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POPULATION BIOLOGY OF INFECTIOUS DISEASES: Part 1 and Part 2

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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.

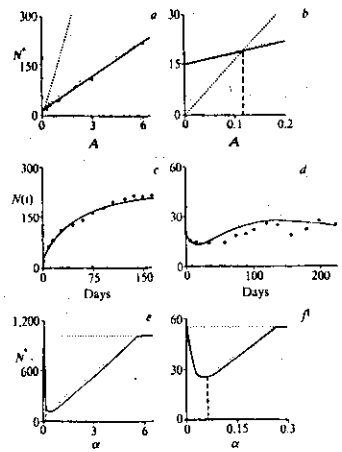

Fig. 1 Population dynamics of *Pasteurella muris* in colonies of laboratory mice. *a*, Relationship between the equilibrium population of mice N^* and the daily rate of input of susceptible mice A (solid dots are observed levels[46,47]; the solid line is the best linear fit, equation (6)). The dashed 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[28,48]. 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 ($\gamma \to \infty$)	$r-\alpha$	$(\alpha+b+\upsilon)/\beta$
Life-long immunity ($\gamma = 0$)	$r[1+(\upsilon/b)]-\alpha$	$(\alpha+b+\upsilon)/\beta$
Transient immunity (duration $1/\gamma$)	$r[1+\upsilon/(b+\gamma)]-\alpha$	$(\alpha+b+\upsilon)/\beta$
Transient immunity and an incubation (latent) period of duration $1/\sigma$	$r\left[1+\frac{\upsilon}{(b+\gamma)}+\frac{(\alpha+b+\upsilon)}{\sigma}\right]-\alpha$	$\frac{(\alpha+b+\upsilon)(b+\sigma)}{\beta\sigma}$
Transient immunity and disease eliminates reproduction of infected class	$r\upsilon/(b+\gamma)-(b+\alpha)$	$(\alpha+b+\upsilon)/\beta$
Transient immunity and disease reduces birth rate of infected class to $f\alpha$	$r\left[\frac{f\alpha-b}{r}+\frac{\upsilon}{(b+\gamma)}\right]-\alpha$	$(\alpha+b+\upsilon)/\beta$
Vertical (and horizontal) transmission		
Transient immunity and all births from infected class are also infected	$r[1+\upsilon/(b+\gamma)]-\alpha$	$(\alpha+b+\upsilon-a)/\beta$; threshold is zero if $a>\alpha+b+\upsilon$
Transient immunity and a fraction f of births from infected class are also infected	$r[1+\upsilon/(b+\gamma)]-\alpha$	$(\alpha+b+\upsilon-fa)/\beta$; threshold is zero if $fa>\alpha+b+\upsilon$

representing the mortality caused by the disease; there is also a recovery rate υ. 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:

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

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

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

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,

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

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

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

Here D is defined for notational convenience as

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

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 υ can be crudely estimated from life tables for uninfected populations, and from case mortality and recovery rates (we get $b \approx 0.006$, $\alpha \approx 0.06$, $\upsilon \approx 0.04$ 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 $\beta \approx 0.0056$, $\gamma \approx 0.021$ 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 $A_T \approx 0.11$ 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 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.

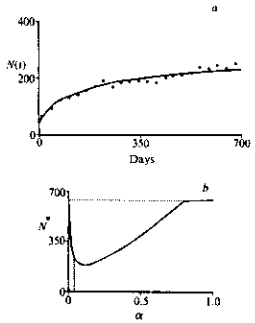

Fig. 2 Population dynamics of ectromelia in colonies of laboratory mice. The data[46–48,49] indicate $b = 0.005$, $\alpha = 0.042$, $\beta = 0.0013$, $\upsilon = 0.014$, $\gamma = 0$; the rate of introduction of susceptible mice was always $A = 3$ (all quantities in units of day^{-1}). *a*, Growth of 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*.

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

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

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

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

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 arise. If

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

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

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

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

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

with $B = \frac{1}{2}(\alpha+b+\upsilon+\gamma-r)$. 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

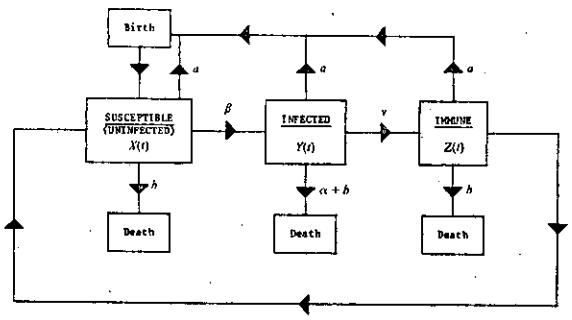

Fig. 3 Diagrammatic flow chart for a directly transmitted infection, described by a compartment model with susceptible (X), infected (Y), and immune (Z) hosts. The flow of individual hosts between compartments is controlled by a set of rate parameters: *per capita* birth rate, a; natural death rate of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

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

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 4a 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. 4a, 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. 4a 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.

