How should pathogen transmission be modelled?

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Host–pathogen models are essential for designing strategies for managing disease threats to humans, wild animals and domestic animals. The behaviour of these models is greatly affected by the way in which transmission between infected and susceptible hosts is modelled. Since host–pathogen models were first developed at the beginning of the 20th century, the 'mass action' assumption has almost always been used for transmission. Recently, however, it has been suggested that mass action has often been modelled wrongly. Alternative models of transmission are beginning to appear, as are empirical tests of transmission dynamics.

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Transmission is the key process in a host–pathogen interaction. In most models of such systems, transmission is assumed to occur via so-called 'MASS ACTION' (see Glossary): if the density of susceptible hosts is represented as S, and that of infected hosts as I, the number of new infected hosts per unit area, per unit of time is βSI, where β is the TRANSMISSION COEFFICIENT. This βSI model assumes that infected and susceptible hosts mix completely with each other and move randomly within an arena of fixed size. If this is the case, there is a direct analogy between densities of susceptible and infected animals and concentrations of two chemical reagents[1,2], to which the law of mass action applies. Obviously, real animals do not behave in exactly the same way as molecules in solution; the question is whether they do so enough that the mass-action model is a good approximation. Until recently, the βSI model was used fairly uncritically in almost all host–pathogen and host–parasite models, except those for sexually transmitted diseases (STDs), although there was confusion over whether S and I represented numbers of hosts or densities of hosts (numbers per unit of area).

However, in 1995, de Jong *et al.*[3] published a paper that has been widely interpreted as claiming that βSI did not represent 'true mass action': rather it was a model of 'pseudo mass action', and transmission following 'true mass action' should be represented by $\beta SI/N$, where N is the total population size. Since then, models have appeared that use either form of transmission, and terminology has become confused. Sometimes βSI is described as 'mass action', sometimes it is called 'DENSITY-DEPENDENT TRANSMISSION'; sometimes $\beta SI/N$ is called 'mass action', sometimes it is called 'FREQUENCY-DEPENDENT TRANSMISSION'. Empirical studies comparing modes of transmission are only just beginning to appear.

Why does it matter?

One of the main conclusions reached by Anderson and May[4–7] was that there is a host density threshold N_T, below which a pathogen cannot invade a population of susceptible individuals. Such a threshold does not exist if transmission follows $\beta SI/N$ (Box 1). Culling to reduce the susceptible host population below N_T is a common policy for handling outbreaks of disease in wildlife or in domestic animals[8], but this will obviously fail if there is no host-density threshold.

The problem has escaped detailed examination by most authors because it is not crucially important for many problems in human disease. In developed countries, most pathogens cause little mortality. Total population size remains more or less constant as an epidemic passes through and the dynamics are the same whether transmission follows βSI or $\beta SI/N$. The effect of pathogens on animal populations is now receiving increased attention. In these systems, population size is a dynamic variable, because pathogens do cause significant host mortality.

The mode of transmission is crucially important for two reasons. First, it determines the probable response of the disease to control. Second, the objective in many models of disease in animals is to predict what will happen when a pathogen is introduced into a system in which it does not currently exist[9,10]. To parameterize these models, it is necessary to estimate the TRANSMISSION RATE based on information from one population, and apply it to another. Because any two animal populations will almost certainly differ in total size and density, it is vital to know how transmission scales with population size and/or density.

Pseudo mass action

One of the greatest sources of confusion is the introduction of the term 'pseudo mass action' by de Jong *et al.*[3] in 1995. They correctly pointed out that βSI only represents 'true mass action' if S and I represent densities of hosts (numbers per unit area). In that situation, the number of random encounters between a susceptible and an infected host per unit time will be proportional to the density of infected hosts I. However, if S and I represent actual numbers of hosts, and if the total host density remains constant as numbers of both classes of host change, the total number of encounters a randomly moving susceptible host has with other hosts will not change. The probability that the susceptible host acquires infection will depend on the proportion (I/N) of those encounters that are with infected hosts. Thus, the transmission rate in this situation, assuming 'true mass action', will be $\beta SI/N$. De Jong *et al.* labelled βSI in this case 'pseudo mass action'.

