



Hantavirus transmission in sylvan and peridomestic environment

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Abstract: We developed a compartmental model for hantavirus infection in deer mice (*Peromyscus maniculatus*) with the goal of comparing relative importance of direct and indirect transmission in sylvan and peridomestic environments. A direct transmission occurs when the infection is mediated by the contact of an infected and an uninfected mouse, while an indirect transmission occurs when the infection is mediated by the contact of an uninfected mouse with, for instance, infected soil. Based on population dynamics data and estimates of hantavirus decay in the two types of environments, our model predicts that direct transmission dominates in the sylvan environment, while both pathways are important in peridomestic environments. The model allows us to compute a basic reproduction number R_0 , which indicates whether the virus will be endemic or eradicated from the mouse population, in both an autonomous and a time-periodic model. Our analysis can be used to evaluate various eradication strategies.

COMMENTS ON REVISED PAPER

T. GEDEON

I would like to thank again the anonymous referees for careful reading of the paper and their thoughtful comments.

In response to both reviewers we went carefully over the paper and corrected many grammatical errors, including all those pointed out by the first reviewer.

We have decided not to remove the text at the beginning of section 3 (Results), because we feel it provides an overview of all the results without technical language and details. Later in section 3 these results are elaborated on and all the details and numbers are provided. However, if the editor and reviewer feel strongly about this issue, we are open to change this part of the paper.

Reviewer #2 raised a very interesting question about the effect of synchrony of S and I on basic reproduction number R_0 . We have tested numerically synchronization in peridomestic situation with periodic birth and death rates. We start with values $\beta = 0.0024$ and $\alpha = 0.0016$ that are discussed in the paper. Then we decreased the value of α to 0.001, 0.0007 and 0.0005 while keeping β fixed. We have also kept α fixed and changed β to 0.015, 0.01 and 0.005. The values of S and I stayed synchronized for all these combinations of parameters. On the other hand, when we increased α to 0.008, I was leading S by about $\pi/4$ and when we increased β to 0.006 I was leading S again by less than $\pi/4$. Since S and I did not change their mutual synchrony as we lowered both α and β , the synchronization (or the lack of thereof) does not seem to explain greater fragility of periodically forced peridomestic population at higher R_0 .

Abstract

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Figure 1A
[Click here to download Figure: raw_data.pdf](#)

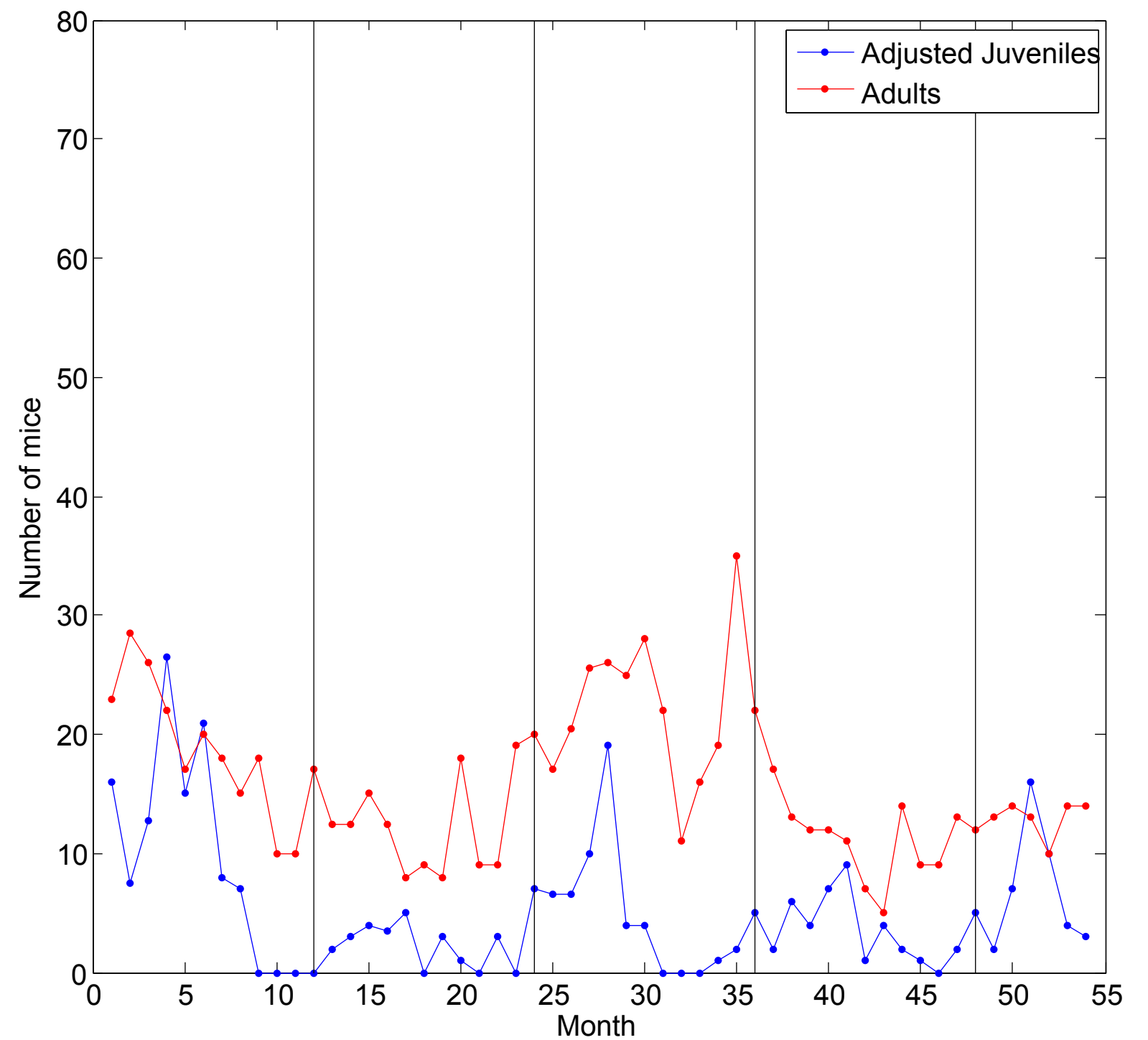


Figure 1B
[Click here to download Figure: raw_MNA_infec.pdf](#)

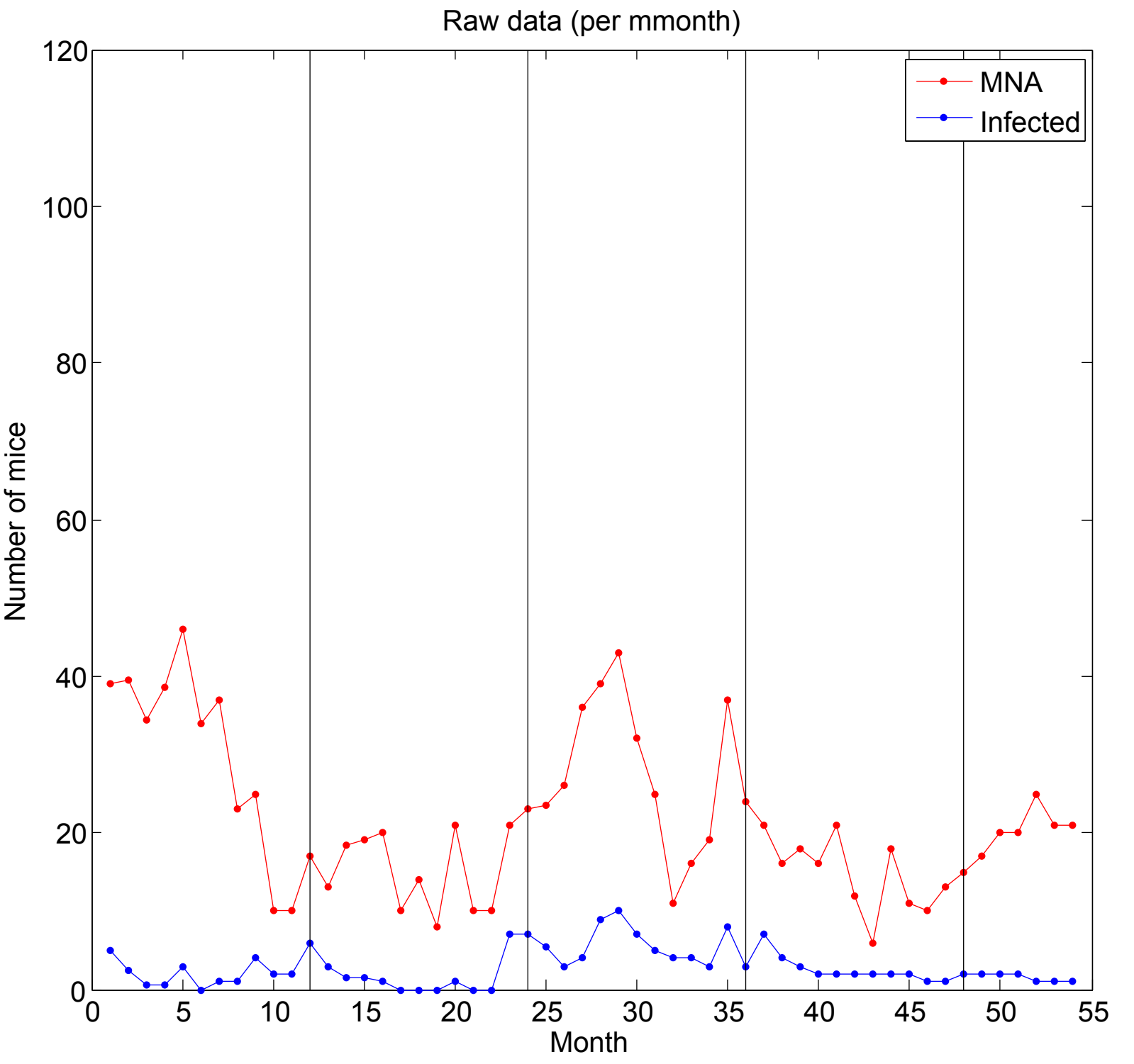


Figure 2A
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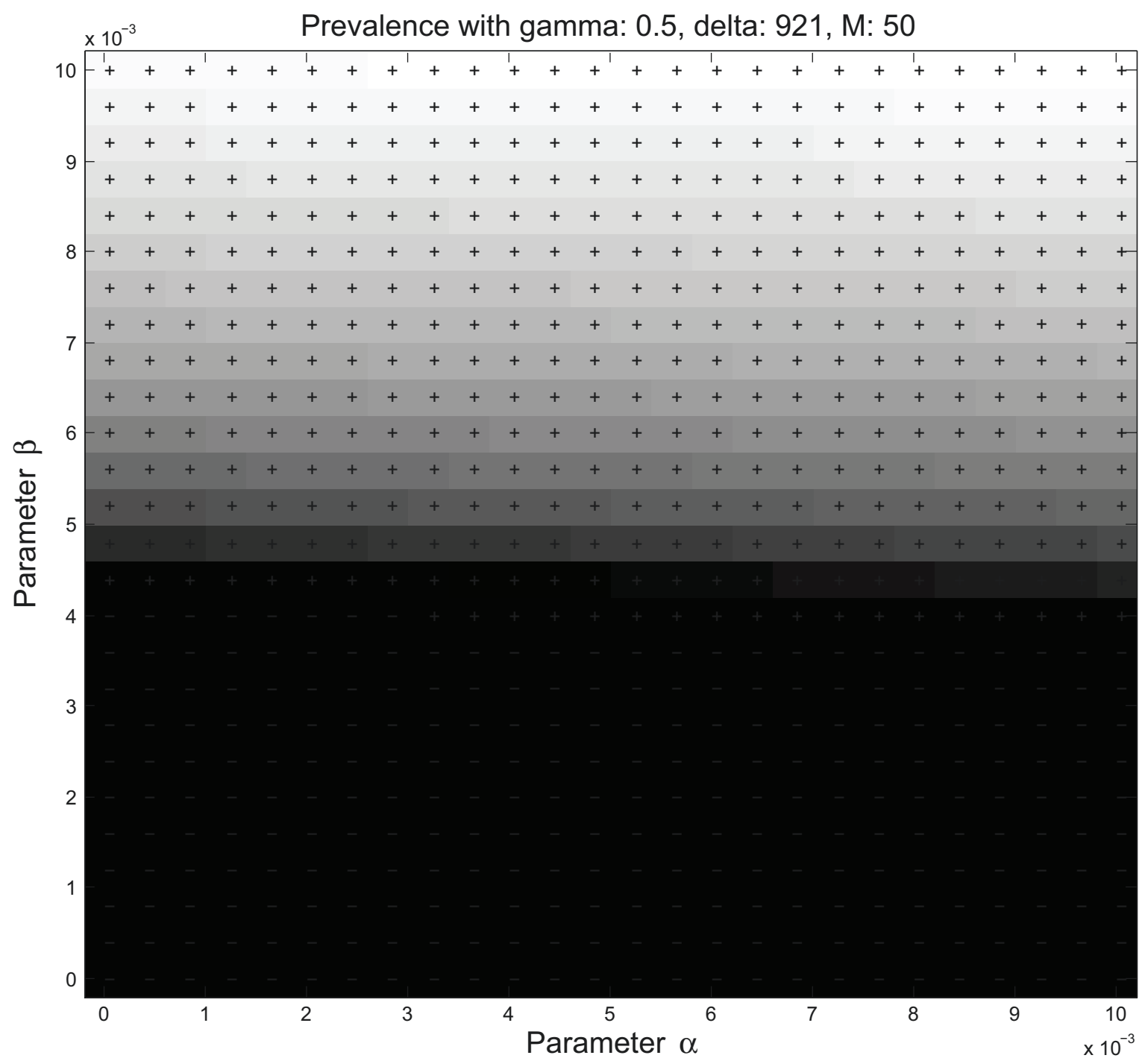


