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VIRUS TRANSMISSION IN GYPSY MOTHS IS NOT A SIMPLE MASS ACTION PROCESS[1]

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Abstract. We used the nuclear polyhedrosis virus (LdNPV) of the gypsy moth, *Lymantria dispar* (Lepidoptera: Lymantriidae), to test one of the basic assumptions of most models of disease dynamics, that the rate of horizontal transmission is directly proportional to the product of the densities of healthy larvae and virus. To do this we made measurements of virus transmission, using small-scale experiments in bags on red oak (*Quercus rubra*) foliage and field data on naturally occurring populations from a previous study. We observed a decline in the transmission constant as the densities of both healthy larvae and pathogen increased, indicating that the rate of disease transmission is not directly proportional to the product of these variables.

Key words: gypsy moth; horizontal transmission; mass action; nuclear polyhedrosis virus; transmission coefficients.

INTRODUCTION

Mathematical disease models are widely seen as useful tools in the understanding of disease dynamics in animal populations (Holt 1994). The usefulness of such models, however, is limited by a lack of experimental tests of important assumptions. Of particular importance is the so-called "mass-action" assumption, the assumption that transmission is strictly proportional to the product of the densities of healthy and infected larvae. Mathematically, this assumption can be written as

$$\frac{dI}{dt} \propto SP. \tag{1}$$

Here dI/dt is the rate of increase in the infected population, S is the density of susceptible individuals, I is the density of infected individuals, and P is the density of the pathogen. Since the rate of transmission is linear with respect to both the densities of healthy individuals and the density of the pathogen, the functional form of Eq. 1 is known as "bilinearity." Eq. 1 is appropriate to the insect diseases that we study; more conventional disease models, such as human disease models, substitute I for P in the right-hand side of Eq. 1.

This equation originally comes from the work of Kermack and McKendrick (1927), who in turn based their models on the mass action equations of chemical reactions. In such models, the rate of reaction between two chemical species is proportional to the product of their respective concentrations.

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The functional form of transmission embodied by Eq. 1 is critical to our understanding of disease dynamics, and is common to the vast majority of mathematical disease models (Anderson and May 1978, 1979, Levin and Pimentel 1981, Brown 1984, Murray et al. 1986, Andreasen 1989, Hochberg and Holt 1990). Moreover, there is increasing evidence that modifying this assumption greatly changes disease dynamics. For example, Liu et al. (1986) and Hochberg (1991) independently showed that adding exponents to the densities S and I in conventional disease models, so that

$$\frac{dI}{dt} \propto S^a I^b, \tag{2}$$

can lead to more complicated dynamics than those generated by the corresponding bilinear version of the same models. Anderson and May (1992) catalog more mechanistic alternatives to Eq. 1, showing, for example, that age structure and genetic heterogeneity can lead to changes in the frequency and intensity of disease epizootics in human populations.

In spite of the demonstrated importance of Eq. 1, experimental tests of the assumption that it represents are rare (but see Dwyer 1991). Part of the reason for this rarity is that experimentally tractable animal host–pathogen systems are uncommon. Here we use the nuclear polyhedrosis virus (NPV) of the gypsy moth, *Lymantria dispar,* to test Eq. 1. NPVs are directly transmitted, fatal pathogens of insects, and make ideal field experimental systems (Dwyer 1992). Diseases in particular have been implicated as the mechanism driving the dynamics of various forest insects (Anderson and May 1981); the evidence, however, is heavily depen-

dent upon mathematical models that in turn depend upon the largely untested assumption of Eq. 1 (C. J. Briggs et al., *unpublished manuscript*). A parallel may be drawn between the mass-action assumption in disease models, and the assumption of random search by parasitoids in early host–parasitoid models (Thompson 1930, Nicholson and Baily 1935). These host–parasitoid models were later modified to include the effects of changes in parasitoid searching efficiency (Hassell and Varley 1969, Hassell 1978), variation in host susceptibility (Hassell and Anderson 1984), mutual interference (Hassell 1978), and nonrandom search effects (Hassell and May 1973, 1974, May 1978). Similarly, changes in larval behavior at high densities, variation in the susceptibility of gypsy moth larvae to virus, and nonrandom larval feeding patterns may act to violate the mass-action assumption. By explicitly testing Eq. 1, we hope to shed light upon the usefulness of mathematical models for understanding disease dynamics, not just in insects but in animal hosts in general, including humans.

