review article

Population biology of infectious diseases: Part I

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If the host population is taken to be a dynamic variable (rather than constant, as conventionally assumed), a wider understanding of the population biology of infectious diseases emerges. In this first part of a two-part article, mathematical models are developed, shown to fit data from laboratory experiments, and used to explore the evolutionary relations among transmission parameters. In the second part of the article, to be published in next week's issue, the models are extended to include indirectly transmitted infections, and the general implications for infectious diseases are considered.

ANY contemporary ecology text contains at least one chapter devoted to predator–prey interactions. The discussion typically embraces field and laboratory observations along with simple mathematical models, and emphasizes how the densities of both prey and predator populations may be regulated by their interaction.

In natural communities, however, an accumulating body of evidence suggests that parasites (broadly defined to include viruses, bacteria, protozoans, helminths and arthropods) are likely to play a part analogous, or at least complementary, to that of predators or resource limitation in constraining the growth of plant and animal populations. Examples from the laboratory are Park's[1] experiments in which the sporozoan parasite *Adelina* drastically reduced the population density of the flour beetle *Tribolium casteneum*, and in certain circumstances reversed the outcome of its competition with *T. confusum*, and Lancinani's[2] studies of the way the ectoparasitic water mite *Hydryphantes tenuabilis* influences the population dynamics of the aquatic insect *Hydrometra myrae*. Various studies have indicated the importance of infectious disease as a mortality factor in populations of wild mammals[3,4], and as possibly the predominant such factor in bird populations[5–7]. For example, among bighorn sheep in North America the main cause of death probably is infection by the lungworms *Protostrongylus stilesi* and *P. rushi*, which then predispose the hosts to pathogens causing pneumonia[8,9]. On a grand scale, Pearsall[10] and others suggest that the geographical distribution of most artiodactyl species in Africa today is largely set by a pandemic of rinderpest that occurred towards the end of the nineteenth century; the numerical simulations of Hilborn and Sinclair[11] confirm that rinderpest can have a big influence on wildebeest population levels. Several authors[3,5,12–20] have argued the general case for infectious diseases as regulators of their host populations.

More broadly, it is likely that interplay between the pathogenicity of viral, bacterial, protozoan or helminth infections and the nutritional state of the host contributes importantly to the density-dependent regulation of natural populations[13], with the parasites greatly amplifying the effects of low levels of nutrition. Such phenomena are largely responsible for the dramatic differences between age-specific survival probabilities for people in developed and underdeveloped countries[21,22]. Indeed, McNeill[23] and others[24,25] have speculated that many of the broader patterns of human history are to be interpreted in terms of the evolving relationships between man and his diseases.

Although there does exist a large and mathematically sophisticated literature dealing with the transmission dynamics of parasitic infections of many kinds, this literature[26–34] almost invariably assumes the host population to have some constant value, and then seeks to answer such questions as: Can the infection be stably maintained in the population? Is it endemic or epidemic? What is the time course (in terms of susceptibles, infectives and recovered individuals) of the infection when introduced into a virgin population? This assumption that the total host population is effectively constant derives from a history of medical interest in human diseases (predominantly in developed countries), where population densities do usually remain roughly constant on the time scale appropriate to the pathology of most diseases. On the other hand, in the ecological and parasitological literature attention has recently been given to the population dynamics of host–parasite associations, with particular emphasis on the way protozoan, helminth and arthropod parasites can depress the natural growth rate of their host populations[13–17,35]. Our review aims to weave together these medical and ecological strands, concentrating on the way parasitic infections can influence the growth rate of their host populations.

The article is being published in two parts. This first part begins with a survey of the diverse array of infectious organisms and of their associated life cycles. We then show how a very simple dynamic model can provide a remarkably detailed explanation of a classic series of experiments on infections in laboratory populations of mice. This success gives the confidence to enable us to proceed into areas less well supported by good data, and we next discuss microparasitic infections with direct life cycles in natural populations; particular attention is given to the evolutionary relations among transmission parameters, the factors which determine the pattern of disease behaviour within populations of hosts and the population consequences of acquired immunity.