Figure 2B
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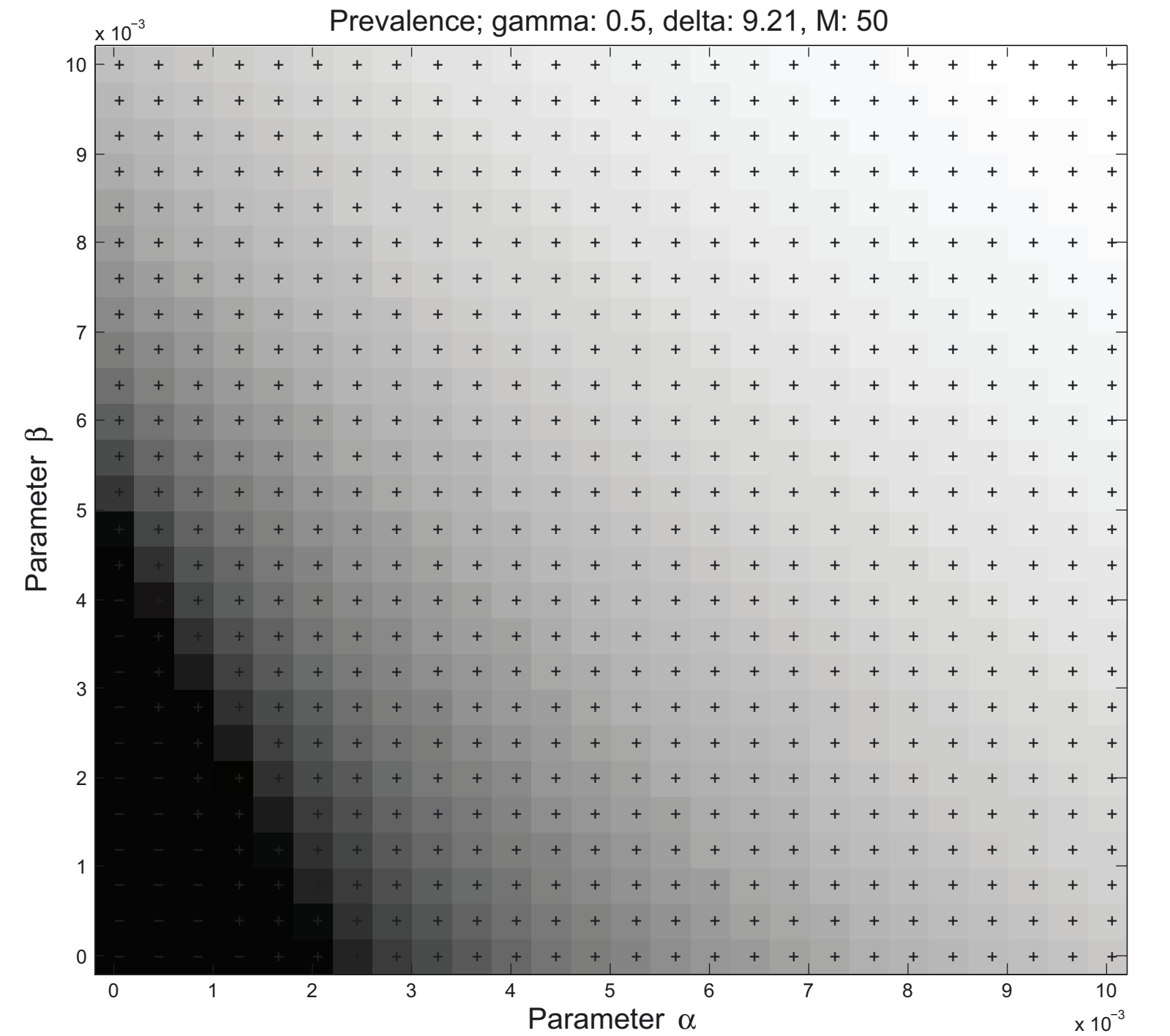


Figure 3
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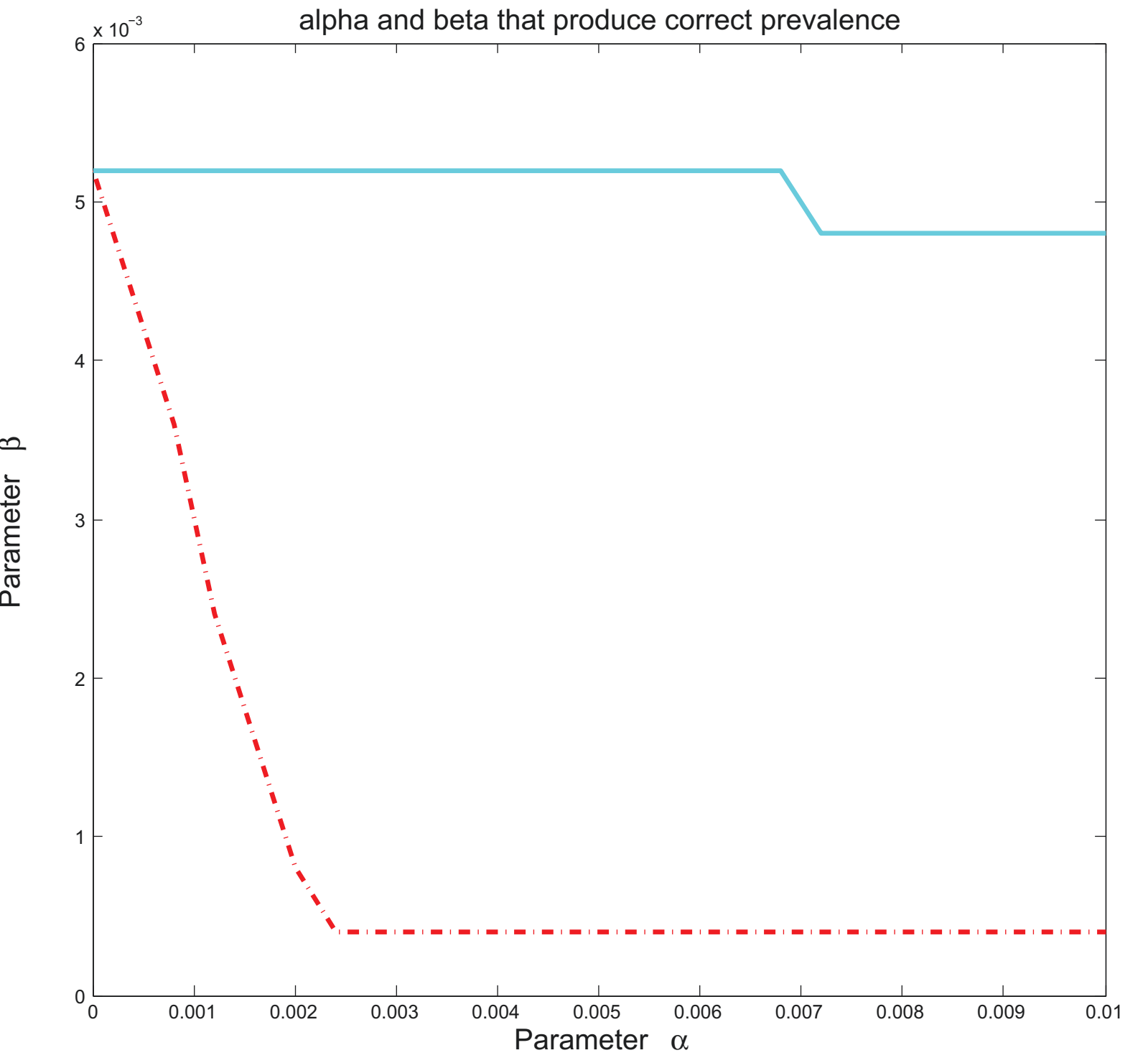


Figure 4A

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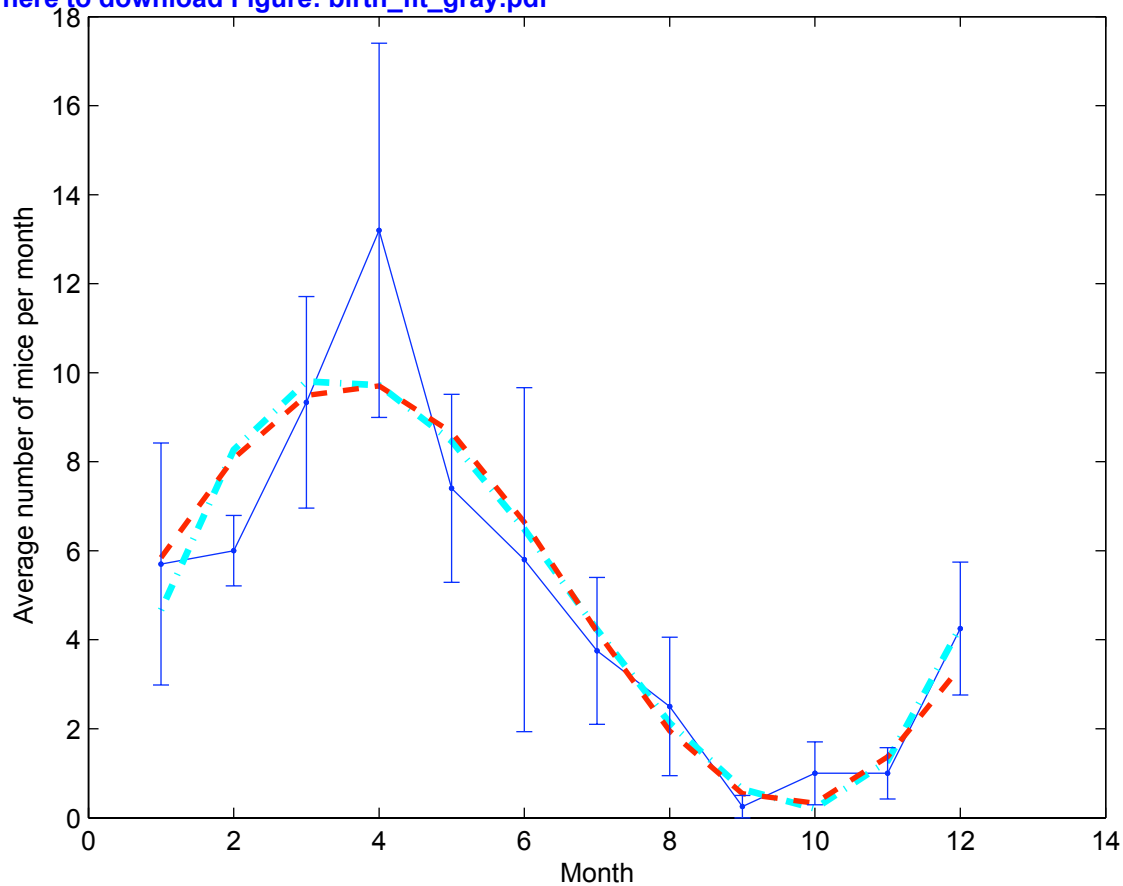


Figure 4B

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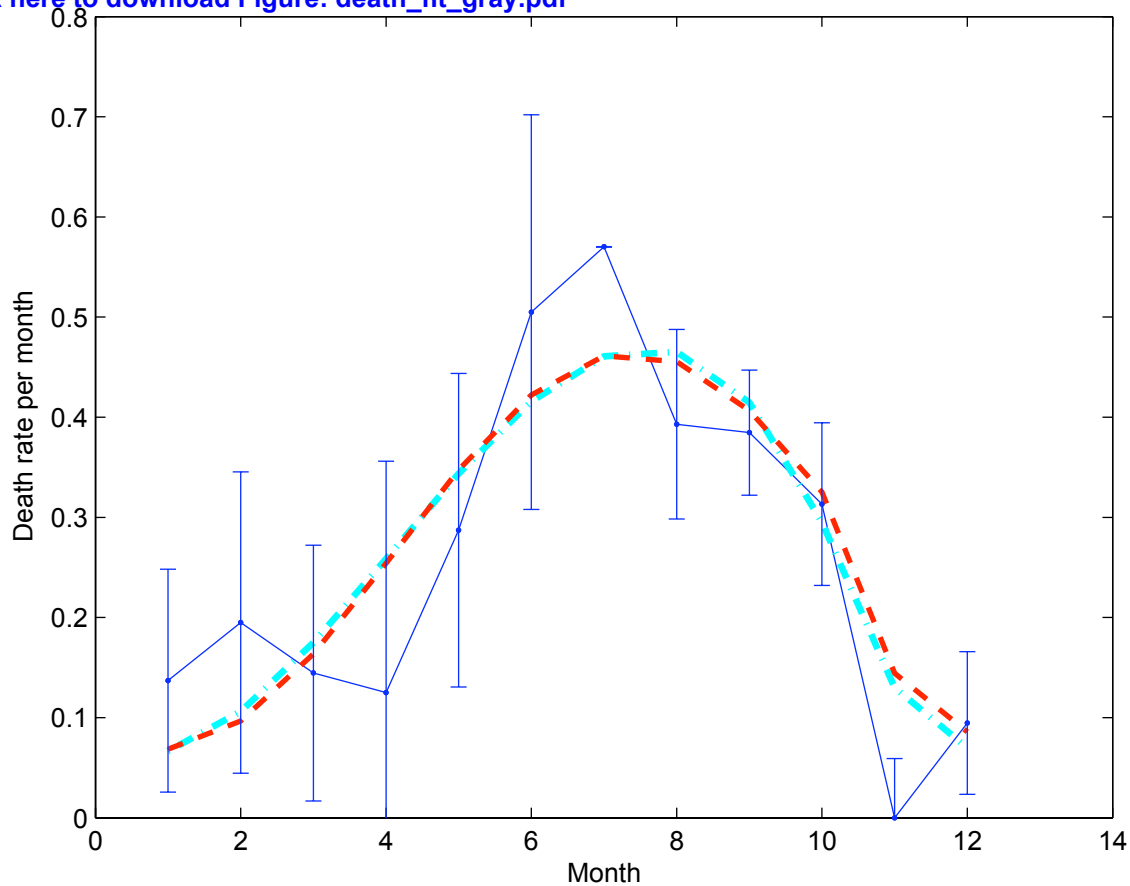


Figure 4C
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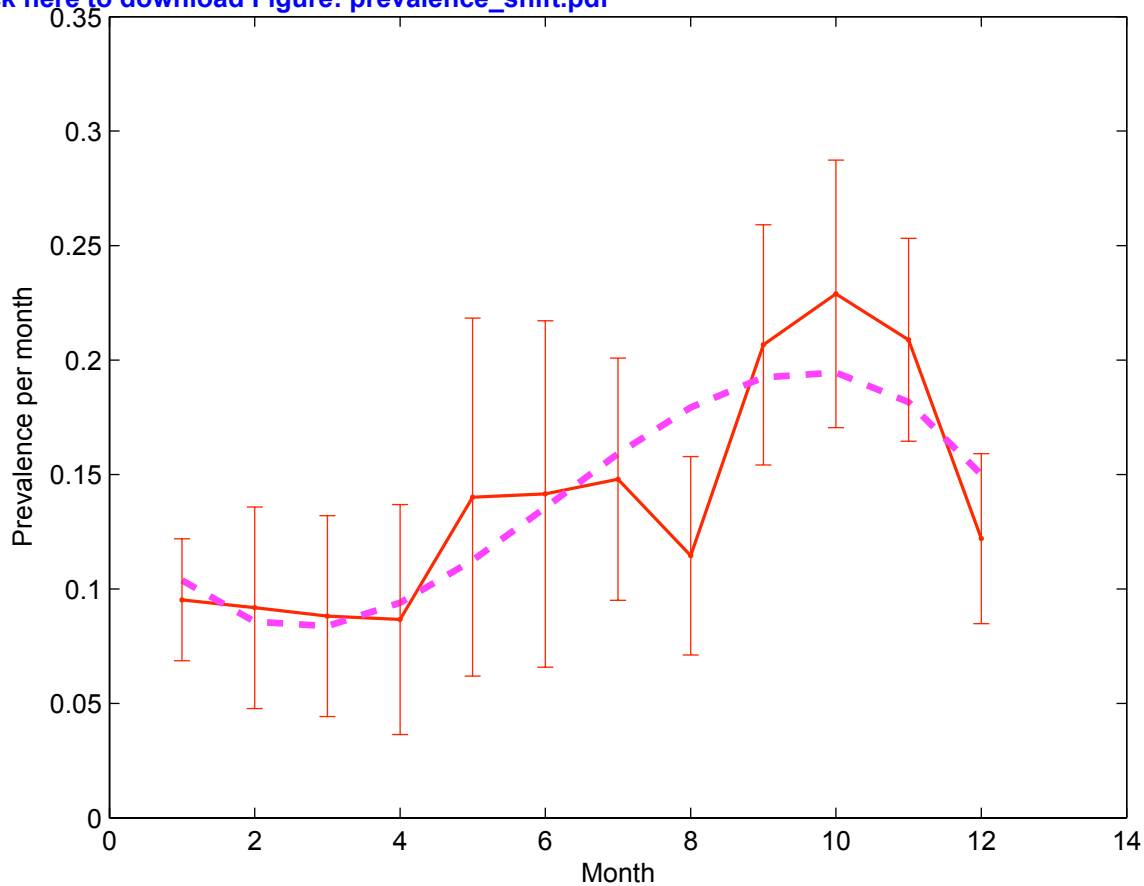


