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HOST HETEROGENEITY IN SUSCEPTIBILITY AND DISEASE DYNAMICS: TESTS OF A MATHEMATICAL MODEL

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Abstract.—Most mathematical models of disease assume that transmission is linearly dependent on the densities of host and pathogen. Recent data for animal diseases, however, have cast doubt on this assumption, without assessing the usefulness of alternative models. In this article, we use a combination of laboratory dose-response experiments, field transmission experiments, and observations of naturally occurring populations to show that virus transmission in gypsy moths is a nonlinear function of virus density, apparently because of heterogeneity among individual gypsy moth larvae in their susceptibility to the virus. Dose-response experiments showed that larvae from a laboratory colony of gypsy moths are substantially less heterogeneous in their susceptibility to the virus than are larvae from feral populations, and field experiments showed that there is a more strongly nonlinear relationship between transmission and virus density for feral larvae than for lab larvae. This nonlinearity in transmission changes the dynamics of the virus in natural populations so that a model incorporating host heterogeneity in susceptibility to the virus gives a much better fit to data on virus dynamics from large-scale field plots than does a classical model that ignores host heterogeneity. Our results suggest that heterogeneity among individuals has important effects on the dynamics of disease in insects at several spatial and temporal scales and that heterogeneity in susceptibility may be of general importance in the ecology of disease.

Mathematical modeling of epidemics began with the pioneering work of Hamer (1906) and Ross (1910) and reached a high level of development in the work of Kermack and McKendrick (1927). Although much of the early theory focused on human diseases, more recently Anderson and May (1978, 1979) adapted human epidemic models to animal diseases, and their work has led to a flowering of interest in nonhuman diseases from both theoretical (Mollison 1995) and empirical perspectives (Holt 1993; Grenfell and Dobson 1995; Alexander et al. 1996). Most disease models, however, follow the simplest of Kermack and McKendrick's models in assuming that horizontal transmission depends linearly on the densities of healthy and infected individuals, the so-called mass-action assumption, so that

$$\frac{dS}{dt} = -\beta SI, \quad (1)$$

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where I is the density of infected individuals, S is the density of uninfected (susceptible) individuals, dS/dt is the rate of decrease (over time t) in the number of uninfected individuals because of horizontal transmission, and β is a transmission parameter (roughly, the fraction of possible encounters between uninfected and infected individuals that occur and lead to infection instantaneously). Because instantaneous transmission (here dS/dt) is linear in both S and I , equation (1) is sometimes known as a "bilinear" model (Liu et al. 1986).

In contrast to equation (1), a growing number of modeling studies have made alternative assumptions about transmission (Anderson and May 1992; Antonovics et al. 1995; Mollison 1995). Perhaps the simplest of these alternative models assumes that transmission depends on some power of host density, pathogen density, or both, so that equation (1) becomes

$$\frac{dS}{dt} = -\beta S^a I^b. \quad (2)$$

Although models incorporating this kind of transmission give different disease dynamics than do models that use equation (1) (Liu et al. 1986; Hochberg 1991), interpreting a and b mechanistically can be difficult. Models that adopt the opposite extreme by including all that is known about the ecology of a particular host-pathogen system (Onstad et al. 1990) can be more easily interpreted mechanistically and also typically show nonlinearities in transmission. These more complex models, however, are usually only used for a single host-pathogen interaction, and it is often difficult to see which model details are truly important to the dynamics of the disease.

Here we show that equation (1) fails to be a useful description of the transmission of nuclear polyhedrosis virus gypsy moths in that transmission is a nonlinear function of virus density. Rather than using a model like equation (2), however, in which the nonlinearity is assumed a priori, we instead incorporate an additional biological mechanism into equation (1) and show that this new mechanism implies nonlinear transmission. Specifically, allowing for host heterogeneity in susceptibility leads to a nonlinear relationship between transmission and virus density. The resulting model is still simple enough that the connection between mechanism and dynamics is clear, and it is general enough that it could be easily applied to other host-pathogen systems. In fact, our model is similar to models used to describe the transmission of HIV in human populations (Anderson et al. 1986; May and Anderson 1988; Anderson and May 1992).

Most experimental tests of equation (1) have used insect pathogens because of their great experimental tractability (Dwyer 1991; Roland and Kaupp 1995), and we are partly motivated by the increasing number of such experiments that demonstrate the flaws of equation (1). Some of this work has shown simply that the transmission parameter (β in eq. [1]) can vary with time for fungal pathogens (Thomas et al. 1995) or with larval stage for viral pathogens (Dwyer 1991; Goulson et al. 1995). Furthermore, our own experimental work with the gypsy moth virus has indirectly suggested that the transmission of this pathogen is nonlinear (D'Amico et al. 1996, 1997; see Knell et al. 1996 for similar effects

in a laboratory system). Indeed, using experimental transmission estimates from a model based on equation (1) to predict full-scale epidemics of the virus in large-scale natural populations leads to accurate predictions of virus dynamics at high host densities but not at low host densities (Dwyer and Elkinton 1993). In other words, the simple model is missing some factor that interacts with density. In this article, we provide empirical evidence that the missing factor in the model is host heterogeneity in susceptibility, and we show that this heterogeneity leads to dramatically different disease dynamics.

METHODS

We begin describing our methods by explaining the models that we use, beginning with the pathogen natural history that underlies the models.

Virus Natural History and General Theoretical Background

In gypsy moths, as in many Lepidoptera, transmission of the nuclear polyhedrosis virus occurs when larvae consume the virus on contaminated foliage, and infection usually leads to death (Evans and Entwistle 1987; Murray et al. 1991; but see Rothman and Myers 1996 for a review of nonlethal effects). By the time of death (10–14 d after infection at field temperatures), much of the larval mass has been converted to virus. When the integument breaks shortly after death, the virus is released onto the foliage where it can infect other larvae, although over time it will be rendered noninfectious by sunlight (Evans and Entwistle 1987). The virus is thus directly transmitted and fatal, and the insect has no appreciable immunological memory (Wood and Granados 1991). The simplicity of this transmission cycle means that measuring the transmission rate of the virus in an ecological field experiment is relatively straightforward.

Our experiments were designed to test both a classical model of infectious disease spread, which we used in an earlier paper (Dwyer and Elkinton 1993) and an important alternative. The earlier, classical, model, which we present here in a slightly different form than previously (see appendix for details), is

$$\frac{dS(t)}{dt} = -vP(t)S(t), \quad (3)$$

$$\frac{dI(t)}{dt} = vP(t)S(t) - vP(t - \tau)S(t - \tau), \quad (4)$$

and

$$\frac{dP(t)}{dt} = vP(t - \tau)S(t - \tau) - \mu P(t). \quad (5)$$

Here, S and I are again the densities of uninfected and infected hosts, respectively; P is the density of virus-killed cadavers; t is time; v is the transmission parameter; τ is the time between infection and death; and μ is the rate at which the virus breaks down in the environment. This is essentially the host-pathogen

model of Anderson and May (1981), adapted to represent a single epidemic in which there is no host reproduction and allowing for a time delay between infection and death.