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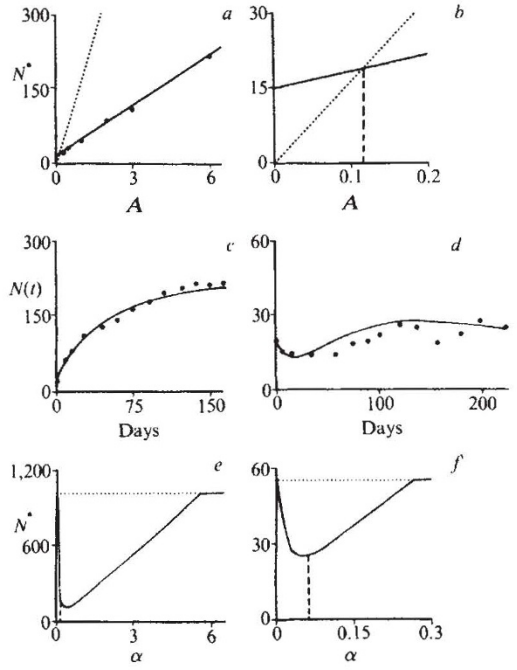

Fig. 1 Population dynamics of *Pasteurella muris* in colonies of laboratory mice. *a*, Relationship between the equilibrium population of mice N^* and the daily rate of input of susceptible mice A (solid dots are observed levels[46,47]; the solid line is the best linear fit, equation (6)). The dashed line shows the estimated relationship between N^* and A in the absence of the disease (the slope is $1/b$, where $b = 0.006$). *b*, An enlargement of that portion of (*a*) where solid and dashed lines intersect, determining the threshold level of immigration A_T, equation (5), below which the disease will not persist. *c*, *d*, Growth of mouse colonies harbouring the disease, from an initial population of 20 mice, for $A = 6.0$ and 0.33, respectively (again, solid dots are the experimental data, and the solid lines are the theoretical predictions described in the text). *e*, *f*, Relationship between the equilibrium population of mice N^* and the disease-induced mortality rate α, as predicted by equations (1)–(3), for $A = 6.0$ and 0.33, respectively. The dotted vertical line shows the actual value of α for *P. muris*.

In the second part of the article[36], we begin with a discussion of macroparasitic infections with direct life cycles in natural populations. Extensions to parasites with indirect life cycles are then briefly indicated, with emphasis on the way the ecology of the general evolutionary trends. Finally, we survey the main mechanisms that can produce cyclic patterns, or multiple stable states, in the levels of infection in the host population.

Diversity of agents causing disease

By using the term 'parasitic infection' to include all organisms—viruses, bacteria, protozoans, helminths and arthropods—on the US Centre of Disease Control's list, we are encompassing a great diversity of life forms and of associated population parameters. Broadly, however, two classes may be distinguished:

Microparasites (viruses, bacteria, protozoans) are characterised by small size, short generation times, extremely high rates of direct reproduction within the host, and a tendency to induce immunity to reinfection in those hosts that survive the initial onslaught[37]. The duration of infection is typically short in relation to the expected lifespan of the host, and therefore is of a transient nature (there are, of course, many exceptions, of which the slow viruses[38] are particularly remarkable).

Macroparasites (parasitic helminths and arthropods) tend to have much longer generation times than microparasites, and direct multiplication within the host is either absent or occurs at a low rate. The immune responses elicited by these metazoans generally depend on the number of parasites present in a given host, and tend to be of relatively short duration[39,40]. Macroparasitic infections therefore tend to be of a persistent nature[13], with hosts being continually reinfected.

Both microparasites and macroparasites may complete their life cycles by passing from one host to the next either directly or indirectly via one or more intermediate host species. Direct transmission may be by contact between hosts (for example, venereal diseases) or by specialised or unspecialised transmission stages of the parasite that are picked up by inhalation (such as common colds), ingestion (such as pinworm) or penetration of the skin (such as hookworm). Indirect transmission can involve biting by vectors (flies, mosquitos, ticks, and others) that serve as intermediate hosts, or penetration by free-living transmission stages that are produced by molluscan or other intermediate hosts. In other cases, the parasite is ingested when an infected intermediate host is eaten by the predatory or scavenging primary host. A special case of direct transmission arises when the infection is conveyed by a parent to its unborn offspring[41] (egg or embryo), as can occur in syphilis and rubella and for many viral infections of arthropods; this process has been termed 'vertical transmission', in contrast to the variety of 'horizontal transmission' processes discussed above.

The natural historian's main concern is often the recondite biological details that make each parasitic infection unique. In contrast, our aim is to understand the basic similarities and differences in terms of: the number of population variables (and consequent equations) needed for a sensible characterisation of the system; the typical relations among the various rate parameters (such as birth, death and recovery rates, transmission coefficients); and the form of the expressions describing the transmission processes. In the absence of such a unified framework, each disease tends to develop its own arcane literature.

Experimental epidemiology: infectious diseases as regulators of laboratory populations of mice

Although there are relatively few studies of the influence of disease upon the dynamics of laboratory populations[1,2,42–45], there is a remarkably detailed body of work of Greenwood *et al.*[46,47], subsequently extended by Fenner[48,49]. These experiments, on laboratory populations of mice infected with various viral and bacterial diseases, have some simplifying features which make them particularly amenable to theoretical analysis. Specifically, the space available to the mice was adjusted to keep the population density constant as absolute levels changed; in addition adult mice were introduced at specified rates, so that the basic process was an immigration–death one (removing the time lags and other complications attendant upon recruiting to the population by natural birth processes). In short, many density-dependent complications are avoided by the design of the experiments.