Figure 5A
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alpha: 0.0016, beta: 0.0024, gamma: 0.5, delta: 9.21, M: 50

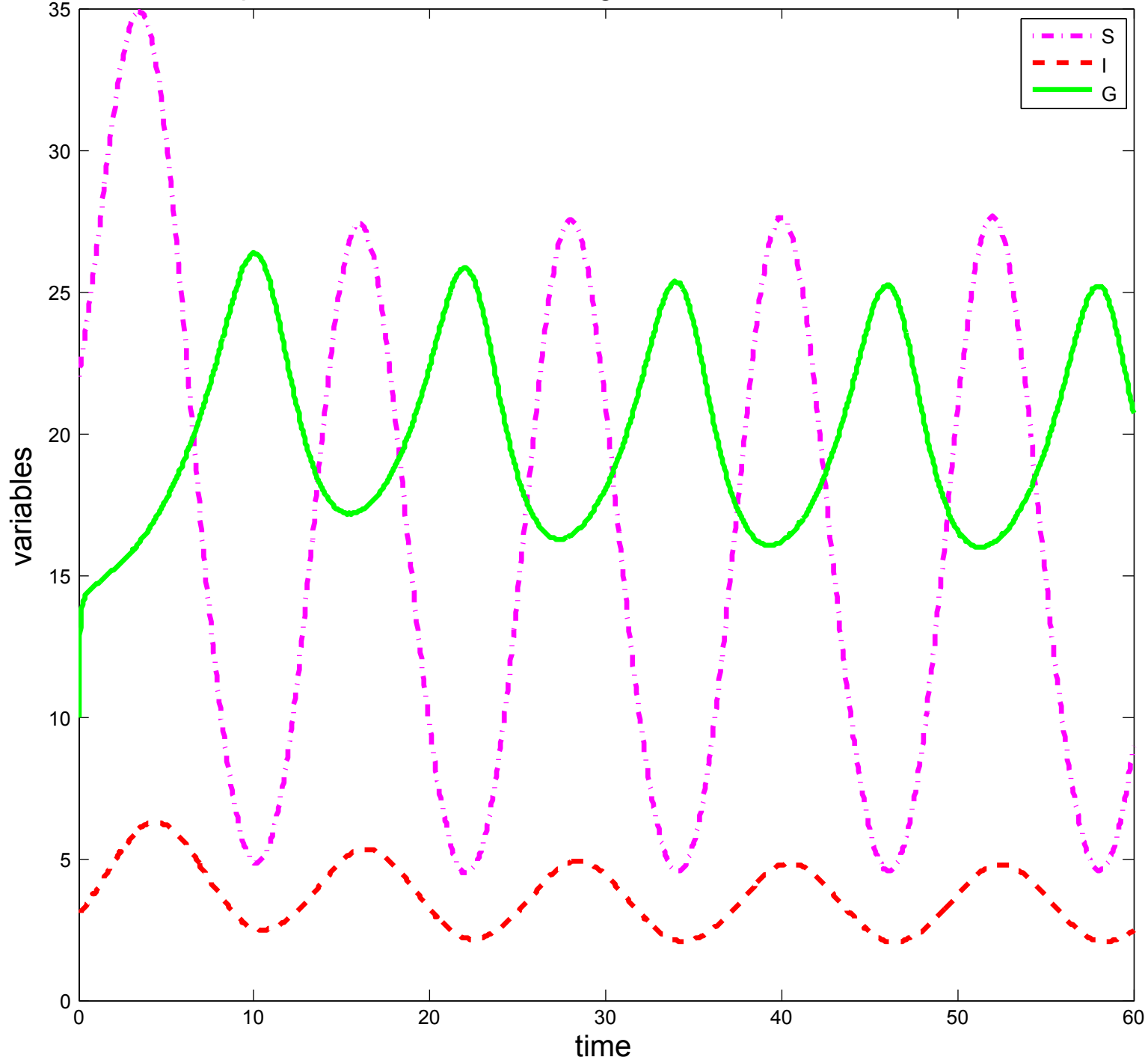


Figure 5B
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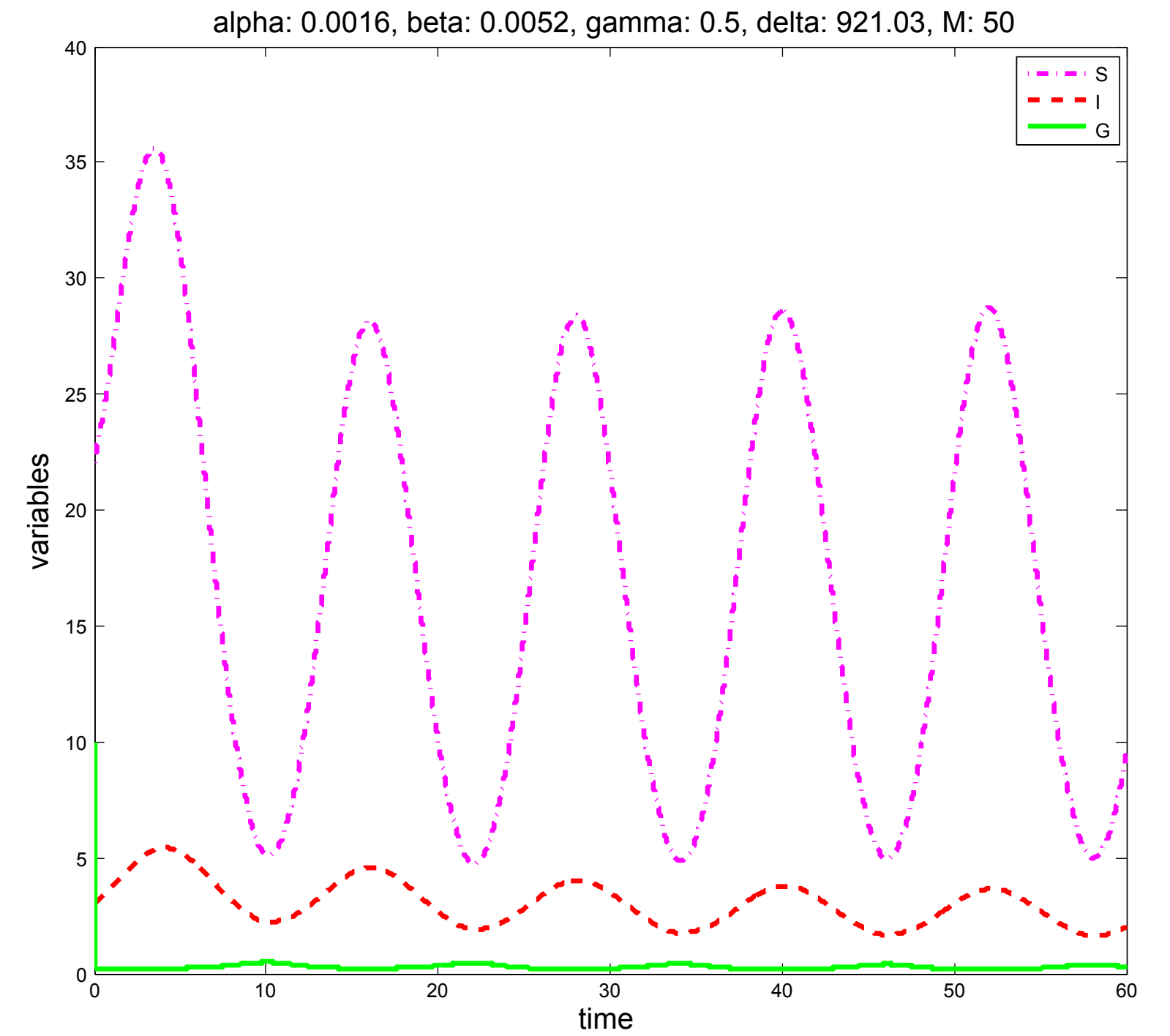


Figure 6A
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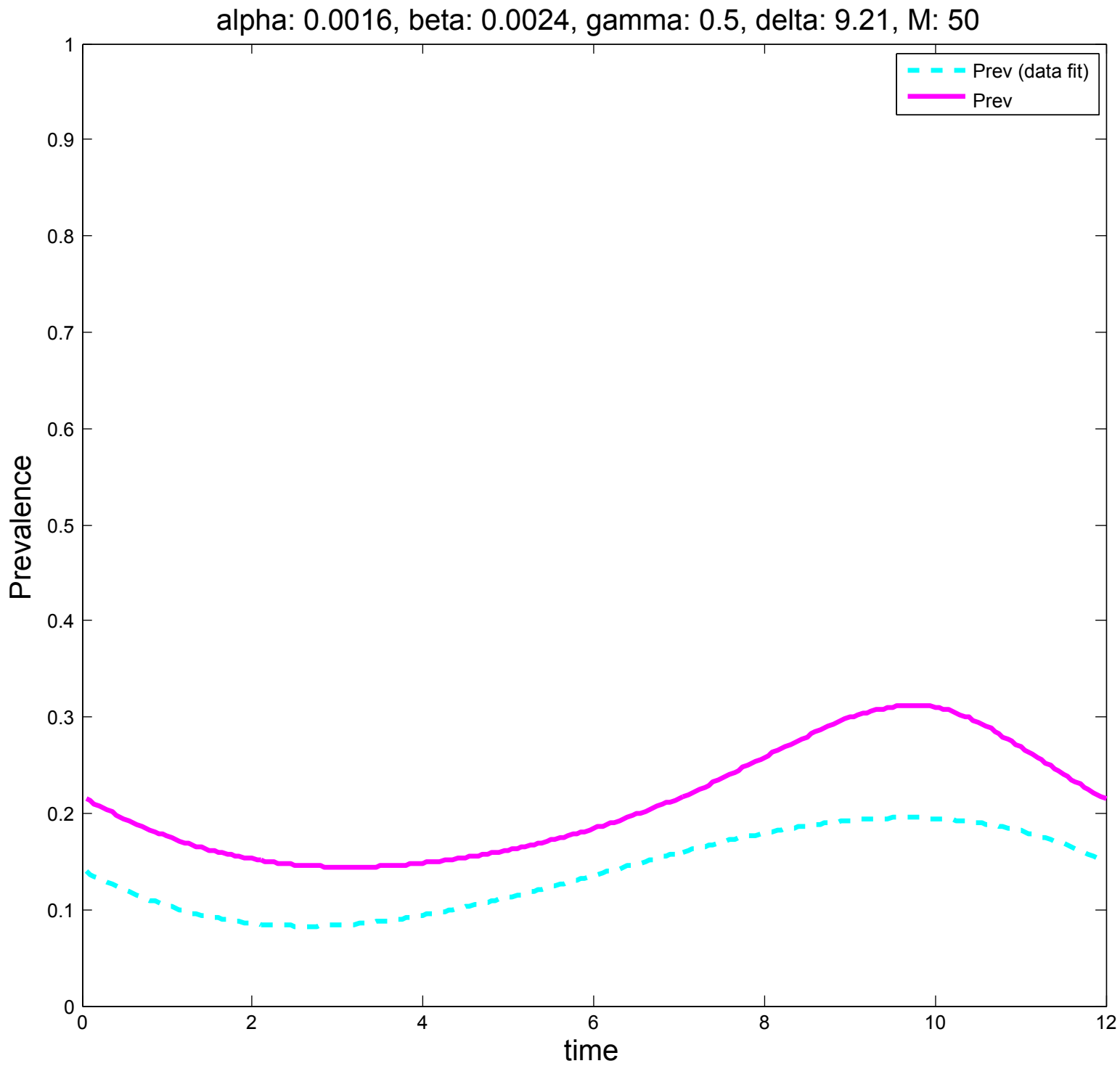