Because equations (3)–(5) are based on assumptions that date to the very first epidemiological models (Mollison 1995), and because they assume that transmission is linearly dependent on pathogen density, we refer to equations (3)–(5) as the bilinear or classical model. Our alternative is the heterogeneity model, for which the uninfected host population is now a function of both time t and transmission parameter v :

$$\frac{\partial S(t, v)}{\partial t} = -vP(t)S(t, v), \quad (6)$$

$$\frac{dI(t)}{dt} = P(t) \int_0^{\infty} vS(t, v)dv - P(t - \tau) \int_0^{\infty} vS(t - \tau, v)dv, \quad (7)$$

and

$$\frac{dP(t)}{dt} = P(t - \tau) \int_0^{\infty} vS(t - \tau, v)dv - \mu P(t). \quad (8)$$

Here the symbols are the same as in equations (3)–(5), except that now the transmission parameter v is assumed to be gamma distributed with mean \bar{v} and shape parameter k (in the appendix, we show that the particular distribution is not of great importance to the model results). The parameter k is the inverse of the squared coefficient of variation, and thus is an inverse measure of the heterogeneity of the host population. The variable $S(0, v)$ is therefore the density of insects that have transmission parameter v at the beginning of the epidemic ($t = 0$). This assumption follows the AIDS model of Anderson and May and their colleagues (Anderson et al. 1986; May and Anderson 1988), except that here the heterogeneity is in susceptibility to the virus rather than in sexual behavior. Although the model equations (6)–(8) are thus reasonably general, they do exclude features known to be important for some diseases, including nonrandom mixing of host individuals, differences among infected hosts in the extent of infectiousness, and distributed incubation times (Anderson and May 1992). For insects and their viruses, there is little evidence for nonrandom mixing, infected larvae only become infectious at death, and the coefficient of variation of the time between infection and death is typically small.

Another mechanism that the model excludes is the possibility that hosts vary in their resistance to the virus but that the resistance of an individual host changes randomly over time, rather than being fixed at birth as we assume in equations (6)–(8). Under these circumstances, the transmission parameter v again has some probability distribution with mean \bar{v} , but the distribution of v does not change with time. Although this may at first seem like a reasonable mechanism, mathematically such a model collapses to the classical model equations (3)–(5). To show this, we note first that equation (6) becomes

$$\frac{d\hat{S}(t)}{dt} = -P(t) \int_0^{\infty} vS(v, t)dv, \quad (9)$$

while equations (7) and (8) are unchanged. Because the distribution of transmission parameters does not change with time, $S(v, t) = \hat{S}(t)f(v)$, where $f(v)$ is the distribution of transmission parameters. As a result, the integrals in this model become just the definition of the mean transmission rate \bar{v} multiplied by \hat{S} , so that

$$\int_0^{\infty} vS(v, t)dv = \hat{S}(t) \int_0^{\infty} vf(v)dv = \bar{v}\hat{S}(t). \quad (10)$$

This model therefore reduces to the classical model, equations (3)–(5), where v in equations (3)–(5) is redefined to indicate the mean transmission parameter. Allowing individual hosts to randomly vary in their disease susceptibility over time thus has no effect on disease dynamics.

General Experimental Methods

The protocol for our field transmission experiments consisted of enclosing uninfected larvae inside mesh bags containing foliage contaminated with virus-infected cadavers. The intent of the experiments was to measure transmission under conditions that are as close as possible to what the insects experience in nature, using the fraction of the uninfected larvae that become infected as a measure of transmission. The bags contained 40 leaves on branches of red oak (*Quercus rubra*) in the field. The mesh allows passage of air and water (Dwyer 1991) but does not allow the virus to break down (G. Dwyer, unpublished data). We then placed a variable number of virus-infected larvae in the bags a few days before they died, and 5 d later, after the initially infected larvae were all dead, we added 25 healthy larvae to each bag. Previous work in our lab has demonstrated that transmission in these experiments is largely unaffected by the density of uninfected larvae in the bag, the time during the summer when the experiment takes place, or predefoliation of the trees (D'Amico and Elkinton 1995; D'Amico et al. 1996, 1997). Because the most important round of transmission in natural epidemics occurs when larvae infected at the time of hatch die and transmit the virus to uninfected larvae in the second to fourth instar (Woods and Elkinton 1987), in these experiments the virus-infected larvae are infected immediately after they hatch and the uninfected larvae begin the experiment in the third instar (although they are typically fourth instars by the end of the experiment). After 7 d, we remove the initially uninfected larvae to the lab and place them in individual cups containing artificial diet to determine whether they have become infected. Because transmission ends when the larvae are moved into the lab, the experiments measure one round of transmission in the field. Moreover, long-distance dispersal of virus by wind or rain is unlikely to play an important role in transmission (Dwyer 1991; D'Amico and Elkinton 1995; Dwyer and Elkinton 1995; D'Amico et al. 1996), so that the experiment measures transmission at the small scale at which transmission occurs naturally.

Choosing the appropriate statistic with which to measure transmission, however, is not immediately obvious, because in equation (1), dS/dt is instantaneous transmission, which cannot be measured in practice. A more convenient measure is the log-transformation of the fraction surviving $-\log(S(t)/S(0))$, which can be easily measured, and, as we now show, retains the distinction between linear and nonlinear transmission. To derive an expression for $-\log(S(t)/S(0))$, we note first that models such as equations (3)–(5) or equations (6)–(8) describe virus epidemics in natural gypsy moth populations, in which there can be as many as four rounds of virus transmission per generation of gypsy moths; our experiments, however, permit only a single round of transmission and do not allow virus decay. For the experiments, we therefore need only the equations for the susceptible populations, either equation (3) or equation (6), each of which can be solved for the fraction surviving (see Dwyer 1991; Dwyer and Elkinton 1993). For the classical model, the resulting expression is

$$-\log\left(\frac{S(t)}{S(0)}\right) = vP(0)t. \quad (11)$$

Here $S(0)$ and $S(t)$ are the densities of uninfected insects at the beginning and end of the experiment, respectively, $P(0)$ is the density of virus during the experiment, and t is the duration of the experiment. For the heterogeneity model, the corresponding expression (essentially obtained by integrating over v in a version of eq. [11]) is

$$-\log\left(\frac{\hat{S}(t)}{\hat{S}(0)}\right) = k \log\left(1 + \frac{\bar{v}}{k} P(0)t\right), \quad (12)$$

where now $\hat{S}(t)$ is the total uninfected host population at time t ($\hat{S}(t) \equiv \int_0^\infty S(t, v)dv$). Comparison of equations (11) and (12) thus makes clear that heterogeneity in the host population causes transmission, as measured by $-\log(S(t)/S(0))$, to be a sublinear function of virus density. In other words, although it is not obvious that instantaneous transmission in equations (6)–(8) is nonlinear, our experimental measure of transmission shows that transmission in this model is indeed a nonlinear function of virus density.