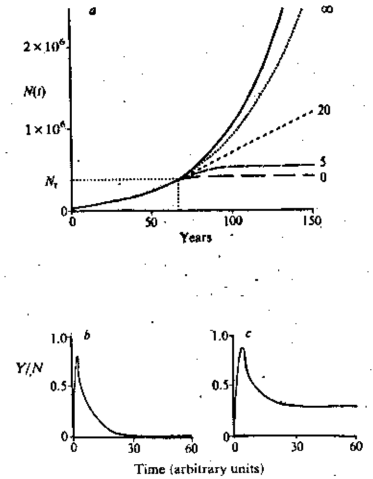

Fig. 4 a An illustration of the way the duration of immunity influences the dynamics of host population growth, $N(t)$, for a hypothetical disease; the various population parameters are assumed to be $r = 0.03$, $b = 0.015$, $v = 13.0$, $\alpha = 6.0$, $\beta = 5 \times 10^{-5}$ (all per year), and $N(0) = 50{,}000$. 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 'fade 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. 4b): 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. 4c.

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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Population biology of infectious diseases: Part II

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In the first part of this two-part article (Nature **280**, *361–367*), *mathematical models of directly transmitted microparasitic infections were developed, taking explicit account of the dynamics of the host population. The discussion is now extended to both microparasites (viruses, bacteria and protozoa) and macroparasites (helminths and arthropods), transmitted either directly or indirectly via one or more intermediate hosts. Consideration is given to the relation between the ecology and evolution of the transmission processes and the overall dynamics, and to the mechanisms that can produce cyclic patterns, or multiple stable states, in the levels of infection in the host population.*

IN the first part of this article[1] we considered the dynamics of microparasitic infections with direct transmission between hosts. We now extend the discussion to other kinds of parasites and transmission processes, and examine the general relations between population behaviour and parasite life cycle structure. The conclusions are broadly similar to those in the first part[1], but there are interesting similarities and differences both in the mathematical structure and in the biological conclusions.

We then give a brief discussion of general evolutionary trends, and end with a survey of the main mechanisms that can produce cyclic patterns, or multiple stable states, in the levels of infection in the host population.

Life cycle structure and disease dynamics

Microparasites with direct life cycles tend to produce persistent infections, with the host harbouring populations of parasites for long periods, due to continual reinfections. Among many examples are the hookworm species of man, *Ancylostoma duodenale* and *Necator americanus* (see Table 1): in endemic areas the prevalence of these infections may approach[2] 100%. For such systems, the pathogenicity to the host, the rate of production of transmission stages of the parasite and any resistance of the host to further infection all typically depend on the number of parasites present in a given host. A crude division of the host population into susceptible, infected and immune classes is therefore not helpful, and a detailed description of the dynamics needs to deal with the full probability distribution of parasites within the host population[3–6] (that is, with the number of hosts harbouring i parasites $N(i)$, where $i = 0, 1, 2, \ldots$). Figure 1, which is to be compared with Fig. 3 of the first part of this article[1], depicts the essential structure of such models.

It is often useful to simplify these models by making a phenomenological assumption about the statistical distribution of parasites among hosts[3,7–10] (or even, occasionally, by making assumptions that permit this distribution to be deduced theoretically[11,12]). A usual phenomenological assumption is that the parasite distribution is a negative binomial[3,7–10,13,14], with the parameter k providing an inverse measure of the degree of parasite 'clumping' or overdispersion within the host population: the limit $k \to \infty$ corresponds to the parasites being distributed in an independently random or Poisson form, while very small k corresponds to very high clumping. It is then possible to use such statistical moments of the $N(i)$ distribution as the total host population ($N = \sum_i N(i)$), the number of uninfected hosts ($X = N(0)$), the total parasite population ($P = \sum_i iN(i)$), and the mean parasite burden per host ($m = P/N$). In this way, models of the kind depicted in Fig. 1 can be brought into correspondence with the coarser models of the kind discussed in Part I (see Fig. 3 of Part I)[1].

The most detailed study of this type[3,4] draws on a synoptic collection of data for direct life cycle parasites (mainly helminths), and describes the dynamics in terms of three differential equations, for the number of hosts N, parasites P, and free-living infective stages w:

$$dN/dt = (a-b)N - \alpha P \quad (1)$$

$$dP/dt = \beta wN - (\mu + b + \alpha)P - \alpha(k+1)P^2/(kN) \quad (2)$$

$$dw/dt = \lambda P - cw - \beta wN \quad (3)$$

Here the birth and death rates a and b are as defined in the first part[1] of this article, as is the transmission parameter β (hosts acquire individual adult parasites at a rate proportional to the number of contacts between hosts and parasite infective stages, βwN). The parasite-induced host death rate (or, equivalently, depression of the birth rate) is taken to be linearly proportional to the parasite burden in a given host, at a rate α per parasite. The parasites are distributed as a negative binomial with parameter k; μ is the natural mortality rate of adult parasites; λ is the rate of production of infective stages by an adult parasite; and c is the death rate of these infective stages. The biological underpinning of these equations, and their dynamical behaviour, have been expounded in detail elsewhere[3,4].