We now outline a simple model that captures the essentials of these experiments, and discuss its fit to the data for two microparasites: one a bacterium (*Pasteurella muris*); the other a virus (ectromelia, a poxvirus). Both parasites multiply directly within the host and induce a long-lasting immunity to reinfection (mice show some loss of immunity to reinfection by *Pasteurella*, but the immunity to ectromelia seems to be lifelong).

Using notation that will be standard throughout this review, we define the absolute number of susceptible (uninfected), infected and immune mice to be X, Y and Z, respectively. The total number of mice, $N = X + Y + Z$, is not assumed to be some independently-set constant, but is set by the dynamics of the infection. A is defined as the rate at which mice are introduced ($A = 2$ means 2 mice introduced per day), and b the natural mortality rate; in the absence of the disease, the mouse population will equilibrate at around $N^* = A/b$. The infection is a direct one, for which the conventional assumption is that the rate at which mice acquire the infection is proportional to the number of encounters between susceptible and infected mice, being βXY where β is some 'transmission coefficient'. The mortality rate for infected mice is taken to be $b + \alpha$, with α

Table 1 The influence of various types of directly transmitted microparasites on host population growth

Type of disease	Growth characteristic (disease regulates host population if expression is negative)	Threshold host population, for successful introduction of the disease
Horizontal transmission		
No immunity ($\gamma \to \infty$)	$r-\alpha$	$(\alpha+b+v)/\beta$
Life-long immunity ($\gamma = 0$)	$r[1+(v/b)]-\alpha$	$(\alpha+b+v)/\beta$
Transient immunity (duration $1/\gamma$)	$r[1+v/(b+\gamma)]-\alpha$	$(\alpha+b+v)/\beta$
Transient immunity and an incubation (latent) period of duration $1/\sigma$	$r\left[1+\frac{v}{(b+\gamma)}+\frac{(\alpha+b+v)}{\sigma}\right]-\alpha$	$\frac{(\alpha+b+v)(b+\sigma)}{\beta\sigma}$
Transient immunity and disease eliminates reproduction of infected class	$rv/(b+\gamma)-(b+\alpha)$	$(\alpha+b+v)/\beta$
Transient immunity and disease reduces birth rate of infected class to fa	$r\left[\frac{fa-b}{r}+\frac{v}{(b+\gamma)}\right]-\alpha$	$(\alpha+b+v)/\beta$
Vertical (and horizontal) transmission		
Transient immunity and all births from infected class are also infected	$r[1+v/(b+\gamma)]-\alpha$	$(\alpha+b+v-a)/\beta$; threshold is zero if $a>\alpha+b+v$
Transient immunity and a fraction f of births from infected class are also infected	$r[1+v/(b+\gamma)]-\alpha$	$(\alpha+b+v-fa)/\beta$; threshold is zero if $fa>\alpha+b+v$

representing the mortality caused by the disease; there is also a recovery rate v. Recovered mice are initially immune, but this immunity can be lost at a rate γ (for permanent immunity, as for ectromelia, $\gamma = 0$). These assumptions lead to the following equations for the dynamics of the infection:

$$dX/dt = A - bX - \beta XY + \gamma Z \quad (1)$$

$$dY/dt = \beta XY - (b+\alpha+v)Y \quad (2)$$

$$dZ/dt = vY - (\gamma+b)Z \quad (3)$$

Adding all three, the equation for the total population of mice is

$$dN/dt = A - bN - \alpha Y \quad (4)$$

This system of equations (which is similar to that illustrated schematically by Fig. 3) differs from usual epidemiological models in that N is a dynamical variable, rather than some specified constant.

The equations have a stable equilibrium solution with the disease maintained in the population if, and only if,

$$A/b > (\alpha+b+v)/\beta \quad (5)$$

Failing this, the disease dies out, and the population settles to its immigration–death equilibrium value at $N^* = A/b$. If equation (5) is satisfied, the disease persists, and the total population is depressed below this infection-free level to the lower value

$$N^* = \frac{A + D(\alpha+b+v)/\beta}{b+D} \quad (6)$$

Here D is defined for notational convenience as

$$D = \alpha/[1+v/(b+\gamma)] \quad (7)$$

Note that the important threshold phenomena, which enter directly when N is a specified constant[26,31–34,50], appear in a more subtle form when N is itself determined by the dynamics of the disease.