The effects of heterogeneity, however, are not always intuitive. First, if we fit both the classical and the heterogeneity models to the same data, at low virus density, equation (12) predicts that transmission will be higher than that predicted by equation (11) because of the presence of highly susceptible larvae in the population (fig. 1A). At high virus density, however, equation (12) predicts that transmission will be lower than that predicted by equation (11) because the remaining uninfected individuals are highly resistant. If instead we have two host strains with the same mean transmission parameter \bar{v} but different levels of heterogeneity k , then the strain with higher heterogeneity (lower k) will have lower transmission (fig. 1B). This occurs even though adding heterogeneity while keeping the mean constant involves adding both more susceptible and less susceptible hosts to the population because most of the highly susceptible hosts

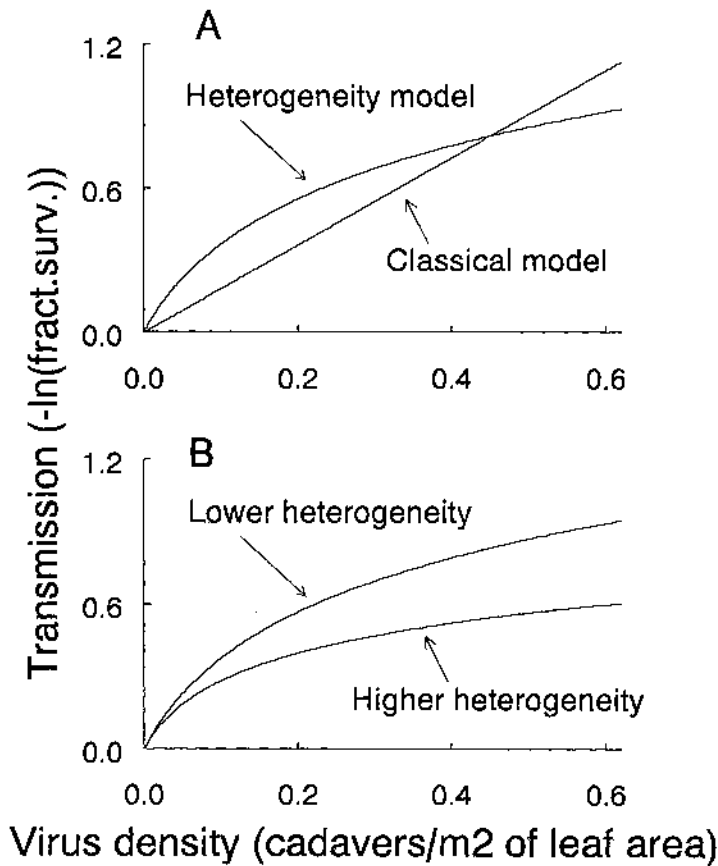


FIG. 1.—*A*, Comparison of predictions of classical model (eq. [11]) and heterogeneity model (eq. [12]) when each is fit to the same transmission data. *B*, Comparison of predictions of heterogeneity model (eq. [12]) when the mean transmission rate \bar{v} is held fixed and the heterogeneity (inverse of k) is increased.

become infected irrespective of the value of k . In contrast, increasing the mean transmission parameter \bar{v} while holding heterogeneity k constant gives higher transmission at both high and low virus densities.

Quantifying the Impact of Host Heterogeneity

Our experiments were designed to test the two models of virus transmission. The questions that we asked were, Is transmission a nonlinear function of virus density, as predicted by equation (12)? And given that transmission is indeed a nonlinear function of virus density, we asked, Is host heterogeneity the mechanism underlying the nonlinearity? Although the first question can be tested directly, we approached the second question indirectly by testing whether the degree of nonlinearity in transmission increases when we perform transmission

experiments with strains of more heterogeneous larvae. The two host strains were a feral strain and a lab strain. The feral strain larvae came from eggs that were collected from different natural populations and then mixed together (1994, all collection sites were in Massachusetts; 1995, collection sites were in Massachusetts and Virginia; 1996, collection sites were in Massachusetts and West Virginia). In contrast, the lab eggs came from a population that has been reared continuously in the lab for more than 40 generations. Because the lab colony has not been exposed to significant levels of virus in 40 generations and because we intentionally made the feral strain as heterogeneous as possible, we hypothesized that the lab strain would have lower levels of heterogeneity in susceptibility to the virus. We tested this hypothesis by performing laboratory dose-response experiments. For all of our experiments, both feral and lab eggs were disinfected (to ensure elimination of preexisting virus on the eggs) by washing first for 90 min with 10% formaldehyde and then rinsing with water (Dwyer and Elkinton 1995). We reared larvae of the two strains under identical conditions in the laboratory on artificial diet until they reached the fourth instar.

In the lab.—Our laboratory dose-response experiments were performed in 1995 and 1996. We used a modification of a standard dose-response bioassay (Hughes and Wood 1986) in which we fed cubes of artificial diet, dosed with one of eight different concentrations of virus that included a zero dose, to larvae that had been starved for 24 h. We discarded any larvae that had not entirely consumed the cube of diet within 24 h. In every case, nearly all (never less than 90%, usually 100%) of the larvae of each host strain at each dose ate the entire diet cube. The number of larvae per dose varied between 25 and 50, depending on the availability of larvae. This approach ensures that larvae are exposed to the same total quantity of virus (Ridout and Fenlon 1991). Also, by using the same virus concentrations for the two host strains, we ensured that any errors in making up the virus concentrations would be the same for the two host strains, and thus would not affect our analyses.