A rough understanding of the relation between this system of equations for typical macroparasites with direct transmission, and the earlier set of equations (8)–(10) of Part I for directly transmitted microparasites, can be obtained as follows. First, note that the lifespan of the free-living infective stages is usually much shorter than that of the host and the adult parasite (compare Table 1). Thus the set of differential equations can be decoupled, by assuming the 'short lived' infective stages are adjusted essentially instantaneously to their equilibrium level ($dw/dt = 0$) for any given value of N and P. This gives

$$dN/dt = rN - \alpha P \quad (4)$$

$$dP/dt = \frac{\lambda NP}{H_0 + N} - (\mu + b + \alpha)P - \frac{\alpha(k+1)P^2}{kN} \quad (5)$$

(where $r = a - b$ and $H_0 = c/\beta$). Second, a phase-plane analysis now lays bare the properties of this pair of equations.

Three patterns of dynamical behaviour are possible[3,4]. (1) If

$$\lambda - (\mu + b + \alpha) > r(k+1)/k \quad (6)$$

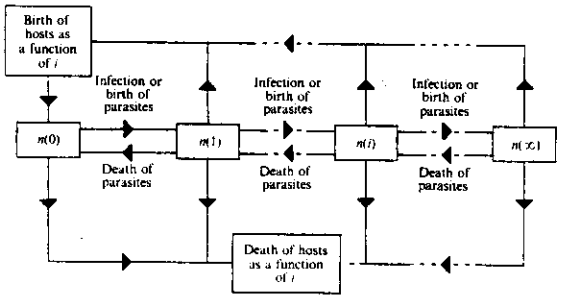

Fig. 1 Diagrammatic flow chart for a directly transmitted infection, based on a model with compartments for the number of hosts, $N(i)$, harbouring i parasites ($i = 0, 1, 2, \ldots, \infty$). The model has a structure similar to, but obviously more complex than, that of Fig. of 3 Part I[1].

the parasite regulates the host population to a stable equilibrium value. The average parasite burden per host settles to

$$m = r/\alpha \tag{7}$$

(2) If Equation (6) is not satisfied, but

$$\lambda - (\mu + b + \alpha) > 0 \tag{8}$$

the host population continues to grow exponentially, but at a rate

$$\rho = r - [\lambda - (\mu + b + \alpha)][k/(k+1)] \tag{9}$$

This is less than the disease-free rate, r. In this case, the mean parasite burden in the exponentially growing host population settles to the value

$$m \to (r - \rho)/\alpha \tag{10}$$

In either event, if the host population is initially below the value

$$N_T \approx \frac{H_0(\mu + b + \alpha)}{\lambda - (\mu + b + \alpha)} \tag{11}$$

the parasite cannot become established ($dP/dt < 0$). However, as long as equation (8) is satisfied, the host population will grow exponentially (at the rate r) until this threshold value N_T is exceeded, whereupon the infection will become established, either regulating the host population or at least slowing its growth rate. Furthermore, in view of the large values for the reproductive output λ of most helminth parasites, N_T will typically be relatively small. This expectation of commonly finding direct life cycle helminth infections persisting in low density host populations is borne out by the evidence[15,16].

(3) Finally, if λ is so small that equation (8) is not satisfied, the infection can never become established (N_T is negative!).

The similarities between cases (1) and (2) here, and the results displayed in Fig. 4 of Part I, are striking. In particular, for measures of the prevalence of infection, notice the exact formal equivalence between equation (15) of Part I and equation (7), and between equation (17) of Part I and equation (10). A dissimilarity is that whereas the ability of a microparasitic infection to regulate its host population essentially depends on its pathogenicity α exceeding the host population growth rate r (weighted by rates of recovery, loss of immunity and so on: see Table 1 of Part I), for a macroparasite it is its net reproductive ability, $\lambda - (\mu + b + \alpha)$, that plays a central role (λ is the 'birth rate', while μ, b and α are the natural parasite, natural host and parasite-induced host death rates). The macroparasitic infection can never persist if this effective net reproductive rate is not positive (equation (8)). The parasite will regulate the host population, or merely slow its growth, depending on whether this effective net reproductive rate $\lambda - (\mu + b + \alpha)$ is, or is not, greater than the host reproductive rate r, weighted by a factor $(k+1)/k$ to allow for the clumped distribution of parasites. Thus equation (6) is for these directly transmitted macroparasites the analogue of the microparasite equation (13) in Part I[1].

Table 1 Expected lifespans of the host and parasitic stages involved in the life cycle of *Schistosoma mansoni* and *Ancylostoma duodenale*

	Population	Lifespan (yr)
S. mansoni (refs 24, 29, 82)	Man (primary host)	50.00
	Adult parasite	5.00
	Infected snails (intermediate host)	0.10
	Cercariae	0.003
	Miracidia	0.0009
A. duodenale (ref. 2)	Man	50.0
	Adult parasite	1.0
	Free-living infective stage	0.1

Indirect life cycles constitute another qualitatively different kind of complication, arising when the life cycle of the parasite involves one or more intermediate hosts. This happens for both microparasites (for example, the arthropod-borne viruses or arboviruses such as yellow fever or Rocky Mountain spotted fever; the protozoan malaria species) and macroparasites (for example, schistosomes, the filarial worms causing onchocerciasis, and other roundworms and flatworms that involve dipteran, molluscan and other intermediate hosts). Malaria and schistosomiasis in human populations are the two parasites whose transmission cycles have been most fully studied and each enjoys its own independent and growing literature, both empirical and theoretical (see Table 2). Their basic dynamical character is, however, in many respects common to all parasites with indirect life cycles.