In practice, a situation in which numbers vary but density does not, on a small enough scale that all individuals in the population can interact, is probably unusual in wild populations. The question might,

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Box 1. Thresholds and the mode of transmission

The threshold for disease introduction is the minimum population size, or population density, of susceptible hosts necessary for the disease to increase. In a simple deterministic model, it can be worked out from the equation for the change in infected hosts, dI/dt (Eqn 1).

For example, given transmission of the form βSI,

$$\frac{dI}{dt} = \beta SI - dI \qquad [1]$$

where d is a parameter describing losses from the infective class, which might be either by death or recovery. If the pathogen is being introduced into an entirely uninfected population, then S, the number or density of susceptible hosts, will be equal to the current population size N, and I (number or density of infected hosts) will be small compared with N. dI/dt will be positive for small values of I if $\beta N > d$ or $N > d/\beta$.

Hence (Eqn 2)

$$N_T = \frac{d}{\beta} \qquad [2]$$

Depending on whether the model was formulated in terms of numbers or density, this will be either a threshold population size, or threshold population density for disease introduction. The BASIC REPRODUCTIVE RATE OF A DISEASE (see Box Glossary), R_0, is $\beta N/d$, and equals 1 when $N = N_T$.

If transmission is of the form $\beta SI/N$ (Eqn 3)

$$\frac{dI}{dt} = \beta SI/N - dI \qquad [3]$$

This will be positive for small I, and $S = N$, if $\beta > d$.

This condition does not involve N at all. If the transmission rate exceeds the loss rate of infected hosts d, the pathogen can become established, regardless of the host population density. In this case, the basic reproductive rate is $\beta I/d$, which is independent of N.

It is important to understand that N_T is a threshold for disease introduction into a population of entirely susceptible hosts. If a proportion of the host population has been vaccinated against disease, then $S \neq N$. For transmission of the form βSI, N_T will then be the population density or size of susceptible hosts, but for transmission in the form $\beta SI/N$, there will be a threshold proportion of susceptible hosts (Eqn 4),

$$\frac{S}{N} = \frac{d}{\beta} \qquad [4]$$

There has been much interesting work on the crucial community size for persistence of infections without 'fadeouts'[a,b]. However, fadeout is a stochastic phenomenon that has nothing to do with N_T and does not lead to any conclusion about whether transmission follows βSI or $\beta SI/N$.

Box Glossary

Basic reproductive rate of a disease: the number of new infections produced in the lifetime of an infected host when introduced to a wholly susceptible population of specified density. Conventionally denoted by R_0 and recently re-named the basic reproductive ratio, basic reproduction number and other variants, because it is strictly dimensionless (units are per disease 'generation'). The original term is retained here as sanctioned by usage and for compatibility with net reproductive rate or finite rate of increase of a macroorganism.

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therefore, be largely hypothetical. However, in one of their initial papers[6], Anderson and May used data from an experiment in which numbers varied, but the arena size was manipulated so that density remained constant. This might have initiated the confusion between host numbers and host density.

In general, transmission rates depend on the number of other individuals with which a given individual might interact. This means that the number of animals in a 'neighbourhood' of the target host is important, rather than the total number of individuals in the population. We therefore recommend that populations of hosts should be represented as densities – numbers per unit area or unit volume, rather than as actual counts. There are a few situations in which numbers might be more appropriate. For example, where disease transmission occurs between seals in discrete, compact colonies[11], it is reasonable to treat the entire colony as the 'neighbourhood' within which transmission occurs.

Modelling pathogen transmission

If S and I represent densities, rather than numbers, βSI does represent 'true mass action'. However, $\beta SI/N$, where N represents total host density, might still give a better representation of the rate of pathogen transmission. Several more complex relationships between the densities of both susceptible and infected hosts and pathogen transmission have also been proposed (Table 1, Fig. 1). For a DIRECTLY TRANSMITTED PATHOGEN, the rate at which new infections occur in a population is the product of three things: (1) the CONTACT RATE; (2) the proportion of those contacts that are with susceptibles; and (3) the proportion of such 'appropriate' contacts that actually result in infection.