At a small-scale in the field.—In 1994, 1995, and 1996, we performed field transmission experiments, following the general protocol that we outlined above. The durations of the experiments were as follows: June 8–15, 1994; July 14–21, 1995; and June 10–17, 1996. Although the 1995 experiment was not in synchrony with natural populations (the 1994 and 1996 experiments were in synchrony), our previous work demonstrated that the timing of an experiment within the summer has little effect on the results (D'Amico et al. 1997). Virus-infected larvae were produced by infecting larvae in the lab through diet contamination with a few milliliters of virus solution at concentrations between 5×10^5 and 5×10^6 virus particles (occlusion bodies) per milliliter. This dose range causes greater than 95% infection, and at 28°C the few larvae that do not become infected can be removed at 4 d postinfection because they molt to the next instar, whereas infected larvae do not molt (Park et al. 1993). To test whether transmission is a nonlinear function of virus density, we varied the density of infected larvae in the mesh bags, with treatments as follows: 1994, 0, 2, 5, 10, 25, 40 cadavers per bag; 1995, 0, 5, 10, 25, 50, 70 cadavers per bag; and 1996, 0, 5, 10, 25, 50, 75 cadavers per bag. To test whether different levels of host

heterogeneity can lead to different degrees of nonlinearity in transmission, we crossed these virus density treatments with a host strain treatment, feral or lab. This design was motivated by our hypothesis that, given that the two strains differ in their degree of heterogeneity in susceptibility to the virus in the lab, the more heterogeneous feral strain should show a more strongly nonlinear response to the virus in transmission in the field.

Each treatment was replicated four times in 1994 and eight times in 1995 and 1996. In 1994 and 1995, a block consisted of a single tree so that each tree in the experiment carried a bag from each treatment. Because we have never seen tree effects in these experiments (D'Amico et al. 1996, 1997) and because there was a small amount of virus mortality in control bags in both 1994 and 1995, in 1996 each block consisted of a set of three trees grouped closely together, and treatments were assigned to trees within a block according to a modified Latin-squares design. In all cases, however, mortality in the control bags was extremely low (<5%, compared with $\geq 15\%$ in the lowest virus density treatments). The 1994 and 1995 experiments were carried out in a stand of mature red oaks on the University of Massachusetts campus in Amherst. The 1996 experiment was carried out using trees that were scattered throughout Cadwell Memorial Forest, an experimental forest in Pelham, Massachusetts, and included both mature and immature red oaks. Within a block in 1996, however, all trees were approximately the same age and size.

To estimate the density of virus in the bags, we quantified the surface area of red oak leaves with a leaf-area meter. Because the leaves in the bags were about 50% defoliated by the end of an experiment, to quantify leaf area, we used red oak leaves from nearby branches of the 1994 trees, calculated the average area of these leaves (57.5 cm²/leaf), and multiplied by 40 to get the total leaf area. Although this is an approximate procedure, leaf area is only an issue when we compare transmission parameters across scales.

At a large-scale in the field.—In order to test the abilities of the classical model equations (3)–(5) and the heterogeneity model equations (6)–(8) to explain virus dynamics at a large scale, we followed our earlier work (Dwyer and Elkinton 1993) in comparing the fit of the models to the large-scale data of another earlier study (Woods and Elkinton 1987). The data come from virus epidemics in natural populations and were collected in large-scale sample plots (areas ranged from 4 to 9 ha). The initial densities of infected and uninfected larvae were estimated from each plot at the beginning of the gypsy moth larval season (see Woods et al. 1991 for details). Here we have discarded three of the plots to which we compared the model earlier because two have fewer than four data points in each plot and because the third was sprayed with the insecticide *Bacillus thuringiensis* (S. Woods, personal communication). We estimated the transmission parameters, v for the classical model and \bar{v} (and k) for the heterogeneity model, by fitting each model to the large-scale data.

Statistical Analyses

Dose-response experiments.—To analyze the dose-response bioassays, we used probit analysis, a standard method of analyzing this kind of data (Finney

1971). In probit analysis, insect susceptibility to the virus, as measured by the virus concentration that would lead to infection, is assumed to be normally distributed (this distribution is known as the "tolerance distribution"). The variability in this susceptibility is what we mean by heterogeneity in susceptibility. Although in the toxicological literature probit analyses usually focus on the mean of the tolerance distribution (the 50% lethal dose, LD_{50}), because we are interested in the heterogeneity of the host insects, we instead focus on the slope of the probit line. Because the slope is the inverse of the standard deviation of the tolerance distribution, shallower slopes indicate greater heterogeneity. To determine if the slopes of the lines for the two strains are significantly different, we use the test statistic

$$D = \frac{m_F - m_L}{\sqrt{s_F^2 + s_L^2}}, \quad (13)$$

where m_F and m_L are the estimated slopes of the probit lines for the feral and lab strains, respectively, and s_F and s_L are the standard errors associated with each slope. The test statistic D is then approximately normally distributed with $\bar{X} = 0$ and $SD = 1$. Because our a priori hypothesis was that the feral larvae were more heterogeneous, we used a one-tailed P value.

Transmission experiments.—To assess the usefulness of our two competing models in describing field transmission data, we asked whether each model provides a good fit to the data, and whether host strain affects the heterogeneity parameter k in the way that we predict (because we used only four replicates in 1994, we restrict our statistical analyses to 1995 and 1996). We further broke down the first question to ask whether the data reject either model and to ask which model provides a better fit to the data. The statistical issues (see appendix for details) thus involve assessments of the fit of nonlinear models, which can be best approached by using test statistics based on log-likelihood ratio functions. A key observation was that for most virus densities in most years the variance in the fraction of larvae that were uninfected in an experiment was considerably larger than one would expect if the variance were entirely due to sampling error (i.e., if the variance was strictly binomial). We therefore used a normal distribution to model the errors in the data, with weights at each virus density that are equal to the reciprocal of the observed variance at each density. Virus density treatments that had lower variance are therefore weighted more heavily. A second important feature is that we used equations (11) and (12) to explain the biology underlying the models, but to avoid potential biases inherent in using log-transformed data, in our statistical analyses we used the nontransformed versions of these equations.

We then assessed the goodness of fit of our two competing models using a lack-of-fit test. For this test, as a null model we used a kind of best-case scenario, in which the expected value of survival at each virus density equals the observed mean at that density. For each of the classical and heterogeneity models, we then asked whether a given model provided a significantly worse fit to the data than the best-case null model. A nonsignificant result of this lack-of-fit

test suggests that a model fit no worse than the best-case scenario calculated from the observed data. In order to compare the relative ability of the two models to explain each data set, we used the Akaike Information Criterion (AIC; Akaike 1973), which chooses the model with the greatest likelihood, adjusted for the number of parameters in each model.

Finally, we tested whether the host strain treatment affected the degree of heterogeneity in transmission. Because low values of k are associated with high levels of heterogeneity, we therefore asked, Do the feral larvae have significantly lower values of k than the lab larvae? To answer this question, we bootstrapped the distribution of the difference in the values of k for each strain. For each strain in each year, we randomly chose eight replicates and calculated values of the parameter k for each strain separately by fitting the appropriate model equation to this data for each strain. We then calculated the difference between the values of k for the two strains and repeated this procedure 1,000 times. The resulting distribution estimates the degree to which the 95% confidence interval of the differences in the k values for the two strains overlapped zero.