If we adopt the approach of equations (8)–(10) and Fig. 3 discussed in part I, namely dividing the host population into susceptible, infected and immune categories, we will in the simplest case have a system of six differential equations: three for the primary host (alternatively referred to as the definitive host, or final host) classes X, Y, Z; three for the intermediate host populations X', Y', Z'. All existing models, however, assume the total populations of both primary host ($N = X + Y + Z$) and the intermediate host ($N' = X' + Y' + Z'$) are constant, unaffected by the dynamics of the disease. This reduces the system to four equations. If, furthermore, immunity is either ignored or handled by specific assumptions about 'superinfection', the Z and Z' classes are effectively removed to give two coupled differential equations for the number of primary hosts Y, and of intermediate vectors Y', that are infected. This, in essence, is the source of the classic Ross-Macdonald[17,18] malaria equations, the Nasell–Hirsch[19] schistosomiasis model, and the Dietz[20] arbovirus equations.

These equations have been subjected to various kinds of more refined treatment, including age structure[20–24], immunity and 'superinfection'[17,21,23–26] and the use of several immunological categories of hosts[26] (intermediate between Fig. 3 of Part I and Fig. 1 of Part II). However, essentially all the existing work on indirectly transmitted parasites retains the assumption that the populations of host and intermediate vector are constant, not dynamically involved with the infection. Analysis of such models reveals threshold relations[17,20,21,27,28] between N and N', analogous to but more complicated than the N_T of the direct life cycle models. If N and N' lie below the threshold combination, the disease cannot be maintained.

For many human, and other animal, infections by parasites with indirect life cycles, what is needed is a theory in which the populations of primary and intermediate hosts are affected, and possibly even determined, by the presence of the infection. While it may often be reasonable to treat a human primary host population as roughly constant, we believe that cases where intermediate host populations are unaffected by the prevalence levels of the infection will be the exception rather than the rule[29]. There is no formal problem in extending our dynamic models of either the 'microparasite' kind of equations (8)–(10), (Part I) or the 'macroparasite' kind of equations (1)–(3) (Part II), to encompass the added complication of one or more intermediate vector populations. Space forbids a full exposition of the emergent properties, but the main trends are indicated in the following section.

Time scales and transmission terms

A full model for an indirectly transmitted parasite might include not only dynamical descriptions of the prevalence of infection in primary and intermediate host populations, but also additional differential equations (analogous to equation (3)) for the free-living transmission stages that carry the parasite from primary to intermediate host, and back again. For example, for schistosomiasis we could add a differential equation describing the miracidial stage (man to snail), and another for the cercarial stage (snail to man), to the usual equations for infection levels in the human and snail populations[30]. The reason this is not commonly done can be seen from Table 1; the dynamics of the free-living stages takes place on a time scale so much shorter than the other time scales in the system that miracidial and cercarial populations can be assumed to have the equilibrium values appropriate to the prevailing conditions among human and snail populations. In just this way, we collapsed the three-equation system (1)–(3) to the two equations (4), (5).

This technique of using biological insights about the time scales of various infection processes can be used to make further rough but useful approximations. For example, the time scales for processes (such as mortality rates) within the intermediate host population are typically significantly shorter than those in the primary host. Again, Table 1 testifies to this. Accordingly, we can assume that the numbers of susceptible, infected and immune intermediate hosts are adjusted to have the equilibrium values ($dX'/dt = 0$, and so on) appropriate to the current levels of infection in the primary hosts. In this way, parasitic infections with indirect life cycles can be approximately brought to a form similar to that of equations (8)–(10) in Part I for direct life cycles[1].

As a concrete example, consider a grossly oversimplified model for malaria, in which 'superinfection'[17,25,26], and mosquito latency[17,23] (and immunity[20,26]), are ignored. Assume also the total mosquito population is constant; $N' = X' + Y' =$ constant. The populations of infected humans Y, and mosquitos Y', then obey

$$dY/dt = \beta' Y' X - (b + \alpha + v)Y \tag{12}$$

$$dY'/dt = \beta Y(N' - Y') - (b' + \alpha' + v')Y' \tag{13}$$

Here β, b, α and v (plain for humans, primed for mosquitos) have their previous meanings; conventionally, most infected humans are assumed to recover ($v \gg \alpha, b$), and most infected mosquitos to die at a rate largely unaffected by the infection ($b' \gg \alpha', v'$). The assumption that mosquito processes happen on a relatively fast time scale enables Y' in equation (12) to be determined by setting $dY'/dt = 0$ in equation (13), leading to

$$dY/dt = Y[(\beta\beta' N' X)/(b' + \alpha' + v' + \beta Y) - (b + \alpha + v)] \tag{14}$$

This is exactly of the form for a directly transmitted infection (equation 9 of Part I), except that the simple transmission coefficient β has been replaced by the more complicated factor $\beta\beta' N'/(b' + \alpha' + v' + \beta Y)$. Similarly, the Nasell–Hirsch two equation model[19] for prevalence of schistosomiasis among humans and snails can be collapsed to Macdonald's[27,28] single equation for prevalence in the human population.