Figure 6B
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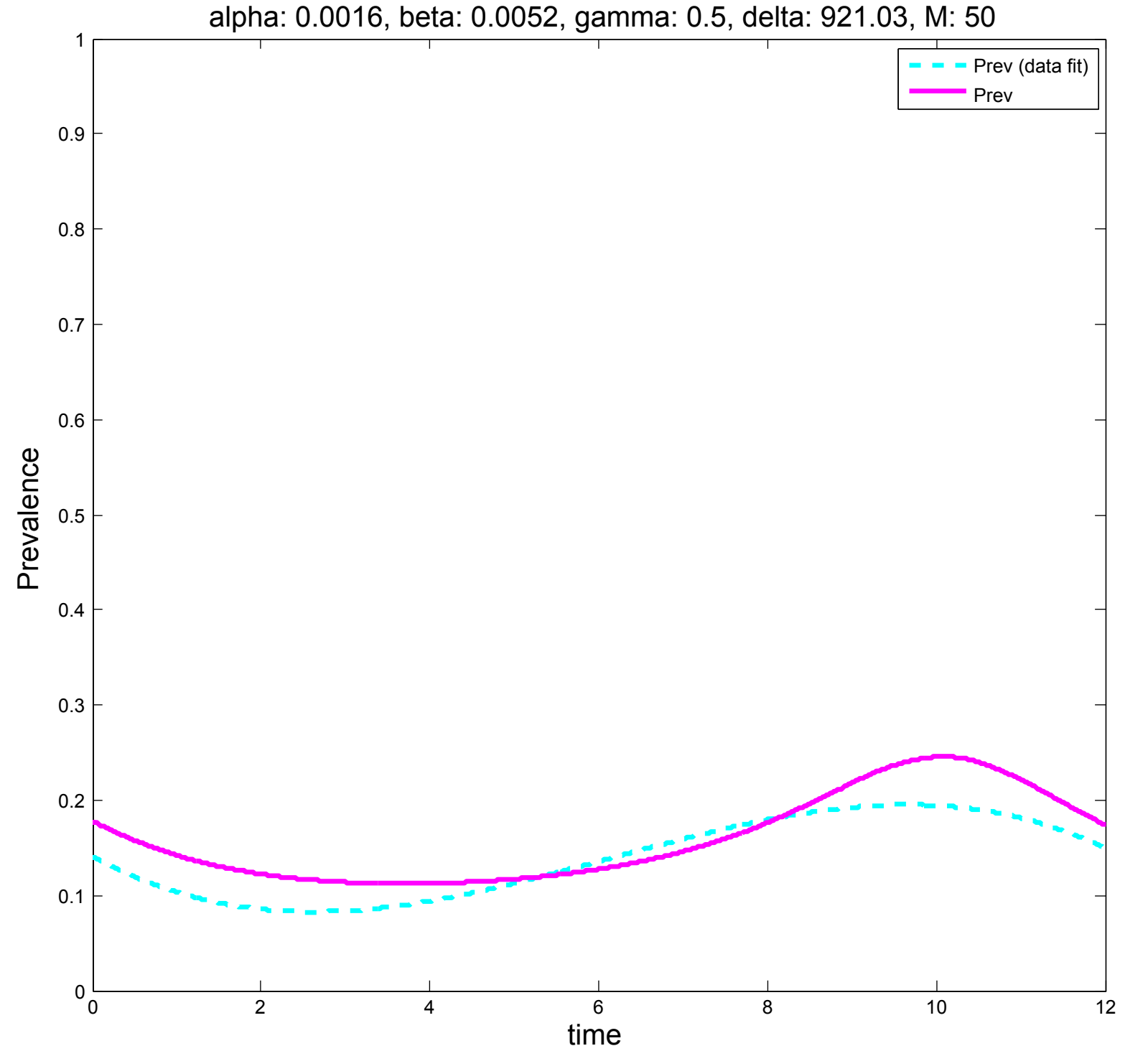
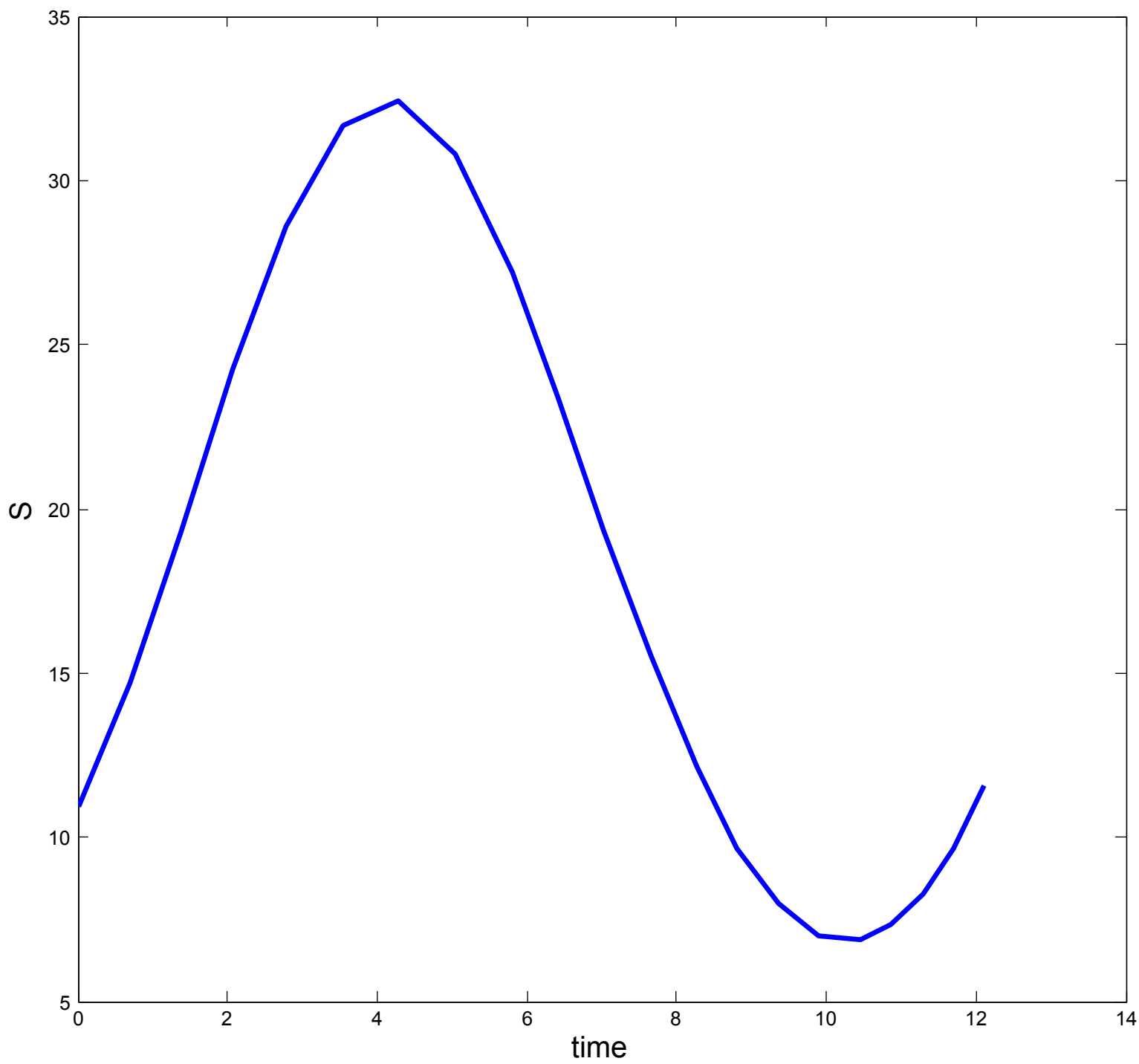


Figure 7
[Click here to download Figure: nonhomo_eq_funct_S.pdf](#)



Hantavirus transmission in sylvan and peridomestic environments

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Abstract

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Key words: Sin Nombre hantavirus, deer mice, compartmental model

1 Introduction

Hantaviruses (family Bunyaviridae, genus Hantavirus) are rodent-borne negative-stranded RNA viruses that may produce chronic infections in their reservoir hosts (species in the family Muridae). In humans, hantaviruses are responsible for hemorrhagic fever with renal syndrome (HFRS) throughout Asia and Europe and hantavirus pulmonary syndrome (HPS) in the Americas [9]. Prior to 1993, only two hantavirus species, Prospect Hill and Seoul viruses, had been described in North America [28, 16] with no significant human diseases associated with either virus in the United States. In 1993, an outbreak of a respiratory illness of unknown etiology in the Four Corners region of the southwestern United States led to the isolation and identification of Sin Nombre virus (SNV) and to the description of Hantavirus Pulmonary Syndrome (HPS) [31]. The fatality/case ratio of HPS is approximately 35% [15]. At least three other etiologic agents of HPS are now known for North America including Bayou virus, New York virus and Black Creek Canal virus, but

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SNV is believed to be responsible for the majority of HPS cases. The primary reservoir of SNV is the deer mouse, *Peromyscus maniculatus* [10]. Epidemiological studies indicate that hantaviruses including SNV are transmitted to humans through inhalation of aerosols generated from urine, feces, and/or saliva shed by infected rodents [36, 14]. Most human cases of HPS are likely acquired in peridomestic settings including human dwellings, out-buildings, corrals and ranch yards [6] through the inhalation of aerosolized saliva and/or excreta of infected rodents [30]. However, deer mice populations occur in both sylvan (natural) and peridomestic settings [26, 25].

There is evidence for different forms of virus transmission. One of them is the direct transmission route. Infected mice are more likely to have scars compared to uninfected mice [1, 8]. This may be evidence of increased fighting between males for dominance and the transmission of the virus during fighting. It may be the cause of higher seroprevalence in males compared to females. However, recent experimental evidence from a study of Andes Hantavirus [32] suggests that, at least in one South American species (*Oligoryzomys longicaudatus*), the primary mode of transmission appears to be direct mucus membrane contact with saliva or respiratory droplets rather than biting. In addition to the above form of transmission, the infected mice shed the virus in their saliva, urine and feces, contaminating the ground. Apart from this being the main transmission route for human infection, susceptible mice could also be indirectly infected [23]. Peridomestic settings in Montana contain numerous out-buildings (barns, storage sheds, grain bins, etc.), which are notoriously dusty. Because these buildings prevent exposure to direct solar ultraviolet (UV) light, which can kill many types of viruses [35], SNV may persist on dust particles in buildings longer than on particles exposed to sunlight. While direct measurements of SNV persistence in sylvan and peridomestic environments are not available, persistence will depend on environmental conditions. Taking into account smaller home ranges and greater densities of peridomestic population [12] as well as the sheltering effect of the buildings, the virus may survive up to about 2 weeks in indoor environments and much shorter periods (perhaps hours) when exposed to sunlight outdoors [34, 18].

In this paper we develop a compartmental deterministic model of hantavirus transmission in deer mice. Our principal goal is to compare the importance of direct and indirect transmission pathways in peridomestic and sylvan environments. In previous modeling work, various aspects of hantavirus contamination of a rodent population have been explored. Abramson *et.al.* [2, 3] modeled SNV epidemics in deer mice. Their model consisted of coupled reaction-diffusion equations and they studied spatial aspects of the epidemics in one-dimensional environments. The population was divided into susceptible and infected classes and growth was driven by the carrying capacity of the environment. The model of Kenkre *et.al.* [19] examined the idea that the spread of SNV was mainly caused by highly mobile juvenile mice, while adult mice were largely confined to their home ranges.

Sauvage *et. al.* [33] applied their model to Puumala virus contamination in bank voles (*Clethrionomys glareolus*). The population was subdivided into susceptible and infected individuals and stratified further to juveniles and adults. Population dynamics were driven by a periodic birth function and a 3-year periodic carrying capacity. Their goal was to assess the role of indirect transmission in virus persistence in a fluctuating population in changing habitats. A further refinement of their model [39] included multiple environmental patches. A general theoretical extension of these models was studied by C. Wolf [38]. He showed the existence and uniqueness of solutions for a structured population model where the population was stratified by birth, chronological age and age since contamination.

Allen *et. al.* [5] studied the dynamics of infection by two viruses, hantavirus and arenavirus, in cotton rats (*Sigmodontine hispidus*). They found that when the transmission of one virus occurred by vertical transmission (transmission occurred during the prenatal period or at birth) and the other by horizontal transmission (transmission not occurring during pregnancy and birth), the two viruses could coexist in the same population. Allen *et. al.* [4] also developed a SEIR (Susceptible-Exposed-Infected-Recovered) model with the population divided into males and females. The ordinary differential equation version of the model captured higher seroprevalence in males, while the stochastic version of the model captured variability in seroprevalence levels.

In this paper, we examine the role of direct and indirect transmission of SNV infection in deer mice, similar to Sauvage *et. al.* [33]. However, since SNV transmission to humans occur almost exclusively in peridomestic situations, where most control methods are likely to be applied, we explore this question in the context of peridomestic and sylvan environments. Because of the widely varying time scales of virus persistence in the two environments, we hypothesize that the relative strength of direct and indirect transmission routes

are different in the two environments. To test this hypothesis, we estimated the decay time of the virus in both sylvan (mostly natural settings like open grassland) and peridomestic environments and developed a compartmental epidemiological model for hantavirus infection of deer mice. Population parameters were estimated from field data collected at a study site located near Anaconda, Montana, which provides over four and a half years of data. A detailed description of the study site and trapping methodology can be found in Kuenzi *et.al.* [27]. We used both an autonomous model, where the birth and death rate are (estimated) constants, and a more realistic time periodic model where these rates are periodic functions of time (with a period of one year). The autonomous model has the advantage that the basic reproduction number, R_0 , which indicates whether the virus will be endemic or eradicated from the mice population, can be computed analytically.

Using the autonomous model, values of direct and indirect transmission rates were estimated by matching the output of the model to the average prevalence of the data. We used these constant transmission rates in the periodic model and compared the resulting periodic prevalence to the data-derived periodic prevalence. Although R_0 cannot be computed analytically in the periodic model, we computed the value of R_0 numerically.

The principal qualitative conclusion from both models is that the indirect transmission route is secondary to the direct transmission route in the sylvan environment, but it is clearly important in peridomestic situations. While both models agree in this qualitative conclusion, the quantitative conclusions differ between the two models. While there is a very good match between the output of the autonomous and periodic models in the sylvan environment for both R_0 and the prevalence, we found that in the peridomestic environment, R_0 and the average prevalence were higher in the output of the periodic model than observed in the data.

In both environments we computed the values of the transmission rates which would yield $R_0 < 1$ and hence the eradication of the virus in the population. For the choice of parameters that replicate the data derived prevalence, the autonomous model predicted that in the sylvan environment lowering the direct transmission rate to 40% of the original value would lead to the eradication of the virus, while the prediction from the periodic model was significantly higher (79%). In the peridomestic situation the autonomous model predicted that lowering the indirect transmission rate to 30% would lead to virus eradication, while the corresponding number was 39% for the periodic model.

Our results can be used to evaluate various intervention strategies designed to either lower the prevalence or to completely eradicate hantavirus from deer mice populations. Trapping to remove populations from outbuildings may reduce direct transmission of the virus but not eradicate it. On the other hand, frequent disinfection methods may be more effective in achieving eradication of the virus.

2 Model development

We consider a compartmental model with three compartments: a susceptible population of mice $S(t)$, an infected population of mice $I(t)$, and the number of contaminated sites in the environment $G(t)$. Since there is evidence that mice become infected during adulthood [29], we identify S as the susceptible adult population and I as the infected adult population. To model the environment we assume that there is a discrete number of sites (burrows in the sylvan population and corners and walls for the peridomestic populations) that are visited by mice. Each site is small enough to be infected by a single mouse. We assume that the collection of sites under consideration is statistically representative of all sites. This representation of the environment can also facilitate future fitting of the experimental data, since in many experiments mice are caught and examined at discrete sites. As is the case with discrete populations of infected and susceptible mice, 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, $N := S + I$. The time will be in units of months. We denote by c the number of direct contacts between mice that can lead to transmission of the infection per susceptible mouse per month. These contacts may involve biting and scratching and are thought to occur predominantly between sexually active males [1, 8]. We call these *active contacts*. The number of active contacts per month is then cS . Given a contact between two mice, one of which is susceptible, the probability that the other mouse is infected is the fraction of the infected mice in the population, I/N . Finally, let β be the probability that given an active contact between susceptible and infected mouse, an infection of the susceptible mouse takes place. We call β a *direct transmission rate*. Combining these numbers, the change

in number of susceptible mice due to direct transmission per month is $-\beta cSI/N$.

For the indirect transmission route we let $\bar{c}$ be the number of contacts between a mouse and all the potentially contaminated sites per susceptible mouse per month. Using similar reasoning as above, we model the change in susceptible mice due to the indirect transmission per month as $-\alpha\bar{c}SG/M$, where G/M is the proportion of contaminated sites and α , an *indirect transmission rate*, is the probability that given a contact between susceptible mouse and contaminated site, an infection of the susceptible mouse takes place.

Finally we model the process of site contamination by infected mice. This is analogous to the model of infection of susceptible mice, where the role of susceptible mice is played by the uncontaminated site. Therefore, in analogy to the above, we let d be the number of contacts between the mice and the site that can lead to transmission of the infection per uncontaminated site per month. Then the number of contacts between uncontaminated site and mice per month is $d(M - G)$ and the proportion of such contacts with the infected mice is $d\frac{I}{N}(M - G)$. The *site contamination rate*, γ , is the probability of site contamination, given a contact between an uncontaminated site and an infected mouse. Therefore the change in the number of contaminated sites per month is $\gamma d\frac{I}{N}(M - G)$.

