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Microparasite population dynamics and continuous immunity

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A mathematical model is presented for the transmission of a microparasite where the hosts occupy one of two states, uninfected or infected. In each state, the hosts are distributed over a continuous range of immunity. The immune levels vary within hosts due to the processes of waning of immunity (when uninfected), and increasing immunity (when infected), eventually resulting in recovery. Immunity level also influences the host's ability to infect or be infected. Thus the proposed model incorporates both inter- and intra-host dynamics. It is shown from equilibrium results that this model is a general form of the susceptible–infected–resistant (SIR) and susceptible–infected–susceptible (SIS) family of models, a development that is useful for exploring multistrain pathogen transmission and use of vaccines which confer temporary protection.

Keywords: microparasite population dynamics; partial differential equations; mathematical model; reaction–convection system; continuous immunity; vaccine

1. INTRODUCTION

The vast majority of modelling of microparasite infections have, to date, used the susceptible–infected–resistant (SIR) framework, the principal assumption of which is that individuals, once recovered from infection, are immune for life (Kermack & McKendrick 1927; Anderson & May 1991). The presence of specific antibodies is assumed to be indicative of this immunity, the detection of which allows seroepidemiological studies to determine rates of infection by age. Seroepidemiology has relied on the fact that a single cut-off value of antibody concentration (titre), which marks the differences between those that are antibody negative (and assumed to be susceptible to infection) and those that are antibody positive (assumed to be previously exposed and consequently immune), can be identified (Cox *et al.* 1998*a*).

However, it has been recognized for some time that antibody titres tend to fall with age (presumed to be a function of time since infection), even though this may not be linearly related to the risk of subsequent infection (Gay 1996). This effect has been treated statistically through the use of mixture models to describe the distribution of titres, but this approach does not allow the impact of waning antibody titres to be included in a dynamic model (Gay 1996).

Furthermore, the majority of microparasites are able, to some extent, to reinfect previously infected individuals. It is the common childhood viral infections (principally measles, mumps and rubella, but also the hepatitis-B virus) that are the exception to the rule. Even so, the phenomena of waning immunity, infection following vaccination and reinfection are receiving an increasing amount of attention even with these viruses (Calvert *et al.* 1996; Chen *et al.* 1990). Surprisingly, there has been relatively little attention given to susceptible–infected–susceptible (SIS) frameworks, partly because they do not demonstrate the same array of dynamic behaviour, and more particularly are not able to reproduce the periodicity characteristic of many microparasites (Kermack & McKendrick 1927; Anderson & May 1991; White *et al.* 1998). However, it is also common that those microparasites that are able to infect previously infected individuals demonstrate some form of serotypic diversity, and the reverse is true. It is instructive that it is only the common, childhood viral (monotypic) infections for which vaccines have been developed to prevent reinfection. Thus, it would appear that genetic (strain) diversity in microparasites enables reinfection, although subsequent infections may be less pathogenic: rotavirus infections for example (Offit 1994). Inclusion of this strain diversity in models may also reintroduce a wider spectrum of dynamic behaviour (Andreassen *et al.* 1997).

The model presented is motivated by two factors. First, we want to include antibody titres within transmission dynamic models since it is possible that considerable information is being discarded in the process of conversion of an antibody titre to a binary measure. Second, we wish to include SIR and SIS models as the ends of a spectrum of microparasite–host interactions, an approach that is required in order to more fully understand multistrain microparasite dynamics (White *et al.* 1998; Castillo-Chavez *et al.* 1997). The introduction of factors, such as partial immunity and changes in infectivity of individuals during an infection, also allows the development of models that combine transmission dynamics and the dynamics of immune response and microparasite population during an infection.

A model framework has been developed that describes the proportion of infected and non-infected hosts in terms of time and the level of immunity which they possess. It is intended that level of immunity will be directly related to