Conversely, for humans the total population is often growing on a time scale that is long compared to the relevant time scales of even persistent infections. This is why the total population can be treated as a constant in most epidemiological models. The approximation, whereby the dynamics of the prevalence (Y/N) and of the total population (N) are decoupled, can often be useful in discussing the transmission cycle of the infection, even though the long-term growth or regulation of the host population is affected by the presence of the infection.

Table 2 uses these ideas to attempt to give a schematic account of the relations among some of the many models, of differing degrees of complexity, that are to be found in the literature.

Saturation of transmission terms. The transmission terms obtained in equation (14) by 'collapsing out' the mosquito dynamics of equation (13), and in equation (5) by collapsing equation (3) for the free-living infective stages of the parasite, manifest a feature that is common to all such approximate representations of complex transmission processes[3,4,14,31,32]. Essentially, the simple term βXY for direct transmission

Table 2 Schematic representation of relationships between various kinds of models for parasitic infections, based on relative time scales of population processes

	Host population(s) constant	Host population(s) a dynamic variable
In considering the dynamics of infection, only one species is involved (for example, the host species).	**Direct life cycles**. Classical epidemiological models (refs 21, 56, 65, 67, 83–84, 87). Models for the dynamics of a parasite population within a host population of fixed size (refs 5, 88, 89). **Indirect life cycles**. Models for schistosomiasis (refs 28, 34, 90) and for malaria (refs 17, 18, 21), considering only the dynamics within the human host.	**Direct life cycles**. Models similar to those for classical epidemiology, but with total host population a dynamic variable, determined by birth and death processes (refs 35, 91 and this review). **Direct and indirect life cycles**. Dynamics of models in the compartment below but with all populations but the primary host 'collapsed out' (this review).
In considering the dynamics of infections, two or more species are involved (e.g., primary *and* intermediate host, or host *and* parasite population).	**Direct life cycles**. Models similar to the classical epidemiological equations, but including the dynamics of free-living infective stages (ref. 35). **Indirect life cycles.** Models for schistosomiasis (refs 19, 34, 92), malaria (refs 17, 21, 93) and arbovirus infections (ref. 20) in which both human hosts and intermediate vectors are considered. Models of schistosomiasis where humans, snails, miracidiae and cercariae are all considered (ref. 30).	**Direct life cycles.** Models similar to classical epidemiology, but with host population and free living infective stages both included as dynamic variables (ref. 35). Models for dynamics of host parasite systems (refs 3, 4, 7, 8, 14, 35), sometimes with dynamic aspects of free-living infective stages also included (refs 3, 4). **Indirect life cycles.** Any of the models in the compartment to the left, but with the total host populations treated as dynamic variables (this review).

between susceptible and infected people or βNw for direct transmission between hosts and free-living infective stages are replaced by expressions of the general form $AXY/(1+\nu Y)$ or $ANP/(1+\nu N)$, respectively. In the limit when, for example, νY is small, the expression has the familiar form, proportional to X and Y. But it can be that νY becomes significant compared to unity, whereupon the transmission term saturates to a value (AX/ν) proportional only to X. Such saturation effects can be important in diminishing the ability of the parasite to regulate its host population[3,14].

Ecology of the transmission process. Further complications can arise from the ecological nature of the individual links in the transmission process.

For infections that are communicated directly, the assumption that the net rate is proportional to the number of susceptibles and to the number of infectives is clearly reasonable for many diseases, and strikingly successful in explaining the mouse pox and mouse pasteurellosis data[1]. But for sexually transmitted diseases, for example, this is only plausible in a population that is astonishingly promiscuous and sexually active. In a society whose members typically have only a small number, η, of sexual partners (independent of the absolute population size), the rate at which an infected person propagates the infection is proportional not to the total number of susceptibles, but to η times the probability that a given person is a susceptible; that is, βXY is to be replaced[21] by $\beta\eta XY/N$. Under these very simple assumptions, the condition for maintenance of such diseases is $\beta\eta > (b+\alpha+\nu)$, independent of the population size. In reality, a more careful treatment of the distribution of degrees of sexual activity within the population is needed[33], but the fact remains that infections of this sort are relatively easy to maintain in low density populations.

More broadly, biological insights into the relative time scales associated with the various phases of indirect life cycles enable us to discuss the prevalance of infection in the primary host population by retaining equations (8) and (10) for X and Z, in Part I of this article, but replacing equation (9) with the more general expression

$$\mathrm{d}Y/\mathrm{d}t = Y[h-(a+b+\nu)] \qquad (15)$$

The transmission term is here denoted by h (Ross' 'happenings'[18]), and the threshold condition for the disease to increase upon introduction at low levels is clearly that $h>(a+b+\nu)$ in the limit $Y\to 0$. For the simple circumstances of the indirect life cycle that led to equation (14) above, this requirement comes down to the threshold criterion[20,21]

$$NN' > \frac{(a+b+\nu)(a'+b'+\nu')}{\beta\beta'} \qquad (16)$$

Note that a large population N' of intermediate vectors can enable the disease to persist, even when the primary host population N is small.