Large-scale epidemic data.—Because the large-scale data consist of unreplicated time points from different plots, we could not weight using among-replicate variances, as we did with the experimental transmission data. The alternative assumption that errors are binomial is equivalent to the assumption that the samples are independent, but independence of the samples is unlikely, and testing for independence is impossible. Because of these problems, we fit each model using unweighted least-squares, which, as we will show, clearly indicates that the heterogeneity model is more appropriate than the classical model. More formal analyses would require determination of a variance model.

RESULTS

The slope of the best-fit probit line was considerably steeper for the lab insects than for the feral insects in both years (fig. 2), so that the feral insects had a greater standard deviation of their tolerance distribution (table 1). Tests for differences in the slopes demonstrate that the slopes of the probit lines for the feral larvae were marginally significantly different in both 1995 and 1996 (table 1). The dose-response bioassays thus suggest that the feral larvae were more heterogeneous in their susceptibility to the virus than were the lab larvae.

In the field transmission experiments, the heterogeneity model fit the data much better than did the classical model (fig. 3, table 2). Calculation of the AIC showed that the heterogeneity model gives a better fit than the classical model for both strains in both 1995 and 1996 (table 2). In addition, lack-of-fit tests on the 1995 and 1996 data rejected the classical model but accepted the heterogeneity model for both strains (table 2). The estimated heterogeneity parameter k was higher in all years for the lab strain than for the feral strain (table 3), and bootstrapping the parameter k showed that the 95% confidence interval (CI; using the percentile method, Efron and Tibshirani 1993, p. 170) on the difference in the heterogeneity parameters k barely overlapped zero in 1995 (95% CI = $-50.8:0.52$, 93.4% of 1,000 bootstrapped values were negative) and did not

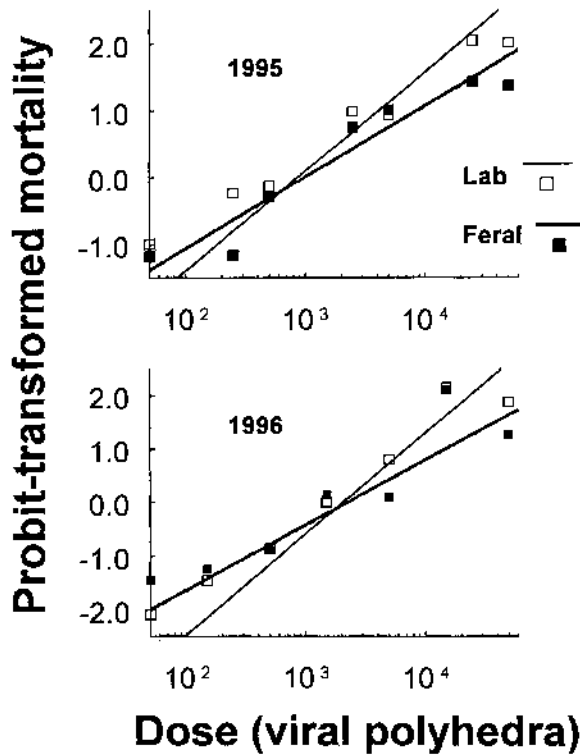


FIG. 2.—Comparison of dose-response bioassay data for lab and feral strains in 1995 and 1996. The lines represent the best-fit probit lines for each strain in each year, while the squares represent the probit-transformed data.

TABLE 1

PARAMETERS OF DOSE-RESPONSE CURVES FOR TWO DIFFERENT STRAINS OF GYPSY MOTH

Year and Strain	LD ₅₀	σ	<i>P</i>
1995			.092
Lab	2.93	.672	
Feral	2.99	.935	
1996			.077
Lab	3.31	.533	
Feral	3.26	.916	

NOTE.—LD₅₀ represents the 50% lethal dose (in terms of log₁₀ of the number of viral occlusion bodies), while σ is the standard deviation of the tolerance distribution. *P* is the significance level at which the slopes of the probits lines of two strains differ within a year.

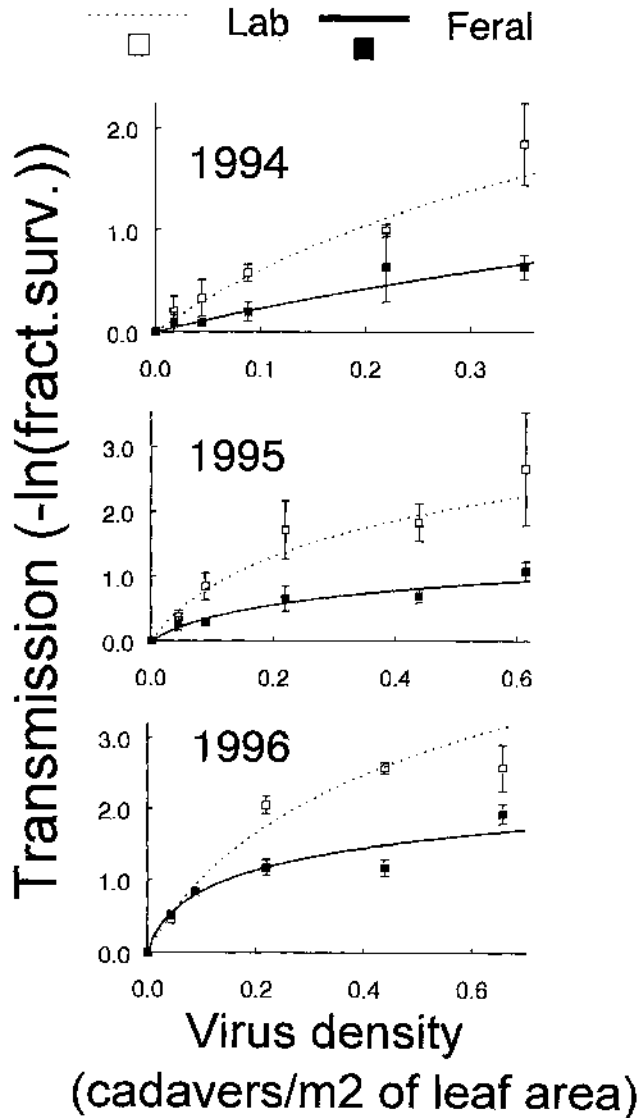


FIG. 3.—Relationship between transmission and virus density, as measured in field experiments in three successive years. The lines are the best fit of the heterogeneity model to the data. To allow for comparison between our measure of transmission and fraction infected, note that a value of 3.0 on the vertical axis corresponds to about 95% infection, 2.0 corresponds to about 87% infection, and 1.0 corresponds to about 63% infection. Because the vertical axis is thus a nonlinear transformation of the infection (or survival) rate, the nonlinearities here are not due to the infection rate approaching 100%.