In their experiments on the maintenance of pasteurellosis, *P. muris*, in mouse populations Greenwood *et al.*[45,46] introduced new mice at rates ranging from $A = 0.33$ to $A = 6$ mice per day. The quantities b, α and v can be crudely estimated from life tables for uninfected populations, and from case mortality and recovery rates (we get $b \simeq 0.006$, $\alpha \simeq 0.06$, $v \simeq 0.04$ days^{-1}). Direct estimate of the parameters β and γ is more difficult.

Using data from Greenwood *et al.*[46,47] (and reanalysing to discard the transient initial population values en route to the steady state), we obtain the experimental results shown in Fig. 1*a* for the equilibrium mouse population N^* as a function of A. These data accord well with the linear relation between N^* and A predicted by equation (6). Furthermore, the parameters β and γ may now be roughly estimated from the fit between the theoretical straight line, equation (6), and the data for N^* versus A (we estimate $\beta \simeq 0.0056$, $\gamma \simeq 0.021$ days^{-1}).

In Fig. 1*a*, the dashed line depicts the equilibrium mouse population in the absence of the disease, $N^* = A/b$. The intercept of this line with the linear fit to the data for N^* in the presence of the disease yields the threshold immigration rate, A_T, below which equation (5) is violated and the disease cannot persist; Fig. 1*b* magnifies this aspect of Fig. 1*a*. We estimate $A_T \simeq 0.11$ mice per day (corresponding to an equilibrium population of about 19 mice). Greenwood *et al.* suggested *P. muris* was always maintained in mice populations, but their lowest introduction rate was $A = 0.33$.

With β and γ determined from Fig. 1*a*, we now have a parameter-free prediction of the temporal development of the infection for any initial number of mice $N(0)$ and introduction rate A. Two such fits between theory and data are shown in Figs. 1*c* and 1*d*, for $A = 6$ and $A = 0.33$, respectively. Note the propensity to damped oscillations at relatively small A values. Bearing in mind the complete absence of adjustable parameters, both the fits are extremely encouraging, and strongly suggest that simple deterministic models can be useful even when the host population is small.

How much does the disease depress the mouse population below the level that would pertain in its absence? This general question is answered in Fig. 1*e* and *f*, which shows N^* as a function of disease pathogenicity α, for $A = 6.0$ and $A = 0.33$ respectively. Two significant points emerge.

First, the maximum depression of the host population is achieved by a disease of intermediate pathogenicity[51]. Too small an α has little effect on N^*, while too large an α violates equation (5) and makes it impossible for the disease to persist. The dashed vertical lines in Fig. 1*e* and *f* show the actual value for α for *P. muris*.

Second, note that the higher the immigration rate A, the greater the degree of depression of the host population (relative

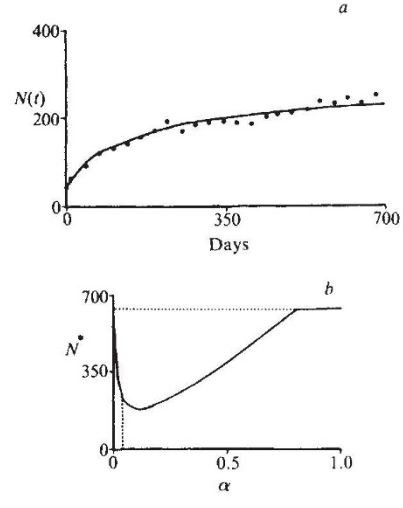

Fig. 2 Population dynamics of ectromelia in colonies of laboratory mice. The data[46,48,49] indicate $b = 0.005$, $\alpha = 0.042$, $\beta = 0.0013$, $v = 0.014$, $\gamma = 0$; the rate of introduction of susceptible mice was always $A = 3$ (all quantities in units of day^{-1}). *a*, Growth of a mouse colony harbouring the disease, from an initial population of 45 mice (dots and solid curve as in Fig. 1*c*, *d*). *b*, Depression of the equilibrium population of mice N^* as a function of pathogenicity α for ectromelia, analogous to Fig. 1*e*, *f*.

to the disease-free equilibrium value). This suggests that diseases caused by microparasites are more likely to persist within, and cause severe reduction of, host populations with high birth (or immigration) rates; this phenomenon derives essentially from the high inflow of susceptibles.

Greenwood *et al.*[46], and later Fenner[48,49], also studied the effects of the mouse pox virus, ectromelia. An analysis, akin to that just outlined, leads to similarly encouraging agreement between our simple theory and the experimental data for ectromelia in laboratory populations of mice. Some of these results are summarised in Fig. 2.

For both *P. muris* and ectromelia, the actual value of the pathogenicity parameter α (indicated by the dashed vertical lines in Figs 1*e*, *f* and 2*b*) lies around the value that induces maximum depression of the host population. Is this coincidence, or does it reflect evolutionary pressures? The question is intriguing, but difficult to pursue in the absence of a larger body of information about a wider range of diseases.