Part of our motivation for questioning the validity of Eq. 1 is based upon earlier efforts in our laboratory to predict the timing and intensity of gypsy moth epizootics within a season (Dwyer and Elkinton 1993). Dwyer and Elkinton used a simple mathematical model based closely upon Anderson and May's (1981) insect host–pathogen model, in conjunction with estimates of transmission from a small-scale experiment. Given the number of factors that have been shown to influence transmission (reviewed in Dwyer 1991), the model was surprisingly successful, in that its predictions for epizootic intensity in high density populations were very close to field data from natural populations in 4–9 ha plots. The model was thus able to extrapolate from small to large spatial scales. In intermediate density populations, however, the intensity of epizootics in the model was far less than the intensity in natural populations. It was possible to increase the virus transmission rate in the model so that it fit sufficiently at all densities, except that the best fitting transmission rate varied among densities. Similar efforts to fit the other model parameters, such as the time between infection and death or the virus decay rate μ, did not lead to an improvement in the fit of the model to the data, suggesting that the missing factor in the model has something to do with the transmission rate. This variability in the fit of the model with respect to density suggests that the model neglects some important aspect of NPV transmission. In other words, it appears that Eq. 1 may be inaccurate.

As Dwyer and Elkinton have shown, however, small-scale field experiments can be extrapolated to large-scale dynamics. Here we are attempting to extend their approach by more thoroughly exploring the effects of density on NPV transmission at a small scale, to see if such effects can explain the failure of the model at larger scales.

Materials and Methods

In order to explore the effects of host and pathogen density upon pathogen transmission rates, we performed a series of small-scale transmission experiments. The basis of these experiments is the creation of short-term, small-scale virus epizootics on red oak (*Quercus rubra* L.) foliage. The time scale is short enough that only one round of transmission occurs, and the spatial scale is small enough to allow easy manipulation of the larvae. To perform these experiments, we place healthy and LdNPV-infected gypsy moth larvae on red oak branches on naturally growing trees. To mimic the most important round of LdNPV transmission in nature (Woods and Elkinton 1987), the infected larvae are infected shortly after they hatch, while the uninfected larvae are reared to the beginning of the third instar before being placed on the foliage. To keep the larvae from wandering away from the experimental leaves, we surround the leaves with bags made of spunbonded polyester (Reemay). The Reemay bags admit much of the natural spectrum of light, and allow passage of air and water while containing the larvae.

We performed the experiments in the vicinity of Amherst, Massachusetts, USA. At a test site near the Lawrence Swamp Conservation area we used three red oaks from 20 May to 29 May 1990 and eight red oaks from 16 June to 24 June 1992. Five red oaks were used from 30 May to 10 June 1991 at a site in Cadwell Memorial Forest. The trees that we used in this study were young, healthy, and ranged from 5 to 8 m in height.

On each tree we created four density treatments by varying the number of larvae and the number of leaves in each bag. Two of the four bags on each tree contained 40 leaves and two bags contained 10 leaves. One bag of each leaf density contained 20 infected first instars, and one contained 5 infected first instars. These larvae were infected at hatching with a dose of the gypsy moth nuclear polyhedrosis virus (LdNPV) high enough to cause death to all neonate larvae after 4 d at 28°C in the laboratory, followed by $\approx$5 d outdoors (Murray et al. 1991). These initially infected larvae served as a source of virus to infect the initially healthy larvae. The densities of virus that we used correspond to virus densities during virus epizootics (Campbell 1981). We chose these densities for logistical reasons; the level of mortality produced had to be sufficient to allow us to see analyzable results with a reasonable number of replicates. All of the larvae that we used in this study were hatched from egg masses supplied by the USDA Otis Methods Development Laboratory.