However, for malaria and many other infections borne by biting arthropods, the intermediate vector tends to make a fixed number of bites per week, independent of the number of primary hosts available to feed on. Thus the transmission rate from infected arthropods to people (and from infected people back to susceptible arthropods) is proportional to the biting rate ω times the probability that a given human is susceptible (or infected), and not simply proportional to the number of susceptible (or infected) people. That is, in equations (12) and (13), β and β' are to be replaced by ω/N. The threshold condition (16) is accordingly modified to[17,18,20]

$$\frac{N'}{N} > \frac{(a+b+\nu)(a'+b'+\nu')}{\omega^2} \qquad (17)$$

Note that latency effects have been neglected here, although they can be important in infections with indirect life cycles, and they certainly modify threshold conditions significantly for malaria[17] and schistosomiasis[29]. Infections with intermediate vectors of this character are relatively easy to maintain at low population densities of the primary host, provided only that the ratio of intermediate to primary hosts is sufficiently high. Indeed, equation (17) suggests the infection is actually easier to maintain at low host population levels; the mosquito or other intermediate host population N' is, however, typically dependent on the primary host for blood meals or the like, so that things are not as simple as they might seem. (A more general discussion, from which the threshold relations (16) and (17) emerge as limiting cases, has been given by Dietz[20]).

Yet another form of complication enters with parasites that have sexual stages, yet can have low densities, in a host. Schistosomiasis is one such example[10,19,27,28,34]. At high levels of prevalence of the infection in the human population, people tend to have worm burdens such that most adult female schistosomes are mated, and the circumstances leading to equation (16) are well approximated. But at low levels of prevalence, it can be that the average female is not mated, which tends to require that the transmission link from snail to man be counted twice in considering the overall cycle, thus giving complicated threshold conditions (very roughly of the form $N[N']^2 > \text{constant}$[19,34]).

Finally, note that (apart from the laboratory experiments on mice[1]) in all our models the host population either is regulated to some stable value by the disease, or else it grows exponentially. In practice, other constraints, set by resources, predators or the like, will eventually limit population growth. Such biological realities can be included in all our models, by introducing a logistic constraint (at a 'carrying capacity' K) in the growth of the disease-free population[35]. The resulting situation, for both direct and indirect parasite life cycles, is similar to that illustrated in Figs 1*e*, *f* and 2*b* in Part I, with the host population depressed below its disease-free level K, provided the parasite-induced host mortality α is not too large'. Too small an α leads to relatively little depression of the host population; too large an α renders the disease unable to persist, and the host population remains at K; maximum parasite-induced depression of the host population is attained for intermediate levels of pathogenicity[1,36]. This broad statement glosses over many intricacies that can arise (R.M.M. and R.M.A., in preparation), particularly with indirect life cycles when the intermediate vector has a constant biting rate (producing threshold conditions such as equation (17) in simpler models), but the gist is true.

Population parameters and evolutionary trends

Any discussion of the relations among the population parameters that characterize an infectious disease must ultimately take account of the evolutionary pressures on both hosts and parasites. Population dynamics is always confounded by population genetics.

For example, even if we assume no genetic change in the parasite, its action on the host will select for individuals with reduced susceptibility to the disease. For this reason alone, the pathogenicity of the parasite will tend to decrease through evolutionary time. Conspicuous examples are provided by the presence of the sickling gene (and other blood-group phenomena) in regions where malaria is endemic[37], and by the history of myxomatosis in rabbit populations in Australia[38]. An interesting theoretical discussion has been given by Gillespie[39].

Selective forces also act strongly on the parasites[40,41]. As we have seen, the persistence of a disease is facilitated by low pathogenicity and by long duration of infection[1]. Countervailing forces can, however, act to increase the virulence of an infectious disease; increased pathogenicity may often be associated with enhanced rates of production (within the host) of the parasite's transmission stages[36,42,43].

The regulatory potential of an infectious disease will, therefore, typically change as time goes by. A parasite may stably regulate its host population during their early association. But, as selective pressures reduce the average susceptibility of the hosts, such regulatory effects will tend to wane. Eventually, the host population may escape being controlled by the parasitic infection.

Because the generation times of most hosts are several orders of magnitude longer than those of their parasites, it is tempting to conclude that selection acts more rapidly on the parasites. However, the way parasitic infections act within host populations makes it likely that the parasites force the pace of host evolution to keep in step with, or even ahead of, their own evolution.

Among the recondite variety of strategies that parasites have evolved for persistence and transmission, some general trends can be discovered. For example, many parasitic species traverse links in community food webs by virtue of predator–prey associations between primary and intermediate hosts. Such associations, which include biting arthropods feeding on vertebrates, have played an important part in the evolution of complex life cycles. The high transmission efficiency β of these links suggest the threshold host populations for maintenance of such parasites will be low (see equations (16) and (17)). Consequently, we expect indirect life cycles to predominate among parasitic infections of hosts that exist at low density.

In contrast, directly transmitted microparasites that require high host densities in order to persist should be more commonly associated with animals that exhibit herd or shoaling behaviour, or breed in large colonies. Empirical evidence in support of these ideas comes from the abundance of directly transmitted viral and bacterial infections within modern human societies[42,44], large herds of ungulates[45], breeding colonies of sea birds[46,47], and the social insects[48,49]. Those diseases with direct life cycles that do persist within low density host populations should possess distinctive characteristics, such as long-lived infective stages[50,51], failure to induce lasting immunity[33,52–55], or ability to persist within the host for very long times[54].