Our model of the transmission process assumes that c , $\bar{c}$ and d are independent of the population size. This is a reasonable assumption because the population, even at its highest density, is relatively dispersed and the time unit is relatively long. The basic model is as follows.

$$\begin{aligned}\dot{S} &= B - \mu S - \alpha\bar{c}\frac{SG}{M} - \beta c\frac{SI}{N} \\ \dot{I} &= -\mu I + \alpha\bar{c}\frac{SG}{M} + \beta c\frac{SI}{N} \\ \dot{G} &= \gamma d\frac{I}{N}(M - G) - \delta G.\end{aligned}\tag{1}$$

The constant B is a supply rate of the susceptible population. Our data have three age classes of mice: juvenile, subadult and adult. Since S is the susceptible adult population, B is the rate of transfer from the subadult to the adult age class. Subadult mice are very mobile [21, 20] and are likely to move from areas where they were born to new areas. Since the new supply of adult susceptible mice may arise as a promotion of subadults from the local population, or by an influx of subadults from neighboring communities, we model this influx by a constant (or a periodic) rate. If the new susceptibles were strictly the progeny of the local population, then a growth term proportional to the total local population or a logistic growth term would be appropriate. Our model is consistent with other epidemiological models where the susceptibles come from sources other than local population growth. In order to simplify our terminology we will refer to B in the rest of the paper as the *susceptible birth rate* or simply as the *birth rate*.

The constant μ is the death rate, which we assume is the same for the infected and the susceptible class, since hantavirus is not lethal to mice [29]. The mice are infected for the rest of their lives [29, 24] so there is no re-entry into the susceptible population.

The constant δ is the *disinfection rate*, which measures how quickly the sites become uncontaminated after being contaminated. This parameter is different in sylvan and peridomestic situations, since in the former, sunlight disinfects the virus present in urine within hours, while in a sheltered place, like a barn, the virus may be active for a couple of weeks [18].

Notice that the constants α , β and γ , being conditional probabilities, satisfy $0 \leq \alpha, \beta, \gamma \leq 1$. We estimate the parameters B and μ from experimental data.

2.1 Parameter estimation

Parameter estimation was based on the data collected at the Anaconda site in Montana, from May 2002 to December 2006 [27]. There was at least one data collection session every month during this period, although the exact dates of data collection varied slightly by month. The data consist of the Minimum Number Alive (MNA) per session, the Minimal Number of Infected mice (MNI) per session (determined from blood samples extracted from each mouse), the number of adult mice (divided into males and females) per session, and the numbers of juvenile and subadults animals (again divided in males and females) per session. The MNA index was calculated by taking the total number of individual deer mice captured during each 3-day

trapping session and adding to that sum the number that were captured on at least 1 previous and also on 1 subsequent session [22], but not during the month of interest. Even though they were not caught, these mice must have been alive during the month of interest. The minimum number of infected (hantavirus antibody-positive) mice (MNI) was calculated in the same way.

Figure 1 shows the MNA and the MNI for the 54 months that the data were collected, t is in months. For comparison with our simulations, the MNA was taken as the total population of deer mice ($N(t)$) and the MNI as the number of infected mice ($I(t)$) at a given month. In months when there were multiple measurements, we averaged these measurements to get the data point for that month. The number of susceptible mice was determined as $S(t) = MNA(t) - MNI(t)$ and the prevalence of infection was estimated as MNI/MNA for a given month.

2.1.1 Birth rate.

The number of juvenile mice caught in traps is very likely to be an underestimate of the actual juvenile population, because juvenile mice stay in burrows and do not venture out as much as older mice. To estimate the number of mice born in month t we added the number of juvenile mice caught in month t to the number of subadults caught in the month $t + 1$. Since mice become adults in approximately 6-8 week this is a better estimate of the true susceptible influx rate. Furthermore, since a very small number of juvenile mice are caught again a month later as subadults (we do not have any recorded evidence of this), it is unlikely that the summation would count any mice twice. With this data we estimated the constant birth rate as an average over the 54 months of data collection and got $B = 5.85$.

2.1.2 Death rate

To estimate the number of mice $e(t)$ that died in month t we subtract the number of live adult mice MNA(t) in month t from the available supply of adult mice that could be alive in month t . The second number is the sum of the adult and subadult mice in month $t - 1$, that is MNA($t - 1$) + sub($t - 1$). Therefore

$$e(t) := \text{MNA}(t - 1) + \text{sub}(t - 1) - \text{MNA}(t).$$

The death rate in month t was then computed by dividing the number $e(t)$ of dead adult mice in month t by the number of adult live mice in month $t - 1$. If this number is negative we set the death rate to zero

$$\mu(t) = \max\{0, e(t)/\text{MNA}(t - 1)\}.$$

The average value μ of $\mu(t)$ over 54 months was $\mu = 0.246$.

2.1.3 Disinfection rate δ

The constant δ represents the disinfection rate of the contaminated sites. Since exposure to UV light kills the virus [35], these rates will be substantially different for sylvan populations and peridomestic populations. We have estimated that sunlight likely kills all but a negligible amount of the virus in about 4 hours [34]. We use this estimate when modeling sylvan environments. Recent experimental data [18] have shown that even without exposure to direct sunlight, Puumala virus was deactivated in 24 hours at 37°C. In the peridomestic situation the virus is shed in places with no direct sunlight, which usually have lower temperatures. The same study [18] found that virus can remain infectious for two weeks in contaminated beddings of voles. Therefore we use this estimate, two weeks, for our peridomestic settings.

To turn these estimates into an estimate of δ , we observe that δ satisfies $\dot{G} = -\delta G$ and thus is the exponential decay coefficient of the solution $G(t) = G_0 e^{-\delta t}$. We will consider one percent of the initially contaminated sites as “negligible” contamination. Then, the time t_d that it takes for a site to cease to be infectious satisfies the equation $0.01G_0 = G_0 e^{-\delta t_d}$, where G_0 is the initial number of infected sites. Hence

$$\delta = -\ln 0.01/t_d.$$

Because the data is in units of months, we express t_d in months. For peridomestic environment we have $t_d = 0.5$ months, corresponding to two weeks, and for sylvan environment $t_d = 0.005$ months which corresponds to approximately four hours. Using these values and solving for δ , one gets a peridomestic value of $\delta = 9.21$ and a sylvan value of $\delta = 921$.

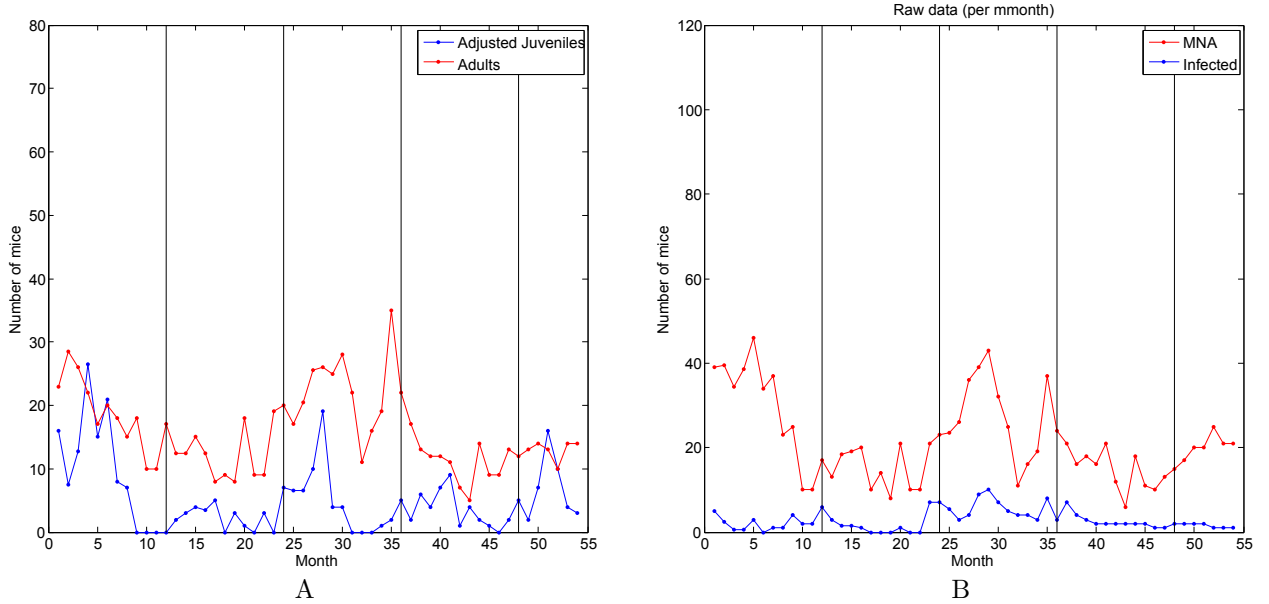


Figure 1: Raw data collected at the Anaconda site in Montana. The upper curve is the Minimum Number Alive (MNA) mice per month during the 54 months that the data was collected. (A) The lower curve is the sum of juveniles in month t and subadults in month $t + 1$; (B) The lower curve is the infected number of mice (I). Vertical lines at every 12 months of data collection.

2.1.4 Site contamination rate γ

We cannot estimate the site contamination rate γ . In order to concentrate on the qualitative comparison between the direct and indirect transmission rates, we will keep γ constant at $\gamma = 0.5$. Since γ represents contamination rate of a site given the contact between an infected mice and an uncontaminated site, the constant γ will be much larger than the rates α and β . We have seen only modest qualitative changes in our results when the parameter γ varied in its range $\gamma \in [0.1, 1]$ (figure not shown). In general larger γ makes the indirect route more important relative to the direct infection route, as expected. This effect is, however, dominated by the effect of δ .

2.1.5 Number of contacts c , $\bar{c}$ and d .

The number of contacts is very difficult to estimate. For simplicity, we will keep these numbers constant at $c = \bar{c} = d = 60$ for our simulations, but in a general form in the analysis in the Appendix. We have found that doubling this common value has no qualitative effect on our results. Since c , $\bar{c}$ and d always multiply one of the parameters α, β, γ , their effect is to effectively shift the values of α, β and γ . We choose to model c , $\bar{c}$ and d separately from α, β and γ because the latter constants have an interpretation of conditional probability and hence have values between zero and one. For further discussion on the effect of c , $\bar{c}$ and d on our results see section 3.5.

2.1.6 Mean prevalence

We can compute the mean prevalence from the data as the mean of the ratio of MNI/MNA over 54 months. This gives a prevalence value of 0.1535 with a standard error of 0.002. The mean prevalence of 15% is in general agreement with the 13% mean prevalence at sylvan sites throughout Montana reported by Douglass *et al.* [13] and the mean prevalence of 16% at sylvan sites reported by Kuenzi *et al.* [26]. Since our data were collected on a trapping grid that is adjacent to both peridomestic habitat and sylvan habitat, we can associate the computed prevalence to both environments. Therefore we will test the model assuming that the 15% represents the prevalence in both sylvan and peridomestic environments, even though there is some

evidence [26] that the prevalence may be higher in the peridomestic setting.

3 Results

The results are divided into four parts. We will first examine the autonomous model where we assume that the population parameters (birth rate and death rate) are constant throughout the year. Although biologically unrealistic, this assumption allows us to completely analyze the model and derive closed form expression for the basic reproductive ratio R_0 as a function of the parameters. If $R_0 > 1$ then the hantavirus infection is endemic, while if $R_0 < 1$ hantavirus disappears from the population. Further, we numerically simulate

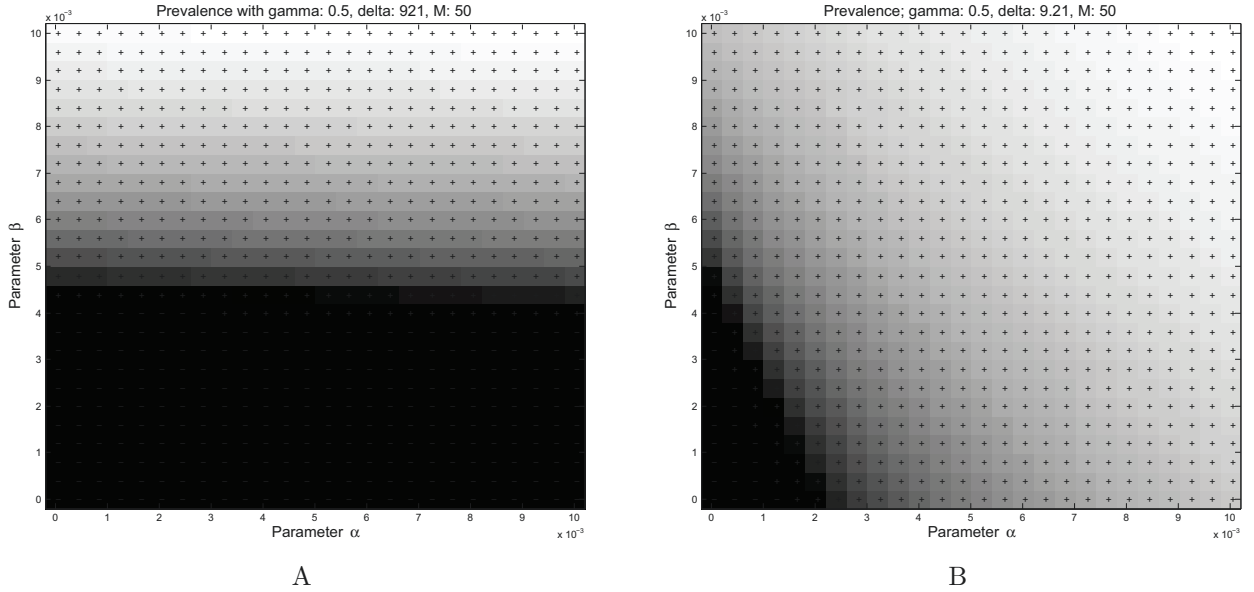


Figure 2: Gray scale-coded values of the prevalence $I^*/(I^* + S^*)$ at the equilibrium of the system (1) for different values of α and β in (A) sylvan ($\delta=921$) and (B) peridomestic ($\delta=9.21$). Dark colors indicate low prevalence and light colors high prevalence. Signs for each combination of α and β indicates the sign of $R_0 - 1$. The 'minus' signs (mostly obscured by dark colors) indicate $R_0 < 1$ and hence a globally stable disease-free equilibrium and 'plus' indicates $R_0 > 1$ and a stable endemic equilibrium.

the autonomous model and find combinations of direct and indirect infection rate values that produce the observed average prevalence of 15%. We find that the prevalence in the model is largely independent of the indirect infection rate in sylvan populations, while it depends on both rates in the peridomestic environment.

With the values of α and β fixed by the autonomous model to match the average prevalence from the data, we fit periodic birth and death rates to the data and computed R_0 for the periodic model in both sylvan and peridomestic case. We found that for the sylvan environment, both autonomous and periodic model produce nearly identical R_0 ($R_0^{aut} = 1.28$ vs. $R_0^{per} = 1.26$) and they are independent on the indirect infection rate α . Furthermore, the prevalence computed by the time-periodic model matches well the data-derived periodic prevalence (Figure 6.B).