When all the infected neonates in the bags were dead, 25 healthy third instars were added to each bag. These test insects represented the susceptible population within the bag. As a check for the presence of any extraneous virus, the control bag on each tree contained $\approx$40 leaves and 25 healthy test larvae, but no infected insects. To minimize the possible effects of differences

between trees, for example in foliage chemistry, each tree was a complete replicate containing a bag for each treatment and a control bag. Instead of cutting leaves off branches, we chose branches with 7–13 or 37–43 leaves. In this way we hoped to avoid possible induced changes in foliage chemistry due to pruning (Rossiter et al. 1988).

After 1 wk in the field, all of the bagged branches were removed from the trees. Test insects were removed and reared individually for 2 wk in the laboratory, in cups containing artificial diet (Bell et al. 1981). Larvae were examined for mortality weekly, and each dead insect was autopsied under the light microscope at 400× to verify virus as the cause of death (Woods and Elkinton 1987).

For statistical analyses, we used the arcsine square root transform (Sokal and Rohlf 1981) on the proportion of insects dying in each treatment, and tested differences between the treatments with the PROC GLM procedure (SAS 1985) using a repeated-measures design. The repeated-measures design is typically used to account for correlation between measurements on a single individual over time. Here we used it to account for correlation between simultaneous measurements within the same experimental unit (tree), that is, correlation in response between treatments on each tree.

These statistical procedures were useful in demonstrating that there was an effect of host and pathogen density on observed mortality, but unlike Eq. 1 they do not specify whether or not the effect of density is linear. To test the bilinearity assumption of Eq. 1, and thus the Anderson and May model, we used our data to calculate the per host and per pathogen transmission rate. The model (Dwyer and Elkinton 1993) that we used for this is

$$\frac{dS}{dt} = -\nu PS \tag{3}$$

$$\frac{dI}{dt} = \nu PS - \nu P(t-\tau)S(t-\tau) \tag{4}$$

$$\frac{dP}{dt} = \Lambda\nu P(t-\tau)S(t-\tau) - \mu P, \tag{5}$$

where S is the density of susceptible hosts, I is the density of infected hosts, P is the density of the pathogen in the environment, ν is the transmission constant, τ is the time between infection and death of the host, Λ is the number of pathogen particles produced by an infected larva, μ is the decay rate of the pathogen, and t is time. The model is intended to represent the basics of the interaction between insects and their associated pathogens. Dwyer and Elkinton (1993) used literature values for τ, Λ, and μ, and used the same kind of small-scale experiments that we describe here to estimate the transmission parameter ν.

We followed Dwyer and Elkinton's methodology in calculating the transmission parameter ν in Eqs. 3–5. Since the transmission experiments last for only 7 d, and the time between infection and death is ≈14 d, there is no addition of virus after the experiment begins. Dwyer and Elkinton additionally assumed that because of the short time scale of this type of experiment, there is no breakdown of virus within the bags, so that the virus decay rate μ is effectively zero. This allows Eqs. 3–5 to be simplified to

$$\frac{dS}{dt} = -\nu P_0 S \tag{6}$$

where P_0 is a constant. Eq. 6 can then be solved to give

$$S_7 = S_0 e^{-\nu P_0 7}, \tag{7}$$

where S_7 is the density of uninfected larvae at the end of the experiment, and S_0 is the density of uninfected larvae at the beginning of the experiment. Subsequent work by Dwyer (*unpublished data*) has shown that the "half-life" of LdNPV is ≈4 d. Although the omission of a decay rate does not significantly change any of our results or conclusions, we have included a decay rate so that Eq. 7 becomes

$$S_7 = S_0 e^{-(\nu/\mu)P_0(1-e^{-\mu 7})}. \tag{8}$$

This can rearranged to the following expression for ν

$$\nu = \frac{\mu}{P_0(e^{-\mu 7} - 1)} \ln\left[\frac{S_7}{S_0}\right]. \tag{9}$$