Another trend to be noted is that highly pathogenic species usually exist, if at all, at low levels of prevalence (see equations (15) and (17) in Part I and equations (7) and (10) in Part II). An example is the digenean parasite *Haematolaechus colaradensis* whose primary host is frogs, but which has a transmission pathway involving first snails, and then dragonflies, as intermediate vectors on the way to the next frog. The prevalence among frogs is high, 60–70%, and the parasite is long-lived and has very low pathogenicity; in dragonflies the fluke induces moderate mortality, and has 30–40% prevalence; while in snails it is highly pathogenic but appears to have only about 5–10% prevalence[56]. These broad patterns, which are often found in helminths with life cycles involving two or three host species, are summarized schematically in Table 3.

Cyclic patterns of disease prevalence

Annual or other cycles in the prevalence of infection are often observed, and can arise in at least three distinct ways.

First, for many short-lived viral and bacterial infections in human populations, there is a propensity for the steady, endemic level of prevalence of infection to be attained by damped oscillations. Particularly if this equilibrium prevalence is low, it is possible for stochastic fluctuations in the number of people infected at the minimum of the cycle to, in effect, keep the cycle 'pumped' and prevent it from damping to equilibrium. This interplay between demographic stochasticity and an inherent propensity to weakly damped oscillations is essentially the mechanism proposed in the classic work of Bartlett[21,56–59] to account for cyclic patterns in the prevalence of measles and other viral infections in large cities. Gurney and Nisbet[60] have proposed a similar mechanism as an explanation for predator–prey cycles.

Table 3 Some population characteristics of diseases caused by indirectly transmitted helminths

Host	Pathogenicity of parasite	Prevalence of infection within host population	Expected life span of host (inversely related to time scaled dynamics)
Final	Low	High	Long
Second intermediate	Medium	Medium	Medium
First intermediate	High	Low	Short

Second, time dependence in any of the population parameters may, in principle, produce cyclic variations in infection. In particular, seasonal variation in the transmission coefficient is important in setting temporal patterns for many parasitic infections, and may often be central for human viral infections[44,61–65]. The mechanisms underlying the seasonality in the transmission rates are poorly understood, but for human viruses the main causes are probably climatic (temperature and humidity) effects influencing survival and dispersal of transmission stages, and seasonal changes in social behaviour[66,67] (children returning to school after the long summer vacation). The seasonal cycles characteristic of the prevalence of measles, chicken pox, poliomyelitis and mumps in large cities could arise in this way[21,44,65].

Annual periodicity in transmission rates can, moreover, produce complicated nonseasonal cycles in the prevalence of infection. Yorke and co-workers[44,61,65], and Dietz[68], have cogently argued that such a mechanism is responsible for the regular biennial cycle, alternating between years of high and low incidence, for measles in New York City between 1948 and 1964; in the same city, mumps and chicken pox showed clear annual cycles. The explanation of Yorke *et al.* is to the contrary of the conventional explanation of these non-seasonal cycles in terms of demographic stochasticity, as described above. Their model is essentially the set of deterministic equations (1)–(3) in Part I, with an assumed constant number of new susceptibles appearing each year, life-long immunity, and with the system enriched by the inclusion of a brief incubation period during which infected hosts are not infective. The basic feature is that the transmission coefficient $\beta(t)$ varies seasonally with a 1 yr period. Within a narrow window of parameter values, the number of infected people can show biennial peaks (Fig. 2*a*) similar to those for measles in New York City. This window separates highly transmissable diseases which produce an epidemic with eventual fade-out, from the diseases with low transmission efficiency which give rise to endemic seasonal patterns of infection (Fig. 2*b*), as usually shown by mumps and chicken pox.

Third, various kinds of nonlinearities in the transmission terms may produce stable limit cycles, whose periods depend on the population parameters and will rarely be seasonal. People familiar with the ease whereby stable limit cycles arise in predator–prey models may be surprised to learn the structure of most host–parasite models is such that stable cycles do not easily occur. However, they can be produced without excessive contrivance. One simple example is to take the basic equations (8)–(10) of part I, and introduce the possibility of saturation in the transmission by replacing βXY by $\lambda XY/(H_0+X)$. Such a modification can arise naturally[4,35], in the manner of the analogous expression in equations (5) and (14), if the term is thought of as deriving from the 'collapsed' dynamics of a free-living infective stage. This system can now exhibit stable limit cycles for a specific range of parameter values (corresponding to λ neither too small nor too large). One such stable cycle is illustrated in Fig. 2*c*. In general, however, little is yet agreed about the kinds of biological processes that can generate nonseasonal patterns of disease prevalence.