TABLE 2
STATISTICAL ANALYSES OF GOODNESS OF FIT TO
TRANSMISSION MODEL

Year and Strain	AIC _C	AIC _H	P _C	P _H
1995				
Feral	157.7	149.7	.016	.385
Lab	158.7	148.9	.011	.493
1996				
Feral	170.4	148.6	1.0 × 10 ⁻⁴	.552
Lab	165.2	152.1	8.3 × 10 ⁻⁴	.155

NOTE.—Model equations were fit to 1995 and 1996 data in figure 3. Subscript "C" indicates the classical model and "H" indicates the heterogeneity model. AIC denotes the Akaike Information Criterion and P_C and P_H indicate the significance level at which a lack of fit test does or does not reject each model (P < .05 indicates model rejection).

TABLE 3
ESTIMATES OF MEAN TRANSMISSION RATES
 \bar{v} AND HETEROGENEITY PARAMETERS k

Year and Strain	\bar{v} m ² /d	k
1994		
Lab	1.072	1.53
Feral	.36	1.23
1995		
Lab	1.94	1.01
Feral	.90	.39
1996		
Lab	2.11	1.68
Feral	3.37	.48
Large-scale estimate	.54	.59

NOTE.—Estimates are for the heterogeneity model fit to experimental data in 1994–1996 (fig. 3) and to large-scale field plots (fig. 4).

overlap zero in 1996 (95% CI = -3.88: -0.067, 98.4% of 1,000 bootstrapped values were negative), demonstrating that transmission to feral larvae was indeed more heterogeneous than was transmission to lab larvae. An important point is that both the mean transmission parameter \bar{v} and the heterogeneity parameter k contribute to the transmission $-\log(S(t)/S(0))$. In 1994 and 1995, the lower transmission among feral larvae (fig. 3) was due to both lower mean transmission parameters \bar{v} and higher heterogeneities (lower k ; table 3). In 1996, however, because the mean transmission parameter \bar{v} for the feral larvae was higher than for the lab larvae (table 3), the lower transmission among feral larvae was entirely as a result of their higher heterogeneity.

The heterogeneity model provides a much better fit to the large-scale data

than does the classical model (fig. 4). We emphasize that the initial peak of virus infection in the early stages of the epidemic in each plot is the same for the two models because this initial peak is determined solely by the initial fraction of larvae that hatch infected in each plot, as estimated by Woods et al. (1991). The delay between the initial peak and the second, higher peak is apparently a result of the time that it takes larvae to encounter the virus and die and supports our modeling decision to include a delay between infection and death. The differences in the two models, however, are seen in the second peak of virus mortality in the late stages of the epidemic. Specifically, the heterogeneity model equations (6)–(8) provide an excellent fit to the data in all five plots, spanning a wide range of densities. In contrast, as we expect from our analysis of the transmission experiments, the classical model equations (3)–(5) drastically underestimate virus mortality in the low density plots and slightly overestimate virus mortality in the highest density plot. Indeed, the classical model predicts that there will be essentially no epidemic in the three lowest density plots, whereas the heterogeneity model accurately predicts epidemic intensity in every plot. Finally, the best-fit values of the heterogeneity parameter k for the heterogeneity model are close to the estimates from the repeated small-scale transmission experiments (table 3), suggesting that similar processes occur at the two different scales.

DISCUSSION

Our field transmission data provide overwhelming evidence that virus transmission in gypsy moths is a nonlinear function of virus density. For both feral and lab larvae, the relationship of transmission to virus density was visually nonlinear in each of 3 yr, and the nonlinearity was statistically significant for the 2 yr in which we had sufficient replication. To the best of our knowledge, this is the first experimental field demonstration of a nonlinear dependence of transmission on pathogen density. The real interest of our work, however, is that it implies that this nonlinearity is due to heterogeneity among larvae in their susceptibility to the virus. Because the dose-response data suggested that both strains were strongly heterogeneous, we expected that both strains would show a nonlinear relationship between transmission and virus density in the field, and figure 3 bears out this expectation. More significant, however, our hypothesis predicted that the higher heterogeneity of the feral larvae in the lab would be translated into more highly nonlinear transmission for feral larvae in the field, and this prediction was also borne out. Encouragingly, our estimates of the heterogeneity parameter k , again for the 2 yr in which we had reasonable replication, are surprisingly consistent within a host strain (table 3).

We emphasize that the processes occurring in the field experiments are more complicated than the processes occurring in the laboratory bioassays. The bioassays measure the probability of infection given consumption of a known virus dose, whereas the field experiments measure simply the probability of infection. The field experiments therefore allow both for the probability of consuming different doses and for the probability of infection given consumption, and so include the effects of larval behavior and natural but uncontrolled doses, as well