Here S_7/S_0 represents the fraction of test larvae that are uninfected at the end of the experiment, P_0 is the initial density of the virus in the environment, ν is the transmission constant, and μ is the decay rate of the virus. Eq. 9 allows us to calculate the transmission constant ν in terms of the fraction of larvae that were uninfected at the end of the experiment.

To estimate the overall transmission coefficient ν under each treatment k, we computed F_k, the average proportion of larvae uninfected in each treatment, and then calculated ν using Eq. 9 with F_k in place of S_7/S_0. We calculated ν for each treatment, rather than for each bag, because doing so minimizes the bias inherent in the estimate of a parameter such as ν, that is obtained through the use of a nonlinear transformation. That is, since the calculation of ν involves a log transformation, our approach leads to a much smaller bias than using a mean per tree transmission coefficient. The approximate bias B for our method can be estimated by

$$B = -\frac{1}{F_k^2}\left(\frac{q_k^2}{2n_k}\right), \tag{10}$$

where n is the number of trees in treatment k (16 in all treatments) and q_k^2 is the sample variance.

The approximate bias was estimated for each treat-

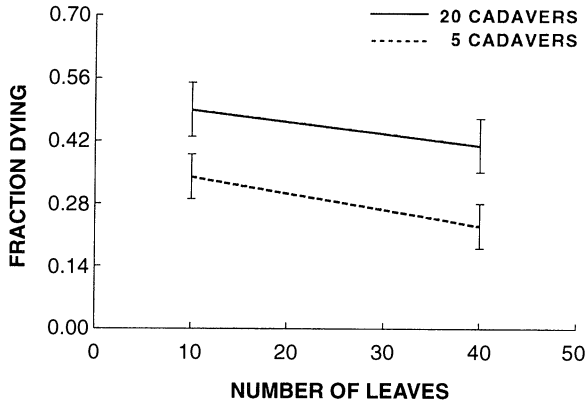

FIG. 1. The effects of foliage density (F = 5.78; df = 1, 15; P = 0.0296) and the density of virus-killed larval cadavers (F = 14.3; df = 1, 15; P = 0.0018) on the proportion of healthy test larvae infected with LdNPV, after 1 wk inside mesh bags on red oak foliage.

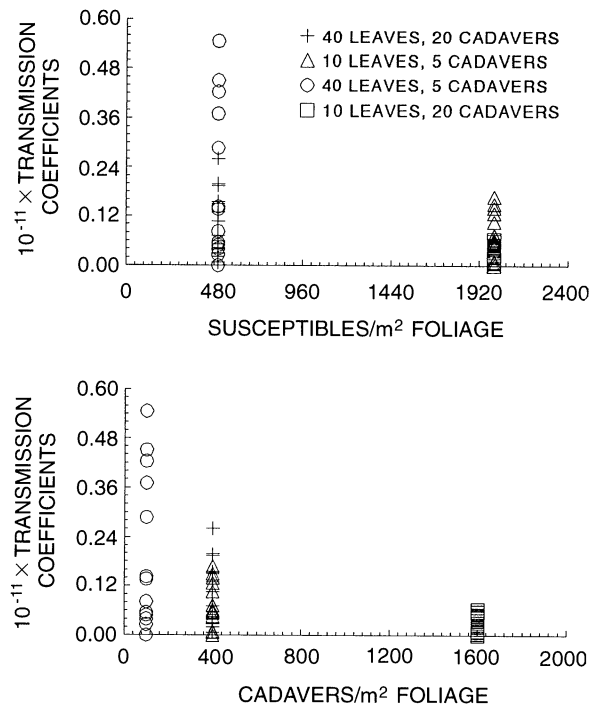

FIG. 2. Transmission coefficients estimated from Eq. 5 plotted against the densities of susceptible larvae and virus-killed larval cadavers inside mesh bags on red oak foliage.