The assumption underlying mass action is that the contact rate is directly proportional to density. At the other extreme, the contact rate might be independent of host density. Assuming that susceptible and infected hosts were randomly mixed, this would lead to transmission following $\beta SI/N$: on average, each susceptible S would make the same number of contacts regardless of host density, and a proportion I/N of these would be with infected hosts. This mode of transmission is often called 'frequency-dependent' or 'density-independent' transmission. It is often assumed in models of STDs, because the number of sexual partners of an individual usually depends on the mating system of the species and is weakly related to host density[12,13].

Various authors have proposed an asymptotic relationship between the contact rate and host density (Table 1). The Holling Type II FUNCTIONAL RESPONSE in

Table 1. Some proposed forms for the transmission function

Number	Function[a]	Comments	Refs
1	βSI	Mass action	4–7
2	$\beta SI/N$	Frequency-dependent transmission	13,15,29,30
3	$\beta S^p I^q$	Power relationship; Constants: $0 < p < 1$, $0 < q < 1$. Phenomenological	23,33–35
4	$\beta I(N - I/q)$; $I < qN$ 0; $I \geq qN$	Constant: $0 < q < 1$. Embodies a refuge effect (q = proportion of the population potentially susceptible, because of spatial or other heterogeneities)	16,28
5	$kS \ln\left(1+\frac{\beta I}{k}\right)$	Negative binomial. Small k corresponds to highly aggregated infection. As $k \to \infty$, expression reduces to βSI (mass action)	23,28,36
6	$\frac{N}{1-\varepsilon+\varepsilon N}\frac{F(S,I)}{N}$	Asymptotic contact function separated from the mixing term $F(S,I)$, which may be any of those above. If constant $\varepsilon = 0$, contacts are proportional to N. If $\varepsilon = 1$, contacts are independent of N	28,37–39
7	$\frac{\beta SI}{c+S+I}$	Asymptotic transmission. c is a constant	4,37–39

[a] I is the density of infected hosts, S is the density of susceptible hosts, and N is the total host density. β is the transmission rate. Other parameters, where necessary, are identified under comments.

predator–prey models[14] is an analogous idea[15]. At low densities, contacts are directly proportional to host density, but a maximum rate of contact is reached at very high densities. By contrast, the standard mass action TRANSMISSION FUNCTION, with contact rate proportional to density, is equivalent to a Holling Type I functional response. There are obvious and important parallels between contact rates in pathogen transmission and functional responses in predator–prey systems.

The proportion of all contacts that are between susceptible and infected hosts might differ from the random-mixing assumption that underlies both the mass action and frequency-dependent transmission models for several reasons. In both of these models, the assumption is that a proportion I/N of all contacts made by a susceptible host are with an infected host. Infection is, however, almost always patchy in space[16], meaning that, on average, each infected host is more likely to have infected neighbours than would be expected under random mixing, and correspondingly, susceptible hosts are less likely to have infected neighbours, decreasing the rate of