In brief, the theory and the facts of these experiments are in accord in showing how infectious diseases can stably regulate their host populations below disease-free levels. They also show the existence of a critical host density (directly tied to the rate at which new susceptibles are introduced, either artificially in the laboratory, or by births in the natural world), below which the infection cannot be maintained. In this sense, equation (5) replaces the threshold condition of conventional epidemiological models in which the host population is an independently determined constant.

Microparasitic infections as regulators of natural populations

The models discussed above are only half-way to a fully dynamic description of host–parasite interactions. Although the death rates are set by natural processes, and are influenced by the parasites, the 'birth' processes are determined artificially by the rate of introduction of new mice. We now consider what happens when the birth rates are also set by natural processes intrinsic to the host population.

To begin with, we focus on diseases caused by microparasites that are transmitted directly, and ask three main questions: what biological characteristics of an infection determine its impact on host population growth; what are the population consequences of immunological responses; and what conditions lead to endemic or to epidemic infections?

Consider the simple situation of an infection whose transmission processes are as described by equations (1)–(3), except that now the new individuals arise by natural births. This situation is illustrated schematically in Fig. 3. If the *per capita* birth rate is a, independent of whether the individual is susceptible, infected or immune, then the net birth rate term is $a(X+Y+Z)$, and the dynamical system of equations (1)–(3) is replaced by

$$dX/dt = a(X+Y+Z) - bX - \beta XY + \gamma Z \quad (8)$$

$$dY/dt = \beta XY - (\alpha + b + v)Y \quad (9)$$

$$dZ/dt = vY - (b+\gamma)Z \quad (10)$$

The total population of hosts, $N = X+Y+Z$, obeys

$$dN/dt = (a-b)N - \alpha Y \quad (11)$$

Equivalently it is useful to define the intrinsic growth rate $r = a-b$ of the disease-free population and to write $y = Y/N$ as the 'prevalence', or fraction of the host population that are infected. This gives

$$dN/dt = (r - \alpha y)N \quad (12)$$

One of two circumstances now arises. If

$$\alpha > r\left[1 + \frac{v}{b+\gamma}\right] \quad (13)$$

the disease regulates the host population to a stable value N^*. This disease-determined population level is

$$N^* = \frac{\alpha(\alpha+b+v)}{\beta[\alpha - r(1+v/\{b+\gamma\})]} \quad (14)$$

Of this steady population, the fraction infected is given trivially from equation (12) as

$$y^* = r/\alpha \quad (15)$$

Conversely, if equation (13) is not satisfied, the system of equations (8)–(10) eventually settles to a state in which the total population grows exponentially at a rate ρ given by

$$\rho = [B^2 - (b+\gamma)(\alpha - r) + rv]^{1/2} - B \quad (16)$$

with $B = \frac{1}{2}(\alpha + b + v + \gamma - r)$. This population growth rate is necessarily less than the disease-free one, $\rho < r$. Asymptotically, the exponentially growing total population contains a constant number of susceptibles X, with essentially all individuals being infected or immune. The asymptotic prevalence of infection is

$$y \equiv Y/N \to (r-\rho)/\alpha \quad (17)$$

Note the similarities and differences between these conclusions and those for conventional models[26,31–50] in which the total population is set at some constant value. In this crude model there are no density-dependent regulatory effects other than the

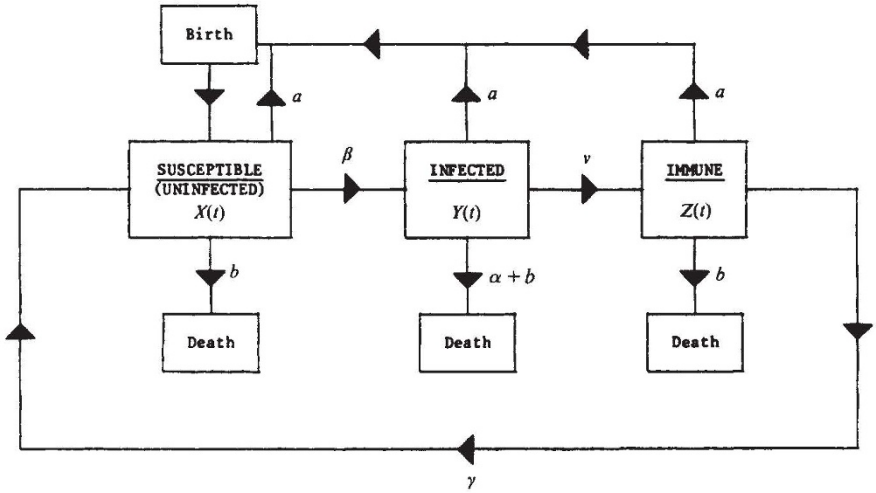

Fig. 3 Diagrammatic flow chart for a directly transmitted infection, described by a compartment model with susceptible (X), infected (Y), and immune (Z) hosts. The flow of individual hosts between compartments is controlled by a set of rate parameters: *per capita* birth rate, a; natural death rate of hosts, b; disease-induced mortality, α, acting on infected hosts; recovery rate, v; transmission rate per encounter between susceptible and infected hosts, β; rate of loss of immunity, γ.