ment using Eq. 10. Standard errors of the estimated transmission coefficients and correlations among them were obtained using the delta method (Rao 1973). These were then used to construct an approximate chi-square Wald test statistic (Seber and Wild 1989) to test the hypothesis of equal transmission coefficients across treatments.

RESULTS

The proportion of test insects that died from virus increased as foliage density decreased and as the density of initially infected larvae increased (Fig. 1). Both foliage density (F = 5.78; df = 1, 15; P = 0.0296) and the density of infected insects (F = 14.3; df = 1, 15; P = 0.0018) significantly affected the proportion of insects dying from LdNPV. There was no significant interaction effect between foliage density and the number of infected insects (F = 0.259; df = 1,15; P= 0.6182). These results suggest that foliage area has a simple effect on the transmission of virus. The increase in the density of virus and uninfected larvae as leaf surface area is reduced leads to a higher probability that larvae will encounter and consume a lethal dose of the virus.

The effects of the density of virus and larvae, however, do not appear to be strictly linear, as assumed in Eqs. 1 and 3–5. That is, the transmission coefficient v in Eqs. 3–5 is a rate constant that is calculated per viral inclusion body and per larval host. Under the assumption of mass action embodied in the Anderson–May model, it should remain constant over all densities of foliage or infected insects. Instead, Fig. 2 demonstrates that the transmission parameter v decreases as densities increase. Mean transmission coefficients in these experiments (Table 1) were found to be significantly different using the Wald test (C = 18.686; df = 3; P = 0.0003).

We used data generated during a study by Woods and Elkinton (1987) from plots on Otis Air Base in eastern Massachusetts, USA to look for similar effects in natural populations. Best fit transmission coefficients for these data were calculated by Dwyer and Elkinton (1993). These are plotted against densities of virus and healthy insect, together with the mean values from the small-scale experiments described above (Fig. 3). The estimates of the transmission constant v from these two data sets clearly show similar tendencies to decline with density.

DISCUSSION

What we have shown in this paper is not merely that some aspect of the transmission of the NPV changes with density, since that was already clear from Dwyer and Elkinton's (1993) work. Instead, we have attempted

TABLE 1. Mean transmission coefficients v, standard errors, and biases for each treatment in small-scale field experiments. Biases are calculated as a proportion of v, using Eq. 10. The number of leaves (leaf) and the numbers of cadavers (cad.) define each treatment.

Treatment	Mean transmission coefficient	Standard error	Approximate bias
40 leaf/20 cad.	6.53×10^{-12}	1.3×10^{-12}	0.04
40 leaf/5 cad.	1.31×10^{-11}	3.3×10^{-12}	0.03
10 leaf/20 cad.	2.12×10^{-12}	3.81×10^{-13}	0.04
10 leaf/5 cad.	5.1×10^{-12}	1.0×10^{-12}	0.03