In contrast, for the peridomestic environment the value $R_0^{aut} = 1.45$ predicted by the autonomous model differs significantly from that predicted by the periodic model $R_0^{per} = 1.60$. Since we matched the autonomous model to the average prevalence to compute direct and indirect transmission rates and these were used in the periodic model, it is not surprising that the higher R_0^{per} causes the prevalence given by the time-periodic model to be higher than the data-derived periodic prevalence (Figure 6.A).

We show in the Appendix that in the autonomous model $R_0^{aut} > 1$ implies that an endemic equilibrium is globally asymptotically stable and hantavirus infection is endemic in the population, while $R_0^{aut} < 1$ indicates that the population is virus-free. For the periodic model $R_0^{per} > 1$ indicates instability, while $R_0^{per} < 1$ local stability of the virus-free periodic solution. Using R_0^{aut} and R_0^{per} , we can evaluate effectiveness of putative

intervention strategies for virus eradication. If the intervention lowers the indirect transmission rate α , then we can compute the value α^* at which either R_0^{aut} or R_0^{per} is equal to one. An explicit expression for R_0^{aut} (defined below in (2)) allows testing intervention strategies that change multiple parameters at the same time.

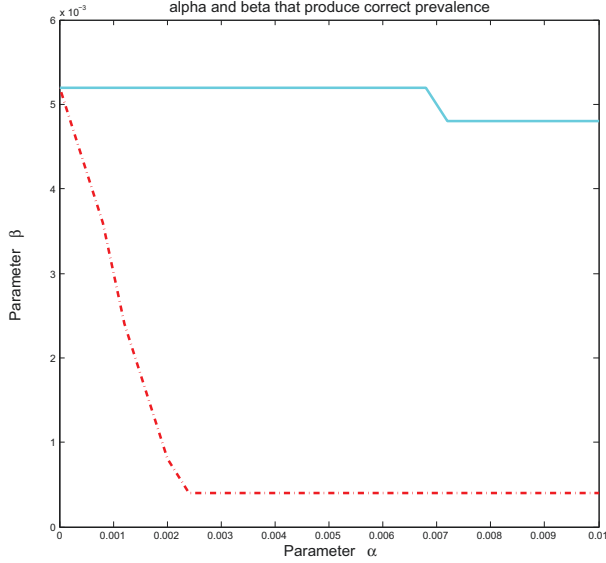


Figure 3: Values of the parameters α and β that match the observed average prevalence of 15% in the population. The axis are the same as in Figure 2. Dashed line represents values of α, β for peridomestic situation ($\delta = 9.21$) and the solid line for sylvan environment $\delta = 921$.

$(B/\mu, 0, 0)$.

To investigate the impact of the direct and indirect transmission rates on prevalence levels, we simulate the system (1) for different values of the parameters α and β in two environmental conditions: sylvan ($\delta = 921$) and peridomestic ($\delta = 9.21$). The parameters $\gamma, c, \bar{c}, d, B$ and μ are fixed at values described in the previous section. We check for convergence to the equilibrium by requiring that the relative error is below 10^{-7} .

In Figure 2 we graph the prevalence $I^*/(S^* + I^*)$ at the equilibrium as a function of the parameters α and β . We take 25 values for both α and β in sylvan (Figure 2.A) and peridomestic (Figure 2.B) environments. The gray scale codes for value of the prevalence where lighter color denote higher prevalence.

We conclude that in the sylvan environment (Figure 2.A) the steady state prevalence is largely independent of the indirect transmission rate α , and depends only on the value of the direct transmission rate β . In other words, the fast disinfection rate outdoors makes the infection level of the population independent of the indirect infection rate. The direct infection rate β largely determines the prevalence in the population. Therefore all measures designed to eradicate hantavirus from sylvan deer mice populations should concentrate on lowering the direct transmission rate β . In peridomestic environment (Figure 2.B) both transmission modes are important.

We can find the values (α, β) at which the prevalence in the model matches the average measured prevalence of 15%. These values form a one-dimensional curve in the α, β parameter space. For each value of δ , we have one such curve. In Figure 3 we present these lines for values of δ that represent sylvan and peridomestic environments.

Comparing the predictions of the autonomous and periodic models we find that in both cases the periodic model suggests easier eradication than the autonomous model. Interestingly, this is true even in the peridomestic situation where the $R_0^{per} > R_0^{aut}$ and the periodic model produces higher prevalence. Therefore the periodic model predicts higher, yet more fragile virus population.

3.1 The autonomous model

We show in the Appendix that for an arbitrary initial condition and arbitrary set of parameters, the corresponding solution of (1) converges to an equilibrium. We show in Proposition 5.1 that the basic reproductive ratio is

$$R_0^{aut} = \frac{\delta\beta c + \sqrt{(\delta\beta c)^2 + 4\delta\mu\alpha\bar{c}\gamma d}}{2\delta\mu}. \quad (2)$$

Further, we show that if $R_0^{aut} > 1$ then all positive solutions converge to an endemic equilibrium $E = (S^*, I^*, G^*)$ with the persistent population of infected mice $I^* > 0$. In this case the prevalence can be computed as $\frac{I^*}{S^* + I^*}$. On the other hand, if $R_0^{aut} < 1$ then all non-negative solutions converge to a disease-free equilibrium F where $(S, I, G) =$

3.2 The time-periodic model

In the previous section we considered all the parameters in the system (1) to be constant and we took averages over all data points to estimate the birth and death rates. It is clear from seasonal changes in mice life cycles, that the birth and death rates are periodic. In this section we look at (1) when the birth rate $B = B(t)$ and the death rate $\mu = \mu(t)$ are periodic functions of time. The model becomes

$$\begin{aligned}\dot{S} &= B(t) - \mu(t)S - \alpha\bar{c}\frac{SG}{M} - \beta c\frac{SI}{N} \\ \dot{I} &= -\mu I + \alpha\bar{c}\frac{SG}{M} + \beta c\frac{SI}{N} \\ \dot{G} &= \gamma d\frac{I}{N}(M - G) - \delta G.\end{aligned}\tag{3}$$

We fit a periodic function to the birth data described in section 2.1.1. We first average the available data for each month of the year. Since we have data for 4 and 1/2 years (54 data points), there are 5 data points for May through October time period and 4 data points for the other months. We used two different ways to fit the data. First, we used the least square best fit to find the best 3-rd degree polynomial. Second, we fitted a periodic function to the data by performing a discrete Fourier transform of the data. After finding the three coefficients with largest modulus and setting other coefficients to zero, we computed the inverse FFT to get the periodic estimate of the birth rate. These two approaches yielded very similar results, see Figure 4.A. The resulting birth function $B(t)$ is periodic with a 12-month period.

The same approach was used to fit the periodic death rate. Comparison between third order polynomial fit and periodic fit are shown in Figure 4.B. The prevalence (MNI/MNA) also varies in time, see Figure 1. As with the birth and death rates, we fitted a 3-rd order polynomial to the prevalence on a period of 12 consecutive months. The results are shown in Figure 4.C. We simulated the system (3) with the

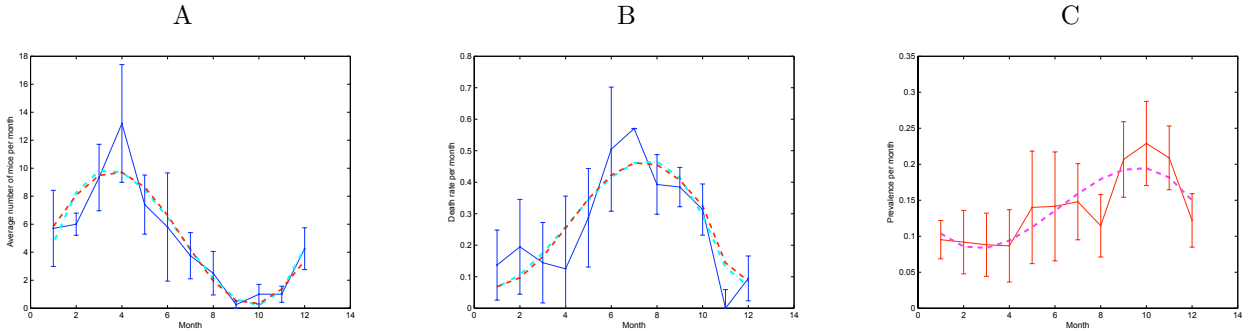


Figure 4: Solid lines represent (A) Average number of newborn mice per month; (B) Average number of dead mice per month; and (C) mean prevalence over a period of 12 consecutive months. Error bars represent the standard error and in all cases dash-dot line is the least square fit by the third order polynomial. In (A) and (B) the dashed curve is the result of Fourier 3-term truncation.

time-periodic birth rate and death rate described in Figure 4. We used the Fourier fit for the birth rate and the polynomial fit for the death rate, but the results are very similar for other combinations of these two choices. We used $\gamma = 0.5$, $M = 50$ and initial conditions $S = 22, I = 3, G = 10$. For each value $\delta = 9.21$ and $\delta = 921$, we used the values of α and β that were determined from the prevalence fit of the autonomous equation. Since for each δ there is a set of (α, β) that produce the same average prevalence 15% (see Figure 3), we chose one set for each δ : for $\delta = 9.21$ we set $(\alpha, \beta) = (0.0016, 0.0024)$ and for $\delta = 921$ we set $(\alpha, \beta) = (0.0016, 0.0052)$. Recent experiments [32] attempted to measure direct infection rate β in *Oligoryzomys longicaudatus* who carry the Andes hantavirus. Susceptible mice were put in close proximity to infected mice for 24 hours and then tested for virus. The results suggested that the infection rate was between 12 – 17%. If $\beta = 0.0052$ and we assume 60 active contacts per month, which is 2 contacts per 24 hour, our model predicts an infection rate of about 1% per 24 hour period. This implies that, under the assumption that mice confined in close proximity have 10-20 times more active contacts than free mice, the

estimate for β lies in $[0.0025, 0.0050]$. We tested multiple choices from this interval for both environments and found no qualitative differences in our results.

The solutions of the two systems averaged over a 5 year period are shown in Figure 5. As expected, when δ is small (Figure 5.A), the amount of contaminated soil (solid curve) becomes more significant.

3.3 Comparison of autonomous and periodic models

The prevalence resulting from our simulations should resemble the prevalence observed in the data. We compared the periodic prevalence computed as an average over 5 years from the simulation shown in Figure 5 to the periodic prevalence from the data, see Figure 4.C. The results are shown in Figure 6. Notice that the prevalence from the periodic model for peridomestic environment is well above the prevalence from the data, while the model for sylvan environment matches data very well. We note that the parameters α and

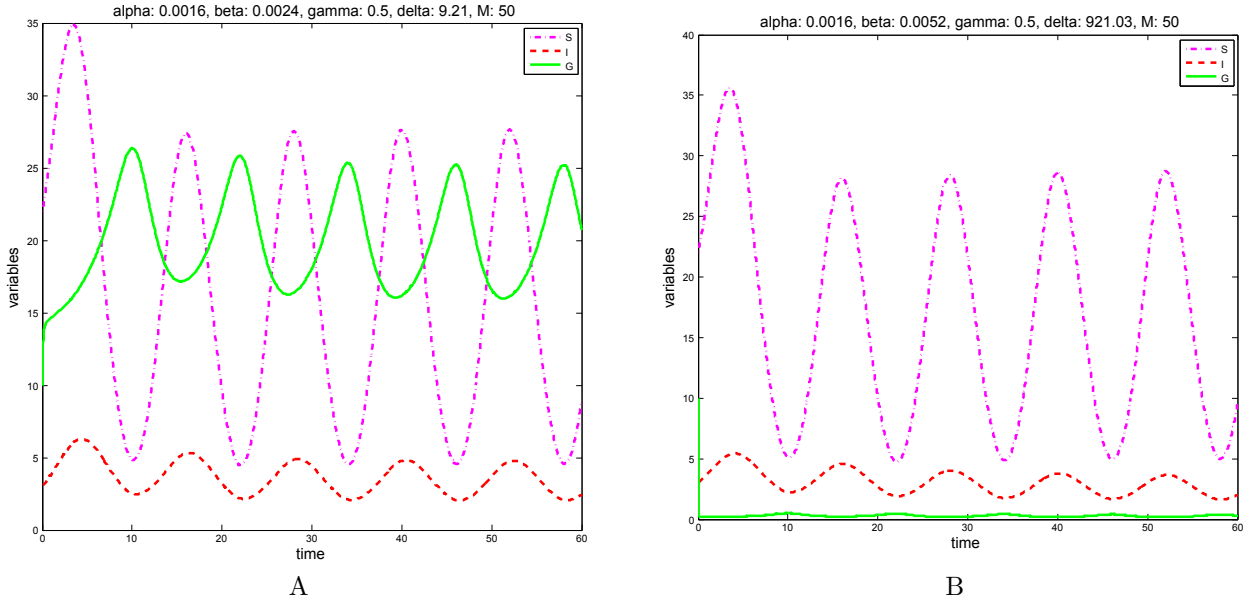


Figure 5: Solutions of the system (3) for $\gamma = 0.5$ and (A) $\delta = 9.21$, $\alpha = 0.0016$, $\beta = 0.0024$ (peridomestic environment); (B) $\delta = 921$, $\alpha = 0.0016$, $\beta = 0.0052$ (sylvan environment) averaged over a time period of 5 years. All parameters lie on the respective curves in Figure 3. The dash-dotted line indicates the number of the susceptible mice, the dashed line the number of infected mice and the solid line the number of infected places in the environment.

β were selected by matching the autonomous system prevalence to the average data prevalence, and the periodic birth and death rate average to the constant birth and death rate used in the autonomous system. To address the source of the discrepancy in the prevalence between the autonomous and periodic models, we computed the basic reproduction number R_0 for both cases.

3.3.1 Peridomestic environment

For the peridomestic environment, we set $\gamma = 0.5$, $c = \bar{c} = d = 60$, $\mu = 0.246$, $\delta = 9.21$, which were used to produce Figure 2.B and then selected $\alpha = 0.0016$ and $\beta = 0.0024$ which produced the prevalence of 15% (see Figure 3) in the autonomous model. Then from (2) we computed the value $R_0^{aut} = 1.45$. There is no closed form expression analogous to (2) for R_0^{per} in the periodic model. We computed R_0^{per} for the periodic model by a method introduced by Bacaer [7] that uses Floquet theory. We obtained $R_0^{per} = 1.60$ (the details of the computation can be found in the Appendix). This higher basic reproduction number is reflected in the higher average prevalence of 21% in the periodic case (see Figure 6.A) compared to 15% in the autonomous case. Therefore in the peridomestic setting seasonal periodicity leads to higher R_0 and higher prevalence. This result should be contrasted with the result of Bacaer [7] for vector-borne diseases which shows that if

the seasonal change is sinusoidal and small, then the first correction term to the autonomous R_0^{aut} due to a periodic forcing is negative and so $R_0^{per} < R_0^{aut}$. Our periodic forcing function $S(t)$, depicted in Figure 7, is not a small perturbation of the identity.