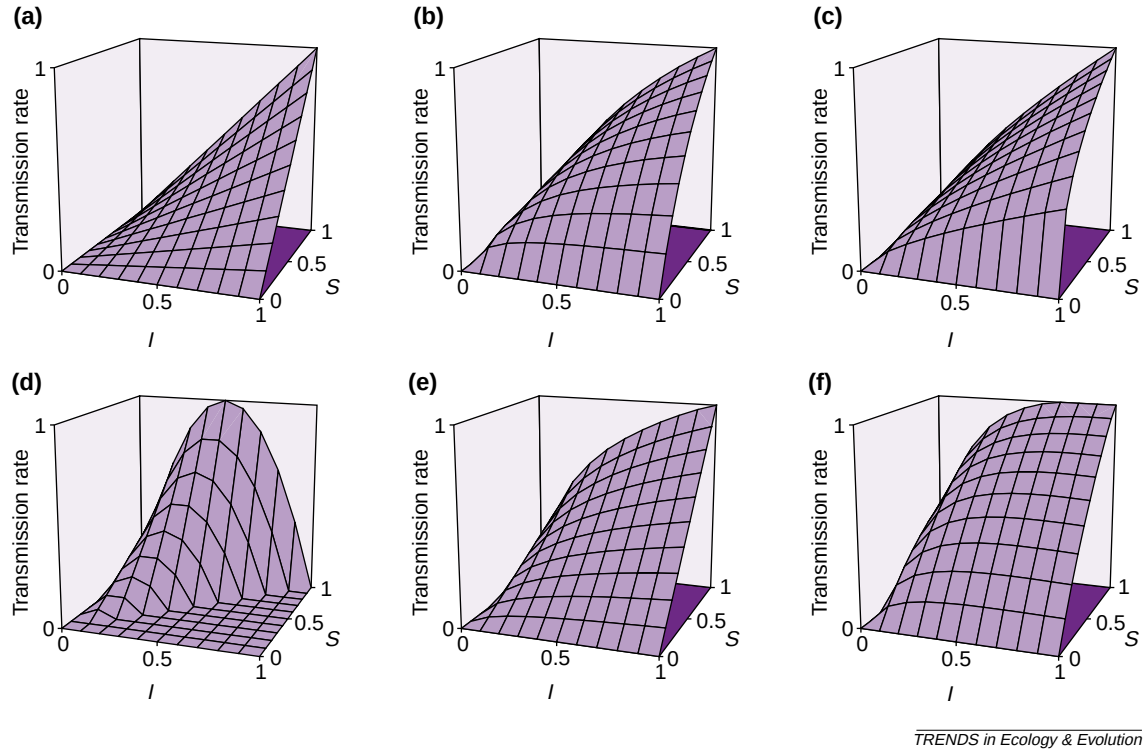

Fig. 1. Infection rates generated by the first six functions in Table 1, with illustrative parameters. The actual functions used are: (a) mass action SI, (b) frequency-dependent transmission $2SI/N$, (c) power relationship $S^{0.7}I^{0.4}$, (d) refuge effect $4I(N-2I)$, (e) negative binomial $0.33S\ln(1+20I)$, (f) asymptotic contact function plus negative binomial $S\ln(1+20)/(1-0.5+0.5N)$. Note that the last function in Table 1 (asymptotic transmission) appears almost identical to (c). The main differences in the functions presented is the obvious dome-shaped response to the density of infecteds in (d), and the linear responses to the density of susceptibles in (a), (d) and (e). I is the density of infected hosts; S is the density of susceptible hosts.

Box 2. More complex modes of transmission

Indirect transmission and vectors

Many pathogens are transmitted via a vector, often a biting arthropod. If the number of contacts between vectors and susceptible hosts is not dependent on host density, then the transmission rate of the pathogen will depend on the probability that the vector has previously been in contact with infected hosts[a]. This means that the transmission rate will depend on the proportion of infected hosts in the population, leading to frequency-dependent transmission.

Free-living infective stages

Infective stages of some pathogens can survive outside their host for extended periods. If this period is sufficiently long, cyclical behaviour in the host population might be produced[b], and the infective stages should be modelled explicitly. Transmission occurs if an infective stage is taken up by a susceptible host before the infective stage dies. If the period that infective stages survive is shorter than the lifespan of the host, this leads to asymptotic transmission.

Multiple host age classes and multiple species

The transmission rate of many pathogens varies between host age classes, social groups, or, for pathogens with more than one host, species. A useful way to describe transmission in such systems is with a 'who acquires infection from whom' (WAIFW) matrix[c]. This has elements β_{ij}, representing the rate at which infectives in class *j* infect susceptibles in class *i*. Usually, density dependent transmission is assumed, but there is no reason why other models should not be used in a WAIFW matrix. Dobson[d] discusses how to use a WAIFW matrix to describe interspecific transmission of rinderpest amongst mammals in the Serengeti.

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pathogen transmission. Theoretically, the infected hosts might be so clustered, or the supply of 'available' susceptibles so limited, that the infection rate might begin to decline at high densities of infected hosts.

Alternatively, there might be physiological heterogeneity in susceptibility. This produces a nonlinear relationship between time and number of new infections acquired. This is because the highly susceptible individuals tend to acquire infection first, with resistant individuals acquiring infection later, and at a slower rate[17]. Box 2 outlines ways of modelling transmission processes more complex than direct contact.