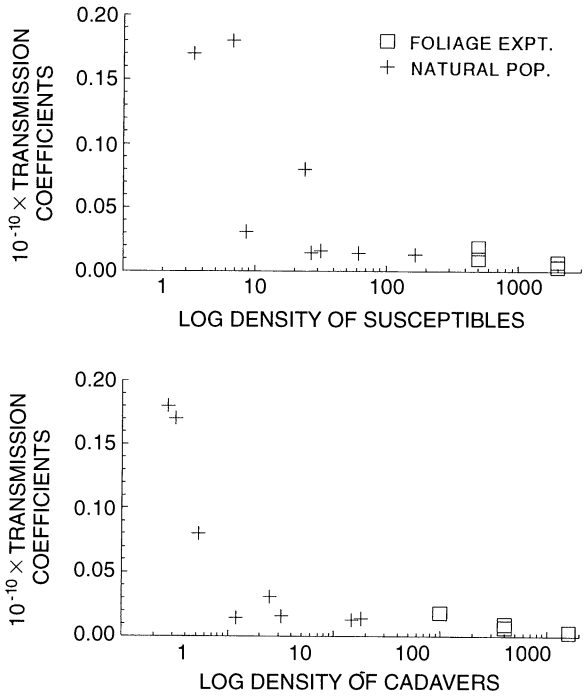

FIG. 3. Transmission coefficients estimated by Dwyer and Elkinton (1993) from data on weekly mortality from LdNPV in a naturally occurring population (Woods and Elkinton 1987), and mean transmission coefficients from small-scale experiments in mesh bags (Fig. 2) plotted against densities of susceptible larvae and virus-killed larval cadavers. Density is measured as no./m^2.

to extend their results by showing that, whatever is driving the variability in the transmission coefficient ν with density, it appears to be acting in a similar fashion at both the large scale of Woods and Elkinton's (1987) data and at the small scale of our mesh-bag experiments. Although we have not identified the mechanism driving this variability in transmission rate, our results provide further support for Dwyer and Elkinton's contention that the large-scale dynamics of gypsy moth NPV are determined by interactions at a small scale. Ultimately, of course, only further experimentation at a large scale can determine whether the small-scale forces drive the large-scale phenomena.

Hunter and Schultz (1993) demonstrated that larval susceptibility, a component of transmission, declines as defoliation increases (see also Keating et al. 1990). Since, in our experiments, branches in treatments using 10 leaves experienced relatively more damage from the 25 test larvae than did treatments with 40 leaves, the decline that we observed in the transmission constant with density may be explained by Hunter and Schultz's results. The effects of this kind of variability in transmissibility upon virus dynamics have not been explored theoretically. Foster et al. (1992), however, observed that the related effect of a decline in larval virus mortality with increasing larval density can alter the possibility that disease can cause cycles in gypsy moth populations.

Another possibility is that small-scale virus clumping or small-scale larval behavior, or a combination of the two, may explain the decline in our estimates of the transmission parameter ν with density. That is, Eqs. 3–5 are based upon the assumption that clumping is of little importance, but in fact the virus may be clumped. Although we are not aware of any attempts to model mechanistically the effects of pathogen clumping upon disease transmission rates (but see Briggs and Godfray 1995), it is well known that clumping can reduce the overall attack rate of parasitoids in host–parasitoid models (e.g., May 1978, Hassell 1982). Similarly, host densities may affect mortality. Although it is known that gypsy moth behavior changes at different densities (Lance et al. 1987), we do not yet understand how these behavioral changes (e.g., foliage consumption rates) translate into changes in transmission rates.

A final possible mechanism has to do with host susceptibility. The mass-action process embodied by the Anderson and May (1981) model does not take into account differences in disease susceptibility among insects; variability in virus susceptibility in gypsy moth larvae may also account for the observed decline in transmission coefficients with density (A. Sharov, *personal communication*). Such effects are known to have significant effects upon the dynamics of human disease models (Anderson and May 1992); in particular, variability in sexual activity has important consequences in the dynamics of AIDS models (Anderson et al. 1986).

In short, there are a variety of possible mechanisms that could underlie the kind of nonbilinear transmission that we have observed for gypsy moth NPV. Few of these have been investigated either theoretically or empirically for insect pathogens. Indeed, the fact that our data lead us to similar conclusions as Dwyer and Elkinton suggests that what is needed at this point is not just immediate further experimentation but first a theoretical cataloguing of mechanisms that (1) could lead to higher transmission rates at lower densities, and (2) could operate at both large and small spatial scales.

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