3.3.2 Sylvan environment

For the sylvan environment, we set $\gamma = 0.5, c = \bar{c} = 60, \mu = 0.246, \delta = 921$ that were used to produce Figure 2.A and then selected $\alpha = 0.0016$ and $\beta = 0.0052$ which produced a prevalence of 15% (see Figure 3) in the autonomous model. Then from (2) we computed the value $R_0^{aut} = 1.28$.

R_0^{per} is defined as a spectral radius of a next generator integral operator $\mathcal{K}$. Since one of the off-diagonal elements of this operator is proportional to the indirect transmission rate α , and since α does not affect the epidemic in the sylvan environment, the operator $\mathcal{K}$ is dominated by its diagonal terms. This has two consequences. On one hand the Floquet theory method of computation of R_0^{per} does not work; on the other we can approximate the next generation operator $\mathcal{K}$ by its diagonal terms and compute R_0^{per} directly from this approximation. This yields $R_0^{per} = 1.26$ (the details of the computation are in the Appendix). We observe that in the sylvan environment $R_0^{aut} \approx R_0^{per}$ and the periodic prevalence matches the prevalence in the data, see Figure 6.B.

3.4 Eradication of the infection

The basic reproduction number R_0 gives us the ability to predict change in transmission parameters α and β that would lead to eradication of SNV infection in deer mice. Recall that to eradicate SNV we have to make $R_0 < 1$. We analyzed how R_0 changed as a function of α and β for both autonomous and periodic models. Since we have a closed form expression for R_0^{aut} in the autonomous model (2), we can make a few analytical observations:

1. If we lower the direct transmission rate β to its lowest possible value of 0 then $R_0^{aut} = \sqrt{\frac{\alpha \bar{c} \gamma d}{\delta \mu}}$. Therefore the eradication by lowering β is only possible if

$$\delta \mu \geq \bar{c} d \alpha \gamma. \quad (4)$$

The left side expresses a decay of infection either by direct disinfection of the ground (δ) or by a removal of the infected mice (μ). The right hand side represents the infection rate in the indirect pathway and includes both the number of contacts between infected mice and uncontaminated sites d and the number of contacts between contaminated sites and susceptible mice $\bar{c}$. We conclude that the strong indirect pathway may prevent eradication of the virus in the population by attempts to lower the direct transmission rate β .

2. When we set $\alpha = 0$ in (2) we recover the standard expression $R_0^{aut} = \frac{\beta \bar{c}}{\mu}$. Thus the eradication by lowering α is only possible if the death rate dominates the direct transmission rate

$$\beta \bar{c} \leq \mu. \quad (5)$$

3. R_0^{aut} does not depend on the birth rate B , or the maximal number of contaminated sites M .

We apply these observations to our models with parameters described in sections 3.3.1 and 3.3.2 .

3.4.1 Peridomestic environment

We set the parameters as in section 3.3.1 which produced $R_0^{aut} = 1.45$. We note that the condition (4) reads $2.27 \geq 2.88$ while the condition (5) reads $0.144 \leq 0.246$. Therefore the disease can be eradicated by lowering α (moving left in Figure 2.B), but not by lowering β (moving down in Figure 2.B). We computed the critical value of α at which the virus is eradicated by setting $R_0^{aut} = 1$ in (2) and solving for $\alpha^{aut} = 0.0005219$. To eradicate hantavirus under these conditions, the indirect infection rate has to drop from $\alpha = 0.0016$ to $\alpha = 0.0005$, that is to 30% of the original value.

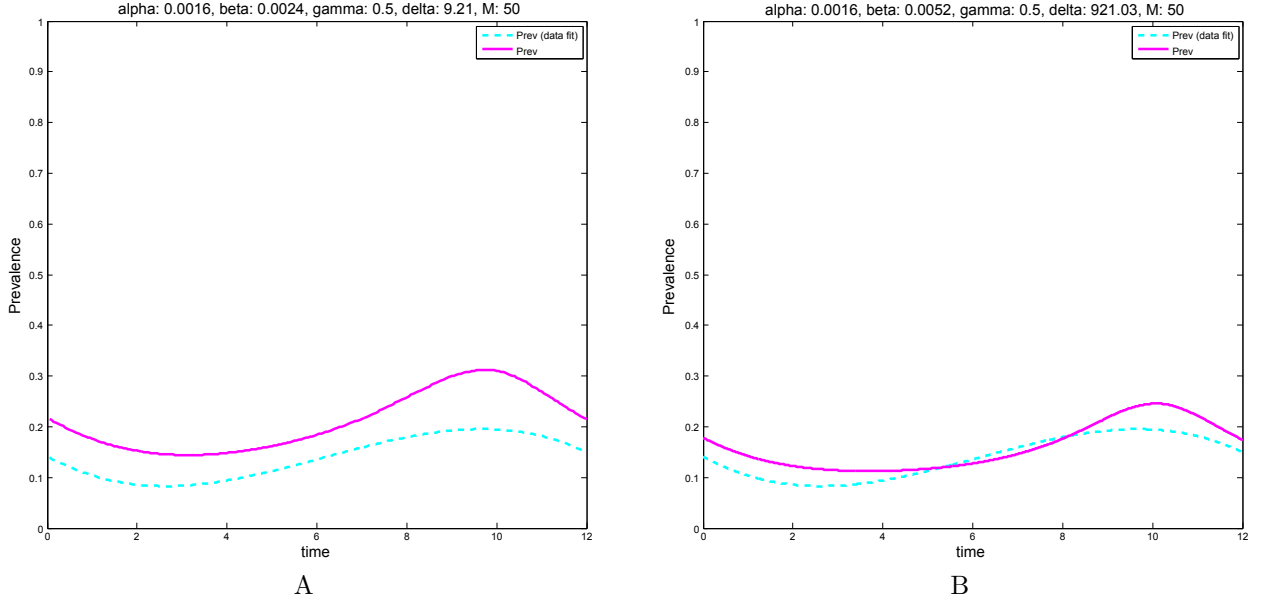


Figure 6: Model prevalence (dashed line) over the last cycle for the simulations shown in Figure 5 compared to fitted prevalence (solid line) shown in Figure 3.

Recall that $R_0^{per} = 1.60$. Using the Floquet method (see Appendix) we computed numerically the critical value α^{per} at which $R_0^{per} = 1$. This value is $\alpha^{per} = 0.00063$, which is 39% of the original value and it is higher than α^{aut} . This leads to an interesting observation. In spite of higher levels of virus predicted by the periodic model, this model also predicts higher sensitivity to change in the rate of indirect transmission and easier eradication. However, since we have not proved that in the periodic model the disease-free solution is globally stable if, and only if $R_0^{per} < 1$, it is possible that the endemic solution persists even for $R_0^{per} < 1$.

3.4.2 Sylvan population

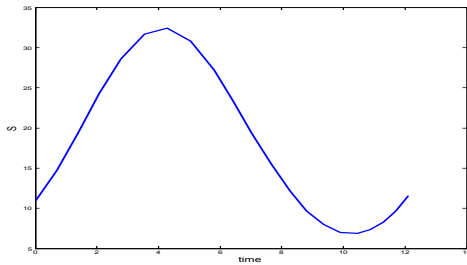


Figure 7: Function $S(t)$ is not a small perturbation of the unity.

We set the parameters as in section 3.3.1 that produced $R_0^{aut} = 1.28$. With these parameters, the condition (4) reads $226.6 \geq 2.88$ and the condition (5) reads $0.246 \geq 55.260$. Therefore we can eradicate SNV by lowering β , but not by lowering α . To find the critical β we solved (2) with $R_0^{aut} = 1$ for $\beta^{aut} = 0.0021$. Therefore, according to the autonomous model, to eradicate hantavirus in sylvan population the direct transmission rate has to drop from $\beta = 0.0052$ to 0.0021 , that is to about 40% of the original value.

Recall that $R_0^{per} = 1.26$. We computed the critical value β^{per} at which $R_0^{per} = 1$ and find $\beta^{per} = 0.0041$, which is about 79% of the original value (see Appendix). Note that as in the peridomestic case, the critical value of the parameter in the

periodic model is higher than in the autonomous model, $\beta^{per} > \beta^{aut}$.

Therefore in both peridomestic and sylvan cases, the periodic model predicts that the virus population is more fragile when compared to the prediction of the autonomous model.

3.5 Effect of the other parameters

So far we have concentrated on the effect of direct and indirect transmission rate on the virus prevalence (Figure 2). We briefly discuss the effect of the other parameters. Since c multiplies β , $\bar{c}$ multiplies α and d multiplies γ the change in value of $c = \bar{c} = d$ does not change the qualitative character of Figure 2. The

larger this common value, the smaller the area in (α, β) space which admits infection free equilibrium. If we keep c fixed and lower $\bar{c} = d$ then Figure 2.B may start to resemble Figure 2.A, but only after the value of $\bar{c} = d$ drops to single digits. Finally, γ has a limited effect on Figure 2 when kept in the range $\gamma \in [0.1, 1]$. If γ is allowed to become smaller than α and β , then Figure 2.B will start to resemble Figure 2.A. However, the site contamination rate should be higher than either the direct or the indirect infection rate.

4 Conclusions

We have developed a compartmental model for hantavirus infection in deer mice with the goal of comparing the relative importance of direct and indirect transmission in sylvan and peridomestic environments. Based on population dynamics data and estimates of Sin Nombre virus persistence in sylvan and peridomestic environments, our autonomous model predicts that direct transmission dominates in the sylvan environment, while both pathways are important in the peridomestic environment. This conclusion has been confirmed by the time-periodic model where we used data-fitted time-periodic birth and death rates.

We computed the basic reproduction number R_0 in both environments and in both types of models. While we found a very good fit between the autonomous and periodic models in sylvan environment in both R_0 and the prevalence, we found that in the peridomestic environment both the R_0 and the average prevalence are higher in the periodic model.

We analyzed R_0 in both models and environments to compute the critical values of the transmission rates which would lead to virus eradication. For one choice of parameters, that replicate the data derived prevalence, our results predicted that completely abolishing indirect transmission would not eradicate virus in the sylvan population. On the other hand, the analysis of the autonomous model shows that lowering the direct transmission to 40% of the original value would lead to eradication of the virus. The corresponding prediction from the periodic model is qualitatively the same but quantitatively different: abolishing the indirect rate would not eradicate the virus, while lowering the direct transmission rate to 79% of the original value would lead to eradication of the virus.

In the peridomestic situation abolishing direct transmission would not lead to eradication, but lowering the indirect transmission rate would. The predictions again vary between the autonomous and periodic models: lowering the indirect transmission rate to 30% (autonomous) or 39% (periodic) would lead to virus eradication.

These results can perhaps be used to guide eradication strategies in peridomestic environments. Trapping to remove the population from outbuildings may reduce direct transmission of the virus but not eradicate it. On the other hand, frequent disinfection methods may be more effective to achieve eradication. We hasten to add, that since the choice of parameters that reproduce the observed prevalence is not unique, these results are only qualitative. Furthermore, while the predictions from the autonomous and periodic models are qualitatively the same, the qualitative predictions differ considerably, with the periodic model suggesting that the virus population is more fragile and can be eradicated more easily.

Our work provides a basic framework for the analysis of hantavirus transmission in a deer mice populations. We hope that as further data collection fills in the values of missing parameters, we will be able to make our model even more quantitative by including seasonal and spatial variation.

5 Appendix

5.1 The equilibria and local stability for the autonomous model

We first observe that by adding the first and second equations in (1) we get

$$\frac{d}{dt}(S + I) = B - \mu(S + I) \quad (6)$$

which implies that $S + I$ converges exponentially to the value $\frac{B}{\mu}$. Therefore any equilibrium (S^*, I^*, G^*) of the system lies on the plane given $S^* + I^* = N = \frac{B}{\mu}$. The disease-free equilibrium $F := (x, y, z) = (N, 0, 0)$ always exists, independently of the value of the parameters. In many epidemiological models the local asymptotic stability of the disease free equilibrium F depends on a threshold parameter R_0 known as a basic

reproduction number. Diekmann *et.al.* [11] defined R_0 as a spectral radius of the next generation matrix and this calculation has been made explicit for a large class of epidemiological models by van den Driessche and Watmough [37].

Proposition 5.1 (Existence and local stability of equilibria) *The basic reproduction number for (1) is*

$$R_0^{aut} = \frac{\delta\beta c + \sqrt{(\delta\beta c)^2 + 4\delta\mu\alpha\bar{c}\gamma d}}{2\delta\mu}.$$

The disease-free equilibrium F is asymptotically stable if, and only if, $R_0^{aut} < 1$. Furthermore, if $R_0^{aut} > 1$, then there exists unique endemic equilibrium $E := (S^*, I^*, G^*)$ with $0 < S^* < N$, $0 < I^* < N$, and $0 < G^* < M$.

Proof. The first part is standard and follows from a general argument in [37]. Indeed, in our model there are two infected compartments I and G and the function $\mathcal{F}$ characterizing the appearance of new infections in these two compartments is $\mathcal{F} = (\alpha\bar{c}\frac{SG}{M} + \beta c\frac{SI}{S+I}, \gamma d\frac{I}{S+I}(M-G))$. The rate of transfer out of these compartments is $\mathcal{V} = (\mu, \delta)$. Then R_0 is the spectral radius of FV^{-1} where $F := [\frac{\partial \mathcal{F}}{\partial I, \partial G}]$ and $V := [\frac{\partial \mathcal{V}}{\partial I, \partial G}]$ are 2×2 restrictions of the Jacobians of $\mathcal{F}$ and $\mathcal{V}$ to variables I and G , evaluated at the disease free equilibrium. A straightforward calculation gives

$$FV^{-1} = \begin{bmatrix} \beta c \frac{1}{\mu} & \alpha\bar{c} \frac{S}{M\delta} \\ \gamma d \frac{M}{S\mu} & 0 \end{bmatrix}$$

and its characteristic equation $\lambda^2\delta\mu - \beta c\delta\lambda - \alpha\bar{c}\gamma d = 0$ from which the value of R_0^{aut} follows.

To prove the second part we compute other equilibria. We first solve for I from the last equation in

$$\begin{aligned} 0 &= B - \mu S - \alpha\bar{c}\frac{SG}{M} - \beta c\frac{SI}{N} \\ 0 &= -\mu I + \alpha\bar{c}\frac{SG}{M} + \beta c\frac{SI}{N} \\ 0 &= \gamma d\frac{I}{N}(M-G) - \delta G \end{aligned} \tag{7}$$

and plug it to the first equation (where we use $B - \mu S = \mu I$) to get

$$0 = G\frac{c}{d} \left(\frac{\mu\delta N}{\gamma c(M-G)} - \frac{\alpha d\bar{c}}{cM} S - S\frac{\beta\delta}{\gamma(M-G)} \right)$$

from which

$$S = \frac{\frac{\mu\delta N}{c\gamma}}{\frac{\beta\delta}{\gamma} + \alpha\frac{\bar{c}d}{cM}(M-G)}. \tag{8}$$

Using $S + I = N$ we compute a quadratic function whose roots determine values of G at equilibria

$$h(G) = \alpha\frac{\bar{c}}{cM}(\gamma d + \delta)G^2 - \left(\frac{\delta^2\beta}{\gamma d} + \frac{\alpha\delta\bar{c}}{c} - \frac{\mu\delta}{c} + \beta\delta + 2\frac{\alpha\bar{c}d\gamma}{c}\right)G + M(\beta\delta + \alpha d\gamma\frac{\bar{c}}{c} - \frac{\mu\delta}{c}) = 0.$$

Observe that the leading coefficient of the quadratic polynomial $h(G)$ is positive and that $h(M) = -\frac{\delta^2\beta}{\gamma d} < 0$. Thus $h(G)$ has one zero at some $G > M$.