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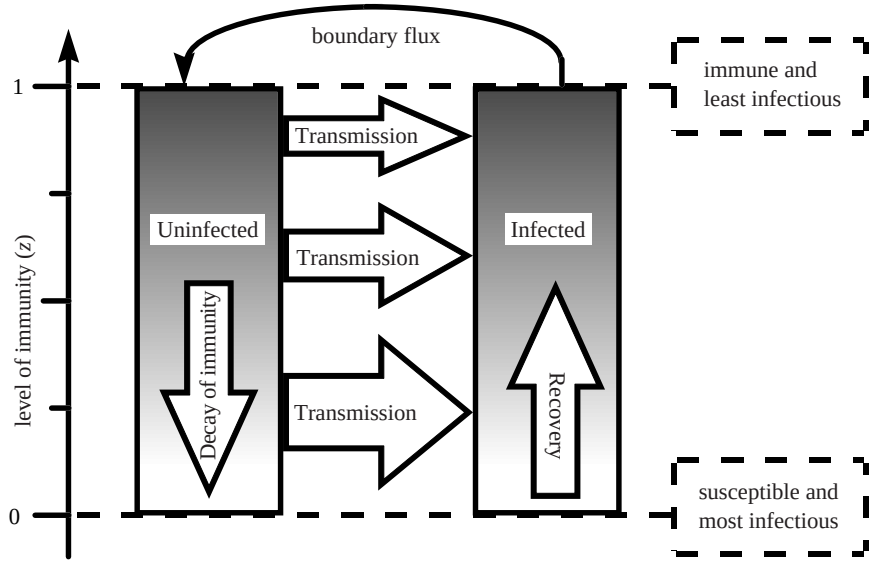

Figure 1. A schematic diagram showing the basic structure of the continuous immunity model.

antibody titre or some other immunological marker of immunity. The model allows the susceptibility to infection and disease and the infectiousness of the host to vary continuously with its level of immunity. We describe the model framework, derive equilibrium results and demonstrate its potential with some illustrative examples.

2. MODEL FRAMEWORK

Let z represent the level of immunity, which is considered as a continuous dimension, and, for the purposes of this paper, constrained between zero and unity ($0 \leqslant z \leqslant 1$), with $z=0$ meaning no immunity and $z=1$ meaning maximum immunity. The densities of the host population that are uninfected and infected at time t are given as $x(z,t)$ and $y(z,t)$, respectively. The varying susceptibility and infectivity are modelled by the functions $p(z)$ and $q(z)$, respectively, which have values between zero (complete immunity and no infectivity, respectively) at $z=1$ and unity at $z=0$ (complete susceptibility and full infectivity, respectively). The process of loss of immunity is modelled as a movement of hosts down through the values of z in the uninfected compartment, $x(z,t)$. The process of recovery is modelled as a movement of hosts up through values of z in the infected compartment, $y(z,t)$, until they have full immunity (at $z=1$), at which point they enter the uninfected compartment at $z=1$. These rates of loss of immunity and recovery are given by k_x and k_y, respectively. Figure 1 is a schematic representation of the model.

The following set of partial differential equations (PDEs) describes the system:

$$\left.\begin{aligned} \frac{\partial x(z,t)}{\partial t} - \frac{\partial [k_x(z)x(z,t)]}{\partial z} &= \mu b(z) - \lambda(t)p(z)x(z,t) - \mu x(z,t) \\ \frac{\partial y(z,t)}{\partial t} + \frac{\partial [k_y(z)y(z,t)]}{\partial z} &= \lambda(t)p(z)x(z,t) - \mu y(z,t) \\ \lambda(t) &= \beta \int_0^1 q(z)y(z,t)\,\mathrm{d}z \\ p(0) = 1, p(1) = 0 & \\ q(0) = 1, q(1) = 0 & \end{aligned}\right\}. \tag{1}$$

These equations are first-order hyperbolic reaction–convection equations. They are similar to age–time PDEs (Anderson & May 1991), apart from the relationship between immunity and time which differs from that between age and time. Note that SIR and SIS equations are reaction equations, and the above system represents the inclusion of the immune response as convection within the host population. The boundary fluxes are given by

$$\left.\begin{aligned} k_x(1)x(1,t) &= k_y(1)y(1,t) \\ k_y(0)y(0,t) &= 0 \end{aligned}\right\}. \tag{2}$$

The conditions in equations (2) must be satisfied in order for the flows in the model to be balanced. In other words, hosts must not 'leak' in and out of the model by entering or leaving at the boundaries of x and y at minimum and maximum immunity. The first condition ensures that hosts recovering from an infection enter the uninfected class (x). The second condition ensures that hosts will not flow out of or into the infectious class, except through mortality or transmission, at minimum immunity. These are the two boundary conditions that are required in this system (at $y(0,t)$ and $x(1,t)$) due to the nature of the PDEs. Additionally, hosts must also not 'leak' out of the uninfected compartment at $z=0$ leading to the following constraint on the system, equation (3)

$$k_x(0)x(0,t) = 0. \tag{3}$$

The rate of infection of uninfected individuals is given by $p(z)\ \lambda(t)$; $b(z)$ is the distribution of births into the uninfected class over z; μ is the death rate of hosts (the infection is presumed as non-lethal, thus the integral of $b(z)$ over the interval of $z=(0,1)$ is unity); and β is the transmission coefficient. This general framework can be made more specific when considering particular infections, as discussed below.