Estimating transmission rates

The transmission coefficient is the most difficult parameter to estimate in any host–pathogen model. Some attempts have been made to establish it 'bottom up' from *a priori* knowledge of host and disease behaviour, to predict probable disease dynamics and control in a host in which it had not yet become established[9]. De Leo and Dobson[18] have suggested a method based on ALLOMETRY that might provide order of magnitude estimates of the transmission rate in the absence of other data.

Two other approaches are more commonly used. One is to deduce the transmission coefficient and the form of the transmission function from results of experiments[19]. The second is to deduce it from observations of disease behaviour in the field, in particular PREVALENCE and dynamic responses to perturbations such as control of the host (such as culling). Finkenstädt and Grenfell[20] have recently developed a statistically rigorous method for estimating transmission rates from a time series of pathogen prevalence.

The quantity that is easiest to measure in practice is the 'FORCE OF INFECTION'. This is an empirical quantity that is usually a function of susceptible and infected host densities, whereas β is a parameter of some specified transmission model. Although it has various problems[21], the usual approach to estimating the force of infection is to introduce uninfected tracer animals and then determine whether they have become infected after a short period of time. The force of infection can also be deduced, in some cases, from age-prevalence data, using newborns as the uninfected tracers[22].

If the force of infection is estimated both at different host densities and at different relative abundances of susceptibles and infecteds, then it should be possible to deduce the forms of the transmission functions and/or CONTACT FUNCTION, as well as the values of the associated parameters. Ideally, densities of the various host categories should be manipulated, rather than merely observed. We know of no published cases, however, where this has been accomplished in the field with free-ranging hosts.

Evidence for modes of transmission

Several laboratory studies have found that the βSI model is inadequate for describing pathogen transmission. Knell *et al.*[23] investigated transmission of the bacterium *Bacillus thuringiensis* in the meal moth *Plodia interpunctella* and also investigated transmission of a granulosis virus in the same host[24]. Both these pathogens are transmitted in *P. interpunctella* by cannibalism of infected cadavers. Assuming mass action, in both cases, the estimated β increased with susceptible host density and decreased with the density of infected cadavers. For the granulosis virus, either negative binomial

transmission, or a power relationship (Table 1), were markedly superior to density-dependent or frequency-dependent transmission. Because transmission of these pathogens requires cannibalism, a predation event, it is perhaps not surprising that transmission models based on a simple type I functional response did not fit observed data well, because type I responses are rarely adequate for predator–prey interactions.

D'Amico *et al.*[25] used a small-scale field experiment with bagged populations of gypsy moth *Lymantria dispar* larvae on red oak *Quercus rubra* trees exposed to varying levels of gypsy moth nuclear polyhedrosis virus (NPV). D'Amico *et al.* fitted a mass-action model and found that the estimated transmission coefficient declined with both infected and susceptible host densities, showing that the mass-action model was inadequate to describe the transmission process.

Bouma *et al.*[26] designed a series of experiments in which domestic pigs were exposed to pseudorabies virus in pens. In three of the experiments, ten pigs were used in enclosures of 8.5 m^2, but in the fourth, there were 40 pigs in an enclosure four times as large. Thus, population density was constant, although actual numbers per enclosure varied. Bouma *et al.* found that the transmission rate was approximately the same in all cases, and claimed that the 'pseudo mass-action' model was therefore rejected. As only one density of pigs was used, the way in which transmission scaled with density cannot be determined from this experiment.

Reeson *et al.*[27] used field experiments to investigate transmission of NPV in larvae of the African army-worm *Spodoptera exempta*. They used three larval densities per plant, equal infective doses, and larvae reared in both crowded and solitary conditions, and then estimated the transmission parameter, assuming mass action. Their conclusion was that rearing density affected the transmission parameter, but density per plant in the experiment did not. The startling conclusion of this study is that density might affect the 'susceptibility' component of transmission, rather than the 'contact' component.

Each of these small-scale experiments showed that simple mass action did not describe transmission adequately. An appropriate alternative model applicable to all cases cannot be identified. A more fundamental problem is that it is difficult, if not impossible, to translate estimated rates, or even functional forms of transmission dynamics, from small-scale, homogeneous enclosures to large-scale, heterogeneous landscapes.