Classical Model

Heterogeneity Model

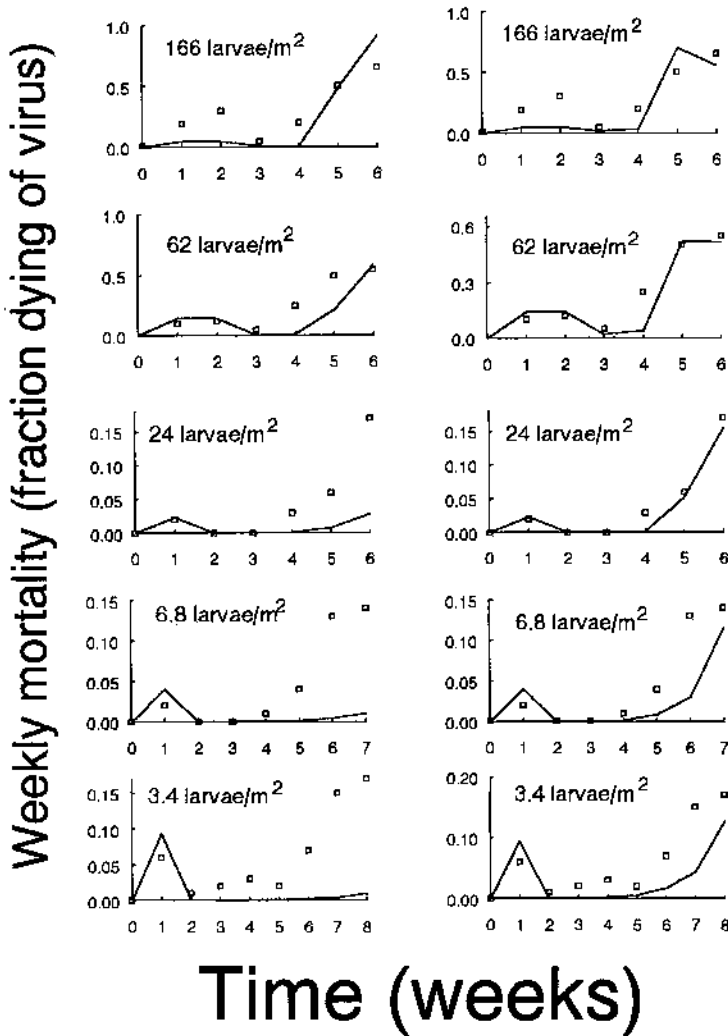


FIG. 4.—Comparison of best fit of classical (eqq. [3]–[5]) and heterogeneity (eqq. [6]–[8]) models to data from large-scale natural epidemics. Model outputs are indicated by lines, while the data are indicated by squares. Each model was fit to all six plots to arrive at either a common value of the transmission parameter ν for the classical model or common values of the mean transmission rate $\bar{\nu}$ and the heterogeneity parameter k for the heterogeneity model. Larval densities (per square meter of foliage, see Dwyer and Elkinton 1993) at the beginning of each season are indicated on each graph. For any given density of larvae (one "row" in the figure), the data for the two models are identical.

as more or less natural conditions of food and weather. In other words, the field experiments suggest that the heterogeneity in susceptibility that we observed in the lab is also important under field conditions.

Although we recognize that the differences in transmission that we observed between the two host strains could be related to some kind of spatial heterogeneity, we note that gypsy moth larvae within the bags were highly mobile, so that the distribution of defoliation within the bags was not particularly patchy. This suggests that, over a single round of transmission, infections are randomly distributed across space, and without heterogeneity in susceptibility this again gives us the classical model. We therefore suspect that spatial structure does not explain our results, but what is needed is a theory that relates the details of insect behavior to risk of infection (see also Dwyer 1991; Goulson et al. 1995). In any case, because the two host strains differed in their heterogeneity in the lab, it is unlikely that the observed differences in levels of heterogeneity in the field arose solely from differences in movement or feeding rates between the two strains but, instead, were at least partly determined by the risk of infection after virus consumption had occurred.

The better fit of the heterogeneity model to the large-scale data, and the close match between the levels of heterogeneity observed in the small-scale experiments and in the large-scale epidemics, together suggest that host heterogeneity plays a crucial role at both large and small spatial scales. An important point is that introducing heterogeneity in host susceptibility leads to a nonlinear relationship between transmission and virus density, yet the resulting model fits better in large-scale epidemics at different host densities. The explanation for the better fit across host densities is partly that initial virus infection levels at high and low host densities tend to be similar, resulting in higher virus densities at higher host densities (10% initial infection in a high-density host population produces more total virus than 10% initial infection in a low-density host population). Also, repeated rounds of transmission in full-scale epidemics tend to amplify initial differences in virus densities. These effects mean that host and virus densities tend to be correlated. As a result, in high-density populations, even highly resistant individuals are overwhelmed by high densities of virus, resulting in very severe epidemics, whereas in low-density populations virus densities climb only high enough to kill mostly larvae of low to moderate resistance.

Over either one round of transmission or many, however, the heterogeneity model involves selection for larvae that have higher resistance. Because we reared the larvae of different strains in our transmission experiments under identical conditions, we suspect that heterogeneity in susceptibility has a genetic component and that, therefore, natural selection for resistance plays a role in virus epidemics in gypsy moths. Nevertheless, heterogeneity that is due instead to differences in environmental conditions experienced by the parents or grandparents of the larvae in our experiments (Rossiter 1991) would give similar results.

The kind of heterogeneity in susceptibility that we have documented has been shown to be important in a wide variety of models of host-parasite population dynamics (at least for the case in which heterogeneity is not genetic). In models of interactions between insect hosts and parasitoids (Hassell et al. 1991) and be-

tween vertebrate hosts and helminths (Anderson and May 1978; May and Anderson 1978), host heterogeneity has a strongly stabilizing effect (but see Adler and Kretschmar 1992). In models of pathogens of insects like gypsy moth in which a seasonal epidemic occurs in a host with discrete generations, nonlinear transmission rates are also stabilizing (Briggs and Godfray 1995). Although these models consider only virus mortality (mouse predation is also important in low-density gypsy moth populations; Elkinton et al. 1996), the consistent effect of host heterogeneity in different models suggests that it may also play an important role in natural gypsy moth dynamics.

It is difficult to know whether host heterogeneity in susceptibility is important in the dynamics of other insects because to our knowledge no other direct attempts have been made to look for the effects of host heterogeneity on disease transmission. Natural selection for disease resistance, however, is one consequence of genetically based heterogeneity in susceptibility, so evidence for natural selection implies an effect of host heterogeneity on population dynamics. Because diseases often cause high mortality in insect populations in the field (Anderson and May 1981; Myers 1988, 1993) and because there is considerable evidence for genetically based heterogeneity in susceptibility in bioassays (Watanabe 1987; Fuxa 1993), it is likely that natural selection for disease resistance often occurs in insects. Indeed, Martignoni (1957 in Watanabe 1987), showed that the larval LD_{50} of field-collected *Eucosma griseana* dropped by a factor of 5 when measured before and after an epidemic. Likewise, Boots and Begon (1993) showed that populations of *Plodia interpunctella* that were exposed to a virus under quasi-natural conditions in the laboratory developed higher resistance than did unexposed populations.

Our results concur with empirical studies of host-parasitoid and host-helminth interactions (Dobson and Merenlender 1991; Pacala and Hassell 1991; Hudson and Dobson 1995), adding to the growing consensus that variability among individuals plays an important role in interspecific interactions. Also, although host heterogeneity is believed to affect the dynamics of a wide variety of human diseases (Weatherall et al. 1988; Anderson and May 1992), to our knowledge our data represent the first experimental evidence for an effect of host heterogeneity in any host-pathogen system. The important effect that heterogeneity in disease susceptibility is likely to have on disease dynamics in insect populations suggests that it should be taken into consideration in attempts to use pathogens as microbial control agents (Podgwaite et al. 1992; Cory et al. 1995).