Table 2 Population characteristics of some common directly transmitted microparasites of man (data from refs 66–69)

Parasite	Incubation period (days)	Duration of infectiousness (communicability) (days)	Infectiousness	Duration of immunity	Lifespan of infective stage	Case mortality rate (pathogenicity)	Transmission (H = horizontal V = vertical)
Measles virus	9–12	5–7	High	Lifelong	Very short	Low–high	H
Smallpox virus	12–14	10	Medium	Lifelong	Long	High	H
Rubella virus	17–20	14	Medium	Lifelong	Very short	Low	H, V
Mumps virus	10–20	7	Medium	Lifelong	Short	Low	H
Bordetella pertussis (whooping cough)	7–10	14+	High	Lifelong	Very short	Medium	H
Polio virus	5–20	Long	High	Lifelong	Medium	Medium	H
Varicella zoster virus (chicken pox and shingles)	13–17	20–30	High	Lifelong	Very short	Low	H (V)
Herpes simplex virus	5–8	Long	Medium	Lifelong	Very short	Very low	H, V
Cytomegalovirus	Long?	Long	Medium	Lifelong	Very short	Very low?	H, V
Epstein–Barr virus	10?	Long?	Medium	Lifelong	Very short	Very low?	H
Clostridium tetani (tetanus)	7+	21–30	Low	Lifelong	Long	High	H
Salmonella typhi (typhoid)	10–14	30+	Low	Short	Medium	High	H
Bacillus anthracus (anthrax)	3–7?	?	Low	Long	Very long	Very high	H
Corynebacterium diphtheriae (diptheria)	2–6	20	Medium	Long	Medium	High	H

disease itself and the population 'runs away' (maintaining the disease within it) at the diminished rate ρ if α is too small to satisfy equation (13). Conversely, if equation (13) is fulfilled, the population settles to the value N given by equation (14). In either case, if N is initially less than a threshold value,

$$N_T = (\alpha + b + v)/\beta \quad (18)$$

then initially Y will decrease and X will increase exponentially at the rate r. However, once X exceeds N_T on this trajectory of exponential increase, then Y will increase, and the system either will converge (steadily or with damped oscillations) on the N^* of equation (14), or will grow at the slower rate ρ of equation (16). Thus the familiar threshold phenomena are found within the more dynamic system of equations (8)–(10).

Equation (13) is clearly a key one. It can be modified to take into account the known biology of a wide range of directly transmitted microparasitic infections. Without discussing the derivations, Table 1 lists the criterion for ability to regulate the host population (generalising equation (13)), and the threshold expression (generalising equation (18)), for a variety of such refinements, including *inter alia* the effects of incubation periods, vertical transmission, and infections that reduce host reproduction.

Several general points emerge from Table 1. (1) For a disease to regulate the host population, the case mortality rate α must be high relative to the intrinsic growth rate r of the disease-free host population. Ability to achieve this degree of regulation is decreased by lasting immunity (γ small) and high rates of recovery from infection (v large, corresponding to infections of short duration). (2) Diseases with long incubation periods, where hosts are infected but not infectious, have less impact on population growth. (3) Diseases which affect the reproductive capacities of infected hosts are more liable to suppress population growth. (4) Vertical transmission lowers the magnitude of the threshold population, N_T needed for successful introduction of the disease; vertical transmission also lowers the equilibrium population of the host in those cases where it is regulated by the disease. (5) The threshold density below which the disease cannot persist within the host population is set by the rate of loss of hosts from the infected class divided by the rate of transmission; high threshold densities are therefore required for the maintenance of diseases with short durations of infection, long incubation periods and high case mortality rates.

Population consequences of immune responses

Although the nature of immunological responses by individual hosts to specific pathogens has received much attention in recent years[37,40,52], relatively little thought has been given to the population consequences of acquired immunity[26,32,53] (sometimes called 'herd immunity' effects). The general insights just culled from equations (13)–(18) can be usefully illuminated by a numerical example. Figure 4*a* shows the growth of a fictitious human population (from an initial size of 50,000) subject to a virus disease and under various assumptions about the duration of immunity. The vital rates and transmission parameter values are as detailed in the figure caption. In more homely terms, they represent a growth rate of the disease-free population of around 3% per annum, a case mortality of about 30% (similar to measles in malnourished human populations with no previous exposure[54]), duration of the infection around 4 weeks, and a transmission coefficient β that implies a threshold population density of $N_T \simeq 380{,}000$ people.