An alternative approach to deducing the nature of transmission dynamics is to compare the fit of alternative transmission models to observed disease dynamics. Barlow[16,28] showed that simple mass action failed to generate disease behaviour that matched observations for bovine TB in brushtail possums *Trichosurus vulpecula*, suggesting a negative binomial alternative[27]. Begon and co-workers[29,30] concluded that $\beta SI/N$ is a better descriptor of transmission dynamics than is density-dependent transmission βSI for cowpox in bank voles *Clethrionomys glareolus* and wood mice *Apodemus sylvaticus*. In their study, S and I represent numbers in 1-ha study plots embedded in larger areas of suitable habitat. This means that S and I represent densities, rather than numbers in a closed population, so mass action is not an appropriate description of transmission.

Dobson and Meagher[31] compared models with density-dependent and frequency-dependent dynamics to the observed epidemiology of brucellosis in the bison *Bison bison* herd of Yellowstone National Park (USA). Although both transmission models captured the qualitative dynamics adequately, frequency dependence more accurately predicted the observed level of disease prevalence. Finally, de Jong *et al.*[3] reanalysed data from the *Pasterella muris* laboratory epidemic in mice modelled by Anderson and May[6], and concluded that both frequency-dependent and density-dependent transmission models fitted the data equally well.

Increasingly, the weight of evidence is that simple mass action is not an adequate model in many situations. A clear default alternative has yet to emerge. We also are still a long way from being able to use transmission parameters estimated for a particular host–pathogen pair in one environment for the same pair in a different environment, particularly if densities are also different. This is of concern for exotic disease contingency planning.

Box 3. Recommendations

- Because of the confusion it has engendered, do not use the term 'pseudo mass action'.
- When constructing or using disease models, explicitly state and justify the form of transmission used (in words or equations) and state whether S, I and N are numbers or densities.
- Evaluate several alternative models of transmission, if possible.
- Estimate the force of infection, which is a quantity that can often be measured directly. In general, this will be a function of the density and distribution of both susceptible hosts and infectious stages. If both of these densities are varied, then the form of the transmission function can be deduced.

The future

Box 3 summarizes our recommendations based on the current state of knowledge, but how should we progress into the future? Pathogen transmission is a process involving spatial proximity. Spatially explicit models are probably necessary to describe transmission adequately[32], and the mode of transmission might well vary according to the spatial scale used[11]. There is a desperate need for more relevant experimental and observational data on transmission dynamics because models of disease transmission and disease dynamics generally outnumber sets of actual data.

Glossary

Allometry: the phenomenon of a variable *Y* scaling with body size *X*, following a relationship of the form $Y = aX^b$, where *a* and *b* are constants.
Contact function: the relationship between contact rate and total population density.
Contact rate: the number of potentially infectious contacts made per infected host per unit time. A potentially infectious contact is one that is capable of resulting in infection if contact is with a susceptible.
Density-dependent transmission: transmission in which the number of new infections per unit time is proportional to the product of the density of infected hosts *I* and the density of susceptible hosts *S*. Synonymous with mass action.
Directly transmitted pathogen: a pathogen in which transmission stages pass directly, and almost instantaneously, from one host to the next, either via physical contact, or via vapour droplets over a very short distance.
Force of infection: the per capita rate at which susceptible hosts acquire infection.
Frequency-dependent transmission: transmission in which the number of new infections per unit time is proportional to the product of the density of infected hosts (I) and the proportion (or frequency) of hosts that are susceptible (S/N).
Functional response: the relationship between the rate at which a predator eats prey, and the density of that prey. A type I response is a positive linear relationship (in practice, with an abrupt upper limit). Type II is an asymptotic form, with the asymptote corresponding to predator satiation.Type III is an S-shaped response also with an upper asymptote.
Mass action: synonymous with density-dependent transmission.
Prevalence: the proportion of individuals in a population carrying a pathogen.
Transmission coefficient: conventionally denoted by β, the constant of proportionality in density-dependent or frequency-dependent transmission or, in more complex forms, of the transmission function.
Transmission function: the function that relates the transmission rate to the densities of susceptible and infectious or infected hosts (e.g. density dependent or mass action and frequency dependent are two forms for the transmission function).
Transmission rate: the number of new infections per unit time. If variables representing host classes are densities per unit area, the transmission rate will likewise be the number of new infections per unit area, per unit time.

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