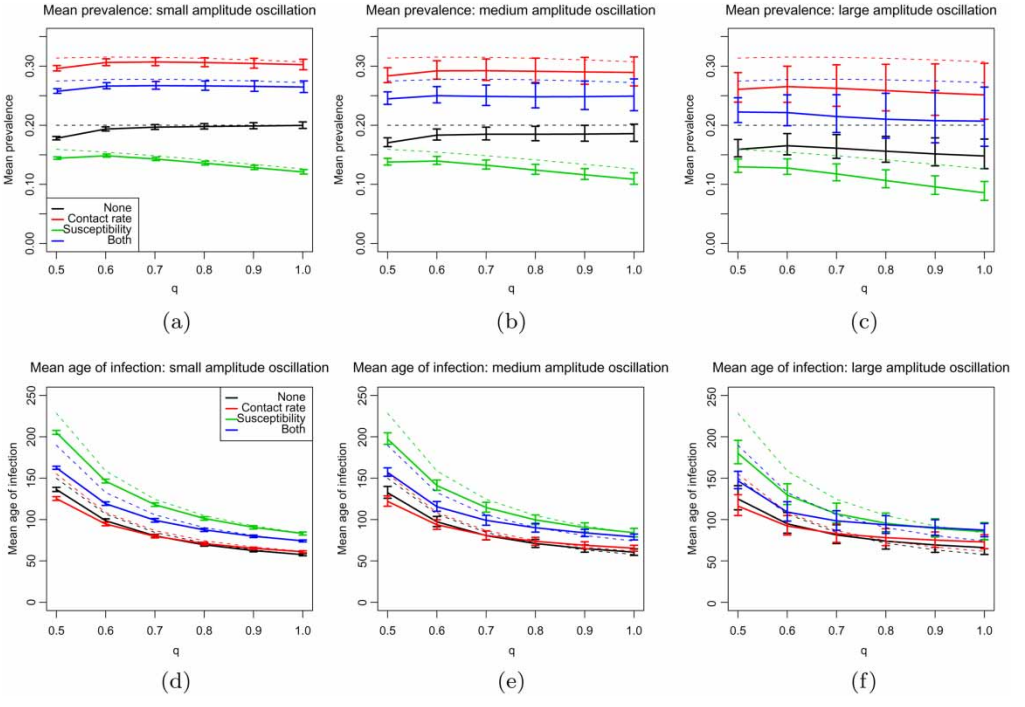

Figure 2. Mean prevalence and mean age of infection over one period of the birth rate fluctuation. Dotted lines represent quantities from the static demographics presented in Figure 1. Bars indicate the amplitude of the fluctuation in prevalence. (a–c) Mean prevalence with respect to the amplitude of birth rate oscillation: (a) small amplitude; (b) medium amplitude; (c) large amplitude. (d–f) Mean age of infection with respect to the amplitude of the fluctuation: (d) small amplitude; (e) medium amplitude; (f) large amplitude.

In all cases examined, fluctuations in population dynamics result in mean prevalence less than that observed when the population was fixed (Figure 2(a–c)). The range of prevalence observed over one period increases with the amplitude of the oscillation in birth rate, with small amplitude oscillations having little effect on mean prevalence. Age-dependent susceptibility alone had little effect on mean prevalence for the range of birth rate oscillations tested, whereas the age-dependent contact rate resulted in a larger range of observed prevalence. Not surprisingly, the range of prevalence increases with the amplitude of oscillation. With age-dependent contact and susceptibility, the observed prevalence is similar to that of the constant parameter static case, and the amplitude of the fluctuation about the mean increases with q.

As in the static demography case, the mean age of infection is a decreasing function of q. With respect to the static case, the mean age of infection is reduced for small q as the amplitude of the oscillation increases, whereas for large q, the mean age of infection increases with the amplitude of oscillation. The range in the mean age of infection increases with the amplitude of the oscillation; however, the range varies little with respect to q.

The amplitude of fluctuations in prevalence increases with q for age-dependent susceptibility, yet the amplitudes are still less than those for the constant parameter case (Figure 3). Age-dependent contact rates generate a larger amplitude oscillation in prevalence when compared with the constant case. For small q, the combined treatment of age-dependent contact rate and susceptibility yields smaller amplitude oscillations than those of the age-dependent contact rate treatment. Yet, following an intermediate value of $q (q \approx 0.85)$, the interaction between contact rate and susceptibility generates larger amplitude oscillations.

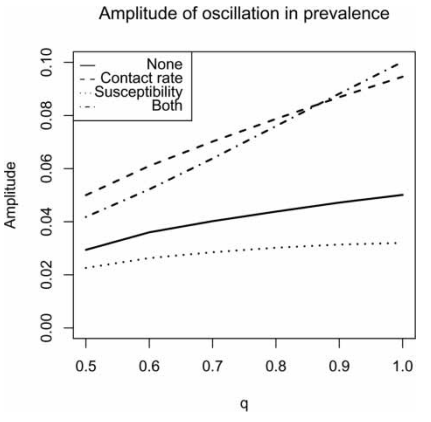

Figure 3. Amplitude of fluctuations in prevalence under large amplitude oscillations in birth rate.