In all cases in Fig. 4*a*, the disease is not maintained and the population grows at its intrinsic 3% rate if it is below the threshold value N_T. Above this point, the population's fate depends on the nature of the immune response. If the duration of the immunity to reinfection ($1/\gamma$) is of short to medium length (less than about 20 yr), the disease is able to regulate the host population at the stable level N^* of equation (14). If the disease induces hardly any immunity (γ large), this equilibrium level N^* will be close to the threshold N_T for maintenance of the disease. Conversely, if the duration of immunity is above 20 yr, the population continues to grow exponentially at some rate lower than 3%; life-long immunity ($\gamma = 0$, as for measles) results asymptotically in 1.6% per annum growth. This example makes plain the important part immunity plays in determining the population consequences of a disease.

The qualitative patterns revealed in Fig. 4*a* are reminiscent of those shown by human population growth[55,56] between the beginning of the Agricultural Revolution (some 10,000 years ago) and the onset of the Industrial-Scientific Revolution (around 300 years ago). In the first 5,000 yr, the global population increased about 20-fold, from around 5 million to around 100 million. The next 5,000 yr saw only a roughly 5-fold increase to around 500 million in the sixteenth century. It may not be unduly fanciful to speculate that the rise of human conglomerations to levels capable of maintaining directly transmitted microparasitic diseases, and the accompanying depression of population growth rates, is at least partly responsible for the observed patterns.

Epidemic and endemic patterns of diseases

Epidemic diseases are characterised by rapid changes in the prevalence of infection. Often such infections disappear from a particular host population for short or long periods. Conversely, endemic infections persist for long times, showing relatively little fluctuation in prevalence. Note that in our dynamic models, equations (8)–(10), the disease always becomes endemic, in the sense that the host population grows to the level $N > N_T$, whereupon the disease is maintained. The prevalence settles to the steady value $y^* = r/\alpha$ if the disease controls the population, and to $y^* \to (r - \rho)/\alpha$ if the population still grows.

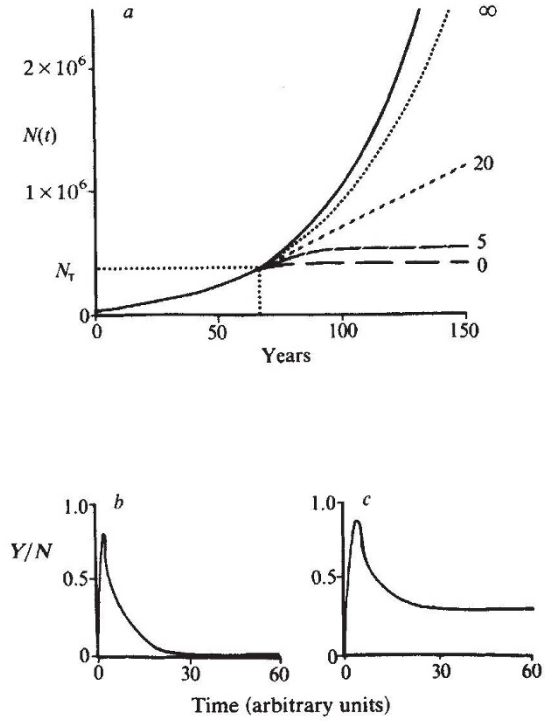

Fig. 4 *a* An illustration of the way the duration of immunity influences the dynamics of host population growth, $N(t)$, for a hypothetical disease; the various population parameters are assumed to be $r = 0.03$, $b = 0.015$, $v = 13.0$, $\alpha = 6.0$, $\beta = 5 \times 10^{-5}$ (all per year), and $N(0) = 50{,}000$. The solid line depicts the population growth in the absence of the infection. The four broken lines depict the effects of immunity of varying duration, namely (as labelled): $1/\gamma = \infty$ (lifelong); $1/\gamma = 20$ yr; $1/\gamma = 5$ yr; and $1/\gamma = 0$ (no immunity). *b*, Temporal changes in the prevalence of infection, Y/N, following the introduction of the above disease into a virgin population of hosts where the equilibrium prevalence level is low. *c* As for (b), except now the equilibrium prevalence is relatively high.

It is well known, however, that diseases which induce long-lasting immunity often exhibit periodic or episodic 'face out', even within relatively large host populations[26,30,57–61]. In particular, the classic work of Bartlett[62,63] on measles epidemics has suggested the importance of stochastic effects in determining whether a disease will persist endemically or as recurrent epidemics.