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APPENDIX

MATHEMATICAL AND STATISTICAL DETAILS

In this appendix, we discuss some of the details behind the numerical and statistical calculations in the text. To begin with, the model equations (3)–(5) differ from our earlier work (Dwyer and Elkinton 1993) in that previously we defined P as the density of the pathogen in the environment. In equations (3)–(5) and (6)–(8), we have redefined P to mean density of virus-killed cadavers. Because the model does not explicitly include spatial structure, this just rescales P and v without affecting the model's dynamics (specifically, if \hat{P} and \hat{v} indicate the pathogen density and transmission parameter in our earlier article, we then have $P \equiv (\hat{P}/\Lambda)$ and $v \equiv \Lambda\hat{v}$). Redefining P in this way allows us to eliminate a parameter (Λ) from the earlier model and leads to a simplification in our estimate of the initial density of virus. Previously, our transmission parameter v was estimated in terms of virus particles (occlusion bodies), and we had separate estimates for the initial density of virus particles in the environment and for the quantity of virus particles produced by dead cadavers of different larval stages. Now, our estimates of the transmission parameters v and \bar{v} are expressed in terms of third-instar cadavers, and we multiply the initial density of first-instar cadavers by the ratio of the number of virus particles produced by a first-instar cadaver (approximately 4×10^6 [M. Shapiro, personal communication], two orders of magnitude lower than the published value [Shapiro et al. 1986]) to the number produced by a third-instar cadaver (approximately 2×10^9 [Shapiro et al. 1986]). As we explained above, this change in the definition of P affects only the scaling of the transmission parameter v in the classical model and the mean transmission parameter \bar{v} in the heterogeneity model and has no effect on the model's predictions. Allowing for differences in the size of cadavers of different stages, however, allows for stage structure in the model. Additional parameter estimates are 12 d for the time between infection and death τ , and 0.15 per d for the decay rate μ (G. Dwyer and J. S. Elkinton, unpublished data).

Given estimates of each of the parameters for the full-scale model equations (3)–(5) and (6)–(8), we can numerically simulate each set of equations on a computer, using numerical versions of a solution technique known as the method of steps (Hairer et al. 1987). For equations (6)–(8), however, the integral in equation (8) becomes numerically intractable for values of $k < 1$. Fortunately, Dushoff (1996) has achieved recent breakthroughs in simplifying this kind of model, which allow us to replace the partial differential equations (6)–(8) with a closely approximating set of ordinary differential equations. Here we briefly present Dushoff's method. First we can define s_j to be the j th moment of $S(v, \tau)$, so that

$$s_j(\tau) \equiv \int_0^{\infty} v^j S(\tau, v) dv. \quad (\text{A1})$$

The variable $s_0(t)$ is thus the total density of the population at time t , $s_1(t)/s_0(t)$ is mean transmission, et cetera. Inserting equation (6) into equations (A1) gives

$$\frac{ds_j(t)}{dt} = -P(t)s_{j+1}(t). \quad (\text{A2})$$

We are thus replacing a single partial differential equation (eq. [6]) with a set of ordinary differential equations that are expressed in terms of the moments of the distribution of transmission. To keep the resulting system tractable, we make the reasonable assumption that the mean of the distribution changes with time but that the coefficient of variation is constant (so that as the variance changes it remains directly proportional to the square of the mean). The mean of the distribution of transmission at time t is defined to be $m_1(t) \equiv s_1(t)/s_0(t)$, which gives us

$$\frac{ds_0(t)}{dt} = -m_1(t)P(t)s_0(t); \quad (\text{A3})$$

$$\frac{dm_1(t)}{dt} = -\frac{1}{k}P(t)m_1^2(t); \quad (\text{A4})$$

$$\frac{dI(t)}{dt} = m_1(t)P(t)s_0(t) - m_1(t - \tau)P(t - \tau)s_0(t - \tau); \quad (\text{A5})$$

and

$$\frac{dP(t)}{dt} = m_1(t - \tau)P(t - \tau)s_0(t - \tau) - \mu P(t). \quad (\text{A6})$$

This system of ordinary differential equations turns out to be a close approximation to the full system of partial differential equations (6)–(8) with an initial gamma distribution of transmission parameters. First of all, the expressions for the fraction infected in a transmission experiment (eq. [12]) are the same for the full model equations (6)–(8) and for the moment-approximation equations (A3)–(A6), as are exact expressions for the fraction infected for each model for $t < \tau$ (essentially eq. [12] with $P(0)$ discounted to allow for virus decay) and for $\tau \rightarrow \infty$ (G. Dwyer, J. Dushoff, and J. S. Elkinton, unpublished manuscript). In fact, the latter two exact expressions can be used to assess the accuracy of the numerical simulations; somewhat surprisingly, numerical simulations of equations (A3)–(A6) are very close to the values calculated from the exact expressions, while simulating equations (6)–(8) (using the method of steps combined with numerical quadrature of the integral in eq. [8]) typically gives substantial error, especially for the small values of k that we observe in our data.

Finally, here we give the likelihood functions for our analysis of the field transmission experiments. The likelihood of either model given the data is

$$L = \prod_{i=1}^{N_D} \prod_{j=1}^{N_T} \frac{1}{\sqrt{2\pi\sigma_i^2}} e^{-((f_{ij} - q_i(\theta, P_i))^2 / 2\sigma_i^2)}, \quad (\text{A7})$$

where L is the likelihood, N_D is the number of different virus densities in any given experiment, N_T is the number of replicates, σ_i^2 is the observed variance in the fraction surviving the virus at virus density i , and f_{ij} is the fraction surviving the virus at virus density i in replicate j (ij thus specifies a particular bag). The variable q_i is the model prediction of the fraction surviving infection at virus density i , which is a function of the vector of parameters θ , where θ consists of the transmission parameter v for the classical model or the mean transmission parameter \bar{v} and the heterogeneity parameter k for the heterogeneity model, and P_i is virus density i . Variable q_i is equivalent to the right-hand side of the non-log-transformed version of equation (11) or (12) as appropriate, and thus depends on the param-

eters of each model. We therefore estimated the model parameters by iteratively adjusting them until we had maximized $\log L$, which in practice means minimizing the sum of the squared errors between the model and the data, weighted by the within-density variances.

As we describe in the main text, we assessed the goodness of fit of our two competing models using a lack-of-fit test, where each model is compared with a null model that assumes that at virus density P_i the expected survival rate is q_i , where q_i is allowed to be different for each density but is not modeled explicitly. The null model therefore has N_D parameters, where again N_D is the number of virus densities. From the asymptotic theory of likelihood-ratio tests, the statistic

$$C = -2\log(L_1/L_2) = 2(\log L_2 - \log L_1) \quad (A8)$$

is approximately chi-square with $N_D - n$ degrees of freedom, where n is the number of parameters in the specified model ($n = 1$ for the classical model and $n = 2$ for the heterogeneity model). Variable L_2 is the likelihood under the null model, and L_1 is the likelihood under the specified model. With the form of the likelihood given here, we have

$$C = SS_2 - SS_1, \quad (A9)$$

where SS_2 is the weighted sum of squares due to error under the null model, and SS_1 is the weighted sum of squares under the specified model. Large values of the χ^2 statistic C indicate that we should reject the null model in favor of the specified model.

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