Multiple stable states of disease prevalence

A growing number of empirical and theoretical studies suggest that many natural assemblies of plants and animals can have a multiplicity of alternative stable states[58]. Once two or more stable statesare possible, the actual state the system settles into

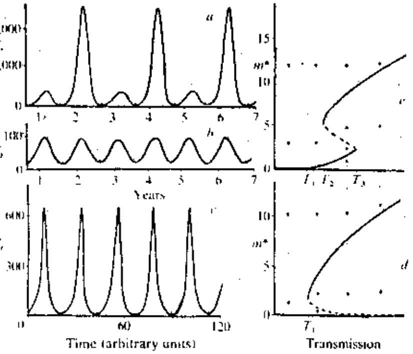

Fig. 2 *a*, Simulations of recurrent outbreaks of measles in New York City, showing biennial peaks superimposed on an underlying seasonal cycle (from London and Yorke[44]). *b*, Simulations[44,63] of recurrent outbreaks of mumps in New York City, with simple seasonal peaks, annually. *c*, Simple limit cycle behaviour generated by the model described in the text. *d*, The transmission threshold, alternative stable states, and 'breakpoint' phenomena that arise in simple models for the transmission dynamics of schistosomiasis[10,19,27,28,34]; the features are as discussed in the text. *e*, Transmission threshold and alternative stable states arising in a model for directly transmitted helminth infections, where it is assumed that the pathogenicity of the disease is related to the nutritional state of the host[35]. The graph shows the mean equilibrium burden of parasites per host, m^*, as a function of a parameter, T, representing transmission efficiency. The infection cannot persist below a threshold value T_1, between T_1 and T_2 there is a unique low level of disease endemicity; between T_2 and T_3 two stable levels of prevalence may occur, one high and the other low, separated by a breakpoint (the dashed line); above T_3 there is again a unique equilibrium level, corresponding to high average parasite burdens per host. The arrows indicate the stable state to which the system will sw from a given initial value.

depends on the initial conditions. The system will tend to recover its original configuration if subject to small disturbance, but sufficiently severe perturbations are liable to precipitate it into an alternative state in a different region of the dynamical landscape.

The nonlinearities in population models for parasitic infections can generate such multiple states by three principal mechanisms: worm pairing for sexual reproduction in the primary host; nonlinearities associated with the transmission from primary to intermediate host, or vice versa (mosquitos biting man for malaria, or predatory primary hosts consuming infected intermediate-host prey); parasite pathogenicity dependent on the nutritional state of the host.

The first and most fully studied of these categories arises for many helminth infections with indirect life cycles, such as schistosomes[10,19,27,28,34]. It serves to exemplify the phenomenon. As portrayed in Fig. 2*e*, the equilibrium value of the mean parasite burden per human host (m) will be zero if the rate of transmission (T) from snail to man is below the threshold value T_1. Above this threshold, two alternative stable states occur, one of endemic infection ($m>0$), the other of parasite absence ($m=0$). The basic reason is that at low levels of m the female worms are unlikely to be mated, so that the disease cannot be maintained, even though the transmission parameters are such as to permit its endemicity if introduced at high values of m. The two stable states (valley bottoms in the dynamical landscape) are separated by a 'breakpoint' (watershed), indicated by the dashed line in Fig. 2*e*: disturbances severe enough to transgress the breakpoint will carry the system from one state to the other.

These threshold and breakpoint concepts are of obvious importance to epidemiologists concerned with disease eradication[10,27,28].

Of special importance are the effects that can arise from the now widely recognised fact that the impact of an infection is often related to the nutritional state of the host[69–75]. Broadly speaking, malnourished hosts have lowered immunological competence, and are less able to withstand the onslaught of infection[76–78]. The effective pathogenicity of a parasite therefore tends to increase as host density rises to a level where competition for available food resources is severe[79,80]. Given certain reasonable assumptions[35] about the exact relation between pathogenicity (α) and host density (N), two stable states may occur for a given set of rate parameters. The outcome of such a model[35], for a directly transmitted helminth infection, is shown in Fig. 2*d*. Both states reflect stable endemic disease: one equilibrium is characterized by high host density and low worm burdens; the other by low host density (severely depressed by the disease) and high average burdens of parasites. As for the schistosome model of Fig. 2*e*, the two states are separated by a breakpoint or unstable equilibrium.

The discontinuous switch from low to high levels of infection, following a disturbance severe enough to cross the breakpoint, will show up as an apparent 'epidemic' outbreak of disease, typically producing many host deaths. Interestingly, many documented accounts of disease outbreaks are for host populations at high densities, where stress induced by overcrowding or malnutrition is present[illegible]. It is very likely that such outbreaks are to be explained[illegible] by the alternative stable states produced by close links between pathogenicity and nutrition or stress, rather than by the commonly accepted hypothesis of enhanced transmission with high density populations[illegible].

Parasitic infections with very complex life cycles may possess more than two stable states, particularly if predator–prey links are involved in the transmission from one host to the next, as is the case for many helminth parasites. There is a desperate paucity of data, from field or laboratory, bearing on these general points.

Conclusion

This two-part article has blended some new theoretical studies and new analysis of existing laboratory data with a review and synthesis of past and present models for the overall transmission dynamics of parasitic infections. We have defined 'parasite' broadly to include viruses, bacteria and protozoans along with the more conventional helminth and arthropod parasites, and we have concentrated attention upon the circumstances under which the infection may significantly alter the growth rate of its host population.

Some of the theoretical conclusions can be pleasingly supported by hard data, while others remain more speculative. On the whole, our main goal is to help elevate the study of host–parasite population dynamics to its proper place in ecological thinking; parasites (broadly defined) are probably at least as important as the more usually-studied predators and insect parasitoids in regulating natural populations.

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