Without entering into the detailed complications of a stochastic formulation, we can use the above model to get some qualitative insights about these patterns. Of particular importance is the rate at which new susceptibles appear; hence the general correlation between endemicity and host population size[64], and the observation that the host birth rate is central. Specifically, consider the case where the hosts' intrinsic growth rate is much smaller than the case mortality rate, $r \ll \alpha$. Then, if $N > N_T$, introduction of the infection results in a classical epidemic (see Fig. 4*b*): the prevalence first rises, attains a peak, and then falls to the value given by equation (15) or equation (17), which in either case is very small. That is, if $r \ll \alpha$, it is likely that prevalence settles to be so small as to give a high probability for stochastic 'fade out' and epidemicity. This can be true even for diseases potentially capable of regulating the host population, if r/α and N^* are both sufficiently small. In addition, epidemics can occur even when $r > \alpha$ if the disease does not regulate the host population but merely slows its growth rate slightly, so that $r - \rho \ll \alpha$ (the details of the interplay among parameters that leads to $\alpha + \rho \gg r > \alpha$ are complicated, and can be deduced from equation (16) for ρ). On the other hand, if neither r nor $r - \rho$ is a lot smaller than α, the disease is likely to be endemic, with relatively high values of y^* making stochastic extinction of the disease improbable[62,63,65,66]. This circumstance is depicted in Fig. 4*c*.

Thus infections of short duration which induce lasting immunity will tend to exhibit epidemic patterns. The classic 'epidemic' disease such as measles, rubella and pertussis are of this character[67–70]. As also stressed by Yorke *et al*[32], a broader examination of viral and bacterial infections of man clearly supports this point (see Table 2). Many authors[57,58,71] have observed that such infections are probably diseases of modern societies; in primitive societies the net inflow of susceptibles into small communities was probably too low to maintain the diseases.

Other infectious agents (for example, herpes simplex virus, cytomegalovirus, Epstein–Barr virus) persist in the host for long periods and are of low pathogenicity. Such diseases are usually endemic in character[57] (see Table 2). Moving beyond human populations, it is important to remember that hosts with high rates of reproduction, such as arthropods, may be able to support endemic disease even if host density is low[72]. Furthermore, infectious organisms that induce life-long immunity, or are of high pathogenicity, can be endemic if they produce free-living infective stages which can survive for a long time in the external environment (anthrax bacillus is an example).

There is no doubt that microparasitic infections can slow population growth[73–75]. Whether a given disease will regulate the host population or merely slow its growth, and whether the infection will be endemic or epidemic, depends on the interplay of many biological parameters[32,70]. Unfortunately, our quantitative knowledge of these parameters is limited, even for viral and bacterial diseases of man.

Conclusion

The effects of microparasitic infections on the dynamics of animal populations depend on the ecology of the interactions between host and parasite. These patterns of disease behaviour involve four principal factors, namely: the host providing a habitat for the parasite; the degree to which the parasite induces host mortality (or diminishes the reproductive capability of the host); the extent to which the host acquires immunity; and the necessity of transmission from one host to the next. Overlaid on these factors are many biological complications, specific to individual host–parasite associations, whose sequential action is determined by life cycle structure.

In the second part of this article, we show how a common set of factors are involved in the dynamics of all infectious diseases, whether they are caused by viral or helminth agents, and whether they are transmitted directly or indirectly between hosts.

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articles

Possible optical observation of the companion star to the binary pulsar PSR1913+16

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Deep R band CCD photographs of the region surrounding the binary pulsar PSR1913+16 have been obtained with the 4-m telescope of the Kitt Peak National Observatory. Using an accurate astrometric solution, we find a star with $M_R = 20.9$ *at the precise coordinates of the pulsar. Possible interpretations of this result, including the unlikely* (<3%) *possibility that it is an accidental superposition of a field star, are discussed. If this object is the physical companion to the pulsar, it is probably a helium star.*

THE discovery of the binary pulsar PSR1913+16[1] has created substantial interest as a system in which various general relativistic effects[2–4] may be measured. The ability to perform these experiments relies critically on two factors: (1) that the pulsar clock should behave in a regular way and (2) that the companion star must be treatable as a point mass. The former point seems to be satisfied[5] so the major remaining issue for tests of relativity to proceed is how to determine the nature of the companion star. Since the optical extinction is probably modest ($A_V = 3.3$; ref. 6) we expect that a non-compact companion should be observable with a sensitive detector on a large telescope. Thus, sensitive observations could establish valuable constraints on the size of the companion star. The small observed apsidal motion in the system already limits the companion star to being either a helium star or a compact object[3].

The observations

We have used the JPL CCD array (400×400 pixels; 0.45″ per pixel) at the prime focus of the 4-m Mayall telescope to observe the region of the binary pulsar PSR1913+16. Our

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