5. Discussion

We set out to investigate the interaction between long-tailed survivorship and age-dependent epidemiology. In a static environment, we found that age-dependent susceptibility alone led to reduced prevalence for all shapes of survivorship function, and prevalence was at its least for exponential survivorship. Similar relationships between prevalence and survivorship were present with a fluctuating environment, while mean prevalence was reduced by fluctuations in all cases.

If older individuals are responsible for maintaining infections and promoting infection persistence, they may do so by buffering fluctuations in prevalence, not by altering the mean prevalence. In Figure 1(c), we see a large increase in R_0 with age-dependent contact rates and long-tailed survivorship functions. This suggests that older mice may serve as a core group of individuals promoting infection with a disproportionately large R_0. Despite the large value of R_0, the overall prevalence remains low.

Differences in demographic or epidemiological parameters across ages provide one possible form of heterogeneity important to epidemiological dynamics. In modelling the same host-hantavirus system, Adler *et al.* [1] found three sex-specific differences with epidemiological relevance. Higher prevalence in males was attributed to either higher susceptibility or higher contact rates in males than in females, and an observed male bias in sex ratio at low population densities suggested reduced male mortality.

We would like to extend this work to incorporate sex-structure to address important demographic and epidemiological differences between the sexes. In addition to this, we would like to explore more realistic fluctuations. Sinusoidal functions, although mathematically convenient, create only short and shallow bottlenecks. Real populations experience long and potentially deep bottlenecks which could provide very different effects. The fluctuations studied so far were the result of temporally varying birth rates; yet temporally varying death rates could be equally important causes of fluctuations. The consequences of temporally varying death rates and their interaction with population age structure are yet to be explored in this system.

The *P. maniculatus*–SNV system has been well-studied since its discovery in 1993. Many questions about the system remain unanswered and open to both theoretical and empirical research. Yet empirical evidence suggests that many factors, including maternal antibodies [5] and variable infectiousness [6], could be important contributors to epidemiological dynamics. The maternally protected class increases the level of heterogeneity within a population since its members are distinguished from other members of the population based not only on their own age but also on the infection status of their mothers at the times of gestation and lactation. Including this class is

of particular interest in fluctuating populations, where an accumulation of maternally protected offspring could jeopardize viral persistence through bottlenecks depending on the composition of the surviving population. Other evidence suggests that viral shedding is not constant during infection. Infection-age could be an important descriptor within the infected class, as recently infected individuals may transmit virus differently from distantly infected individuals.

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Appendix 1. Simplification of R_0

Recall the formula for R_0 (Equation (14)) along with formulae for the steady-state solutions (Equations (8) and (9)).

$$R_0 = \int_0^\infty \left(\int_0^\infty \frac{\gamma(a'+\tau)\ell(a'+\tau)}{\ell(a')\int_0^\infty \gamma(a)N(a)\,\mathrm{d}a}\,\mathrm{d}\tau \right) S(a')\gamma(a')\sigma(a')\,\mathrm{d}a' \tag{A1}$$

$$= \int_0^\infty \left(\int_0^\infty \gamma(a'+\tau)\left(\frac{\ell(a'+\tau)}{\ell(a')}\right)\mathrm{d}\tau \right) \ell(a') \left(\frac{\gamma(a')\sigma(a')}{\int_0^\infty \gamma(a)\ell(a)\,\mathrm{d}a} \right) \mathrm{d}a' \tag{A2}$$

$$= \int_0^\infty \left(\int_0^\infty \gamma(a'+\tau)\ell(a'+\tau)\,\mathrm{d}\tau \right) \left(\frac{\gamma(a')\sigma(a')}{\int_0^\infty \gamma(a)\ell(a)\,\mathrm{d}a} \right) \mathrm{d}a' \tag{A3}$$

$$= \int_0^\infty \left(\int_{a'}^\infty \gamma(a)\ell(a)\,\mathrm{d}a \right) \left(\frac{\gamma(a')\sigma(a')}{\int_0^\infty \gamma(a)\ell(a)\,\mathrm{d}a} \right) \mathrm{d}a' \tag{A4}$$

$$= \int_0^\infty \gamma(a')\sigma(a') \frac{\int_{a'}^\infty \gamma(a)\ell(a)\,\mathrm{d}a}{\int_0^\infty \gamma(a)\ell(a)\,\mathrm{d}a}\,\mathrm{d}a' \tag{A5}$$

$$R_0 = \int_0^\infty \gamma(a')\sigma(a') \left(1 - \frac{\int_0^{a'} \gamma(a)\ell(a)\,\mathrm{d}a}{\int_0^\infty \gamma(a)\ell(a)\,\mathrm{d}a} \right) \mathrm{d}a'. \tag{A6}$$