Note that $h(0) = \frac{M}{c}(\beta\delta c + \alpha d\gamma\bar{c} - \mu\delta)$ and a short computation shows that $h(0) < 0$ if, and only if, $R_0 < 1$. If $h(0) < 0$, then $h(G)$ cannot have a zero in $(0, M)$, and so F is the only equilibrium of (1). If $h(0) > 0$ (and hence $R_0 > 1$) then $h(G)$ has a unique zero G^* in $(0, M)$. To finish, we need to prove that corresponding values S^* and I^* at the equilibrium lie in $(0, N)$. By (8) and the last equation in (7) if $G^* \in (0, M)$ then $S^* > 0$ and $I^* > 0$. Since $S^* + I^* = N$, the result follows. $\square$

Proposition 5.2 (Stability of the endemic equilibrium) *If the endemic equilibrium E exists, then it is always locally asymptotically stable.*

Proof. By (6), the linearization at both equilibria E and F have one negative eigenvalue $-\mu$ which represents a convergence to the carrying capacity $\frac{B}{\mu}$ for the total population $S+I$. The other two eigenvalues govern local dynamics within the invariant plane $S+I = \frac{B}{\mu}$. To find out the signs of these eigenvalues we consider linearization of the last two equations in (1), where we replace S by $\frac{B}{\mu} - I$ to reflect the constraint $S+I = \frac{B}{\mu}$

$$\dot{I} = -\mu I + \alpha \bar{c} \frac{(\frac{B}{\mu} - I)G}{M} + \beta c \frac{(\frac{B}{\mu} - I)I}{N}, \quad \dot{G} = \gamma d \frac{I}{N} (M - G) - \delta G.$$

We rescale the variables $y = \frac{Ic}{N}$ and $z = \frac{G\bar{c}}{M}$ and get

$$\begin{aligned} \dot{y} &= -\mu y + \alpha(c-y)z + \beta y(c-y) \\ \dot{z} &= \gamma \frac{d}{c} y(\bar{c} - z) - \delta z. \end{aligned} \tag{9}$$

We linearize to get

$$Df(y, z) = \begin{bmatrix} -\mu - \alpha z + \beta(c-2y) & \alpha(c-y) \\ \gamma \frac{d}{c}(\bar{c} - z) & -\gamma \frac{d}{c} y - \delta \end{bmatrix}. \tag{10}$$

We evaluate the linearization (10) at the endemic equilibrium $E = (x^*, y^*, z^*)$ and show that $Df(E)$ has a negative trace and a positive determinant. The trace of $Df(E)$ is

$$\text{Tr}(Df(E)) = -\mu - \alpha z^* + \beta(c-2y^*) - \gamma \frac{d}{c} y^* - \delta.$$

Since E is an equilibrium of (1), then it is also an equilibrium of (9) and so $-\mu y^* + \alpha(c-y^*)z^* + \beta y^*(c-y^*) = 0$. This is equivalent to

$$-\mu + \beta(c-y^*) = -\alpha \frac{(c-y^*)z^*}{y^*}. \tag{11}$$

Since $0 < y^*, z^* < c$ plugging this into the expression for the trace, we get

$$\text{Tr}(Df(E)) = -\alpha \frac{(c-y^*)z^*}{y^*} - \beta y^* - \alpha z^* - \gamma \frac{d}{c} y^* - \delta < 0.$$

Now we compute the determinant of (10) at the endemic equilibrium

$$\begin{aligned} \det(Df(E)) &= (-\mu - \alpha z^* + \beta(c-2y^*))(-\gamma \frac{d}{c} y^* - \delta) - \alpha \gamma \frac{d}{c} (\bar{c} - z^*)(c-y^*) \\ &= \left(-\alpha \frac{(c-y^*)z^*}{y^*} - \alpha z^* - \beta y^* \right) (-\gamma \frac{d}{c} y^* - \delta) - \alpha \gamma \frac{d}{c} (\bar{c} - z^*)(c-y^*) \end{aligned}$$

where we used (11). Since from the second equation in (9) we have $y^* = \frac{\delta c}{\gamma d} \frac{z^*}{\bar{c} - z^*}$, we get $\gamma \frac{d}{c} (\bar{c} - z^*) = \frac{\delta z^*}{y^*}$. Using this in the last expression above we get

$$\begin{aligned} \det(Df(E)) &= \left(\alpha \frac{(c-y^*)z^*}{y^*} + \alpha z^* + \beta y^* \right) (\gamma \frac{d}{c} y^* + \delta) - \alpha \frac{\delta z^*}{y^*} (c-y^*) \\ &= (\alpha z^* + \beta y^*) (\gamma \frac{d}{c} y^* + \delta) + \alpha \frac{(c-y^*)z^*}{y^*} (\gamma \frac{d}{c} y^* + \delta) - \alpha \frac{(c-y^*)z^*}{y^*} \delta \\ &= (\alpha z^* + \beta y^*) (\gamma \frac{d}{c} y^* + \delta) + \alpha \gamma \frac{d}{c} (c-y^*) z^* > 0. \end{aligned}$$

□

5.2 Global convergence to the equilibria

Proposition 5.3 *If $R_0^{aut} < 1$ all solutions starting in the non-negative orthant of $\mathbf{R}^3$ converge to the disease-free equilibrium F , and if $R_0^{aut} > 1$ then almost all solutions starting in the non-negative orthant converge to the endemic equilibrium E .*

Proof. All solutions in the non-negative orthant approach exponentially the plane $S + I = N$. Therefore the invariant set lies in the intersection of this plane and the non-negative orthant, which we denote Σ . The rescaled equations describing dynamics on Σ are (9).

When $R_0^{aut} < 1$ then by Proposition 5.1 Σ contains unique equilibrium F on its boundary. Since every closed orbit in the plane has to contain an equilibrium in its interior, there are no periodic orbits in Σ . A local stability of F rules out existence of homoclinic orbits. Therefore by the Poincaré-Bendixson theorem all solutions in Σ converge to F .

When $R_0^{aut} > 1$, by Proposition 5.1 Σ contains two equilibria: F on its boundary and an internal equilibrium E . The equilibrium E is stable by Proposition 5.2. The divergence of the vector field (9) is

$$-\delta - (\mu - c\beta) - 2\beta y - \gamma \frac{d}{c} y.$$

A short calculation shows that $R_0^{aut} > 1$ implies $c\beta - 2\mu > 0$, which in turn shows that the second term above is negative. Since the entire expression is negative, we conclude by Dulac's Criterion [17] that there are no periodic orbits in Σ . A local stability of E (Proposition 5.2) rules out the existence of orbits homoclinic to E and by the Poincaré-Bendixson theorem all solutions in Σ , except those on the stable manifold of F , converge to E . $\square$

5.3 R_0 for the periodic model

The basic reproduction number for the periodic model is a spectral radius of a linear integral operator [11, 7]

$$(\mathcal{K}v)(t) = \int_0^\infty K(t, x)v(t-x)dx \quad (12)$$

where the matrix $K(t, x)$ describes the expected number of newly infected individuals. More specifically, given n infected compartments $I_1, I_2, \dots, I_n$, the (i, j) entry $K_{i,j}(t, x)$ represents the expected number of individuals in compartment I_i that one individual in compartment I_j generates at the beginning of the epidemic per unit time at time t if it has been in the compartment I_j for x units of time. The basic reproduction number determines if the epidemics can invade a disease-free population. In the periodic case this corresponds to a T -periodic solution $F(t) := (S(t), 0, 0)$ where $S(t)$ is the steady state periodic solution of $\dot{S} = B(t) - \mu(t)S$ and $B(t)$ and $\mu(t)$ are the T -periodic birth and death functions. There are two infected compartments I and G and linearizing about $F(t)$ (taking into account that $N(t) = S(t) + I(t)$ we get a linear system

$$\begin{aligned} \dot{I} &= (-\mu(t) + c\beta)I + \frac{\bar{c}\alpha}{M}S(t)G \\ \dot{G} &= \gamma dM \frac{1}{S(t)}I - \delta G. \end{aligned} \quad (13)$$

Solving the first equation we get

$$I(t) = \int_0^\infty \frac{\bar{c}\alpha}{M} S(t-x_1) \exp\left(-\int_{t-x_1}^t (\mu(u) - c\beta)du\right) G(t-x_1) dx_1 \quad (14)$$

and therefore $K_{1,2} = \frac{\bar{c}\alpha}{M} S(t-x_1) \exp(-\int_{t-x_1}^t (\mu(u) - c\beta)du)$. Similarly we solve the second equation

$$G(t) = \int_0^\infty \gamma dM \frac{1}{S(t-x_2)} \exp(-\delta x_2) I(t-x_2) dx_2 \quad (15)$$

and arrive at $K_{2,1} = \gamma dM \frac{1}{S(t-x_2)} \exp(-\delta x_2)$. Then the kernel of the next generation operator (12) is

$$K(t, x) := \begin{bmatrix} 0 & K_{1,2} \\ K_{2,1} & 0 \end{bmatrix}$$

which is T -periodic for every fixed value of $x = x_1 = x_2$ with $x \geq 0$. The eigenvalue problem

$$\int_0^\infty K(t, x)(I(t-x), G(t-x))^T dx = R_0(I(t), G(t))^T \quad (16)$$

on the space T -periodic functions with values in $\mathbf{R}^2$ determines the basic reproduction constant R_0 . Bacaer [7] proposed several ways to compute R_0 . Since both $K_{1,2}$ and $K_{2,1}$ are time dependent, only one of these methods is applicable to our problem. We compute R_0 using Floquet theory for the parameters corresponding to the peridomestic case.

We first note that we can turn the 2×2 integral eigenvalue problem (16) to a scalar problem by substituting for $G(t)$ in (14) from (15) to get

$$(R_0^{per})^2 I(t) = \int_0^\infty \int_0^\infty \bar{c} \alpha \gamma d \frac{S(t-x_1)}{S(t-x_1-x_2)} \exp\left(-\int_{t-x_1}^t (\mu(u) - c\beta) du\right) \exp(-\delta x_2) I(t-x_1-x_2) dx_1 dx_2. \quad (17)$$

By Floquet theory, the equilibrium solution $(I, G) = (0, 0)$ loses stability when the largest characteristic multiplier λ_0 of the periodic system (13) is equal to 1. We introduce a parameter ξ and solve a linear variational equation $\frac{dX}{dt} = AX$ for $X(T, \xi)$ with $X(0)$ an identity matrix and

$$A = \begin{bmatrix} -\mu(t) + c\beta & \frac{\bar{c} \alpha S(t)}{M \xi} \\ \gamma d M \frac{1}{S(t)} & \frac{\delta}{\xi} \end{bmatrix}.$$

By changing the parameter ξ we find a critical value ξ^* such that $X(T, \xi^*)$ has spectral radius $\lambda_0(\xi^*) = 1$. We note that if (I^*, G^*) is the corresponding eigenvector, then I^* is an initial condition of a T -periodic solution $I(t)$ which is an eigenvector of the integral equation

$$I(t) = \int_0^\infty \int_0^\infty \frac{\bar{c} \alpha \gamma d}{\xi^*} \frac{S(t-x_1)}{S(t-x_1-x_2)} \exp\left(-\int_{t-x_1}^t (\mu(u) - c\beta) du\right) \exp(-\delta x_2) I(t-x_1-x_2) dx_1 dx_2. \quad (18)$$

Direct comparison with (17) shows $(R_0^{per})^2 = \xi^*$. By combining a bisection method with the numerical integration of $\frac{dX}{dt} = AX$ we computed in the peridomestic case $\xi^* = 2.55$ and

$$R_0^{per} = \sqrt{\xi^*} = 1.60.$$

We also note that the equation (18) shows that if we replace the value of α by the value α/ξ^* then $R_0^{per} = 1$. Therefore $\alpha^{per} = 0.0016/2.55 = 0.000627$.

Unfortunately, we cannot use this approach for the computation of R_0^{per} in the sylvan case. Since $\delta = 921$ the diagonal terms in A dominate the off-diagonal terms and there is no $\xi > 0$ that would produce $\lambda_0 = 1$. In fact, $\xi = 1$ yields $\lambda_0 = 1.79$ while dropping both off-diagonal terms (this corresponds to $\xi = \infty$) yields $\lambda_0 = 1.74$. Because of the dominance of the diagonal entries in (13) we approximate (13) by a diagonal system

$$\dot{I} = (-\mu(t) + c\beta)I, \quad \dot{G} = -\delta G.$$

Then the matrix operator K is diagonal and the disease-free solution $(I, G) = (0, 0)$ is unstable if, and only if, the integral over one period

$$\int_0^T (-\mu(t) + c\beta) dt > 0.$$

This condition is equivalent to $R_0^{per} > 1$ where $R_0^{per} := \frac{c\beta}{\bar{\mu}}$ and $\bar{\mu} := \frac{\int_0^T \mu(t) dt}{T}$ is the average death rate. In our case $\mu = \bar{\mu} = 0.246$ and $R_0^{per} = 1.26$. Using this formula for R_0^{per} we compute the critical value of β^{per} in the sylvan case $\beta^{per} = 0.0041$.

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COMMENTS ON REVISED PAPER

T. GEDEON

I would like to thank again the anonymous referees for careful reading of the paper and their thoughtful comments.

In response to both reviewers we went carefully over the paper and corrected many grammatical errors, including all those pointed out by the first reviewer.

We have decided not to remove the text at the beginning of section 3 (Results), because we feel it provides an overview of all the results without technical language and details. Later in section 3 these results are elaborated on and all the details and numbers are provided. However, if the editor and reviewer feel strongly about this issue, we are open to change this part of the paper.

Reviewer #2 raised a very interesting question about the effect of synchrony of S and I on basic reproduction number R_0 . We have tested numerically synchronization in peridomestic situation with periodic birth and death rates. We start with values $\beta = 0.0024$ and $\alpha = 0.0016$ that are discussed in the paper. Then we decreased the value of α to 0.001, 0.0007 and 0.0005 while keeping β fixed. We have also kept α fixed and changed β to 0.015, 0.01 and 0.005. The values of S and I stayed synchronized for all these combinations of parameters. On the other hand, when we increased α to 0.008, I was leading S by about $\pi/4$ and when we increased β to 0.006 I was leading S again by less than $\pi/4$. Since S and I did not change their mutual synchrony as we lowered both α and β , the synchronization (or the lack of thereof) does not seem to explain greater fragility of periodically forced peridomestic population at higher R_0 .

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