Numerical solution of this framework is not straightforward (Sulsky 1993; Milner & Rabbio 1992), and we concentrate on equilibrium results. Clearly, there is a trivial equilibrium with no infected hosts, and all (uninfected) hosts with zero immunity. However, we have had to assume, without formal proof, the existence and

stability of a non-trivial equilibrium with respect to time. Given the damped oscillatory nature of the SIR model, it is unlikely that this approach to equilibrium would be monotonic for certain parameter values.

3. EQUILIBRIUM

We consider the situation where the system has reached an equilibrium in time, i.e. the differentials with respect to time in equations (1) are zero. The model equations then become ordinary differential equations with constraints on the parameter values in terms of the boundary fluxes of the original model and also on the definition of the rate of infection

$$\left.\begin{aligned}
\frac{\mathrm{d}x^*(z)}{\mathrm{d}z} &= \left(-\frac{1}{k_x(z)}\right)\left(\mu b(z) - \lambda^* p(z)x^*(z) \right.\\
&\qquad \left. -\mu x^*(z) + \frac{\mathrm{d}}{\mathrm{d}z}(k_x(z))x^*(z)\right)\\
\frac{\mathrm{d}y^*(z)}{\mathrm{d}z} &= \left(\frac{1}{k_y(z)}\right)\left(\lambda^* p(z)x^*(z) - \mu y^*(z)\right.\\
&\qquad \left. -\frac{\mathrm{d}}{\mathrm{d}z}(k_y(z))y^*(z)\right)\\
k_x(1)x^*(1) &- k_y(1)y^*(1) = 0\\
y^*(0) &= 0\\
\lambda^* &= \int_0^1 \beta q(z)y^*(z)\mathrm{d}z
\end{aligned}\right\}, \tag{4}$$

with the solution

$$\left.\begin{aligned}
x^*(z) &= \frac{\mathrm{e}^{F_1(z)}(C_x - F_2(z))}{k_x(z)}\\
y^*(z) &= \frac{F_3(z) - F_3(0)}{\mathrm{e}^{\mu F_4(z)}k_y(z)}\\
C_x &= \frac{F_3(1) - F_3(0)}{\mathrm{e}^{\mu F_4(1)+F_1(1)}} + F_2(1)\\
F_1(z) &= \int_0^z \frac{\lambda^* p(\omega) + \mu}{k_x(\omega)}\mathrm{d}\omega\\
F_2(z) &= \int_0^z \frac{\mu b(\omega)}{\mathrm{e}^{F_1(\omega)}}\mathrm{d}\omega\\
F_3(z) &= \lambda^* \int_0^z \mathrm{e}^{\mu F_4(\omega)}p(\omega)x^*(\omega)\mathrm{d}\omega\\
F_4(z) &= \int_0^z \frac{1}{k_y(\omega)}\mathrm{d}\omega
\end{aligned}\right\}. \tag{5}$$

Integrating the system PDEs (equations (1)) between the limits $z=0$ and $z=1$ and incorporating the boundary conditions (equations (2)) and constraint (equation (3)), we obtain the following ordinary differential equations describing the evolution of the total densities of uninfected and infected hosts in time, $X(t)$ and $Y(t)$

$$\left.\begin{aligned}
\frac{\mathrm{d}X(t)}{\mathrm{d}t} &= \mu - \int_0^1 p(z)\lambda(z,t)x(z,t)\mathrm{d}z - \mu X(t) + k_y(1)y(1,t)\\
\frac{\mathrm{d}Y(t)}{\mathrm{d}t} &= \int_0^1 p(z)\lambda(z,t)x(z,t)\mathrm{d}z - \mu Y(t) - k_y(1)y(1,t)
\end{aligned}\right\}. \tag{6}$$

We define the reproduction number, $R(t)$, to be the quantity that must be greater than unity for the infectious population to be increasing

$$R(t) = \frac{\int_0^1 p(z)\lambda(z,t)x(z,t)\mathrm{d}z}{\mu Y(t) + k_y(1)y(1,t)}. \tag{7}$$

Then the suggested formula for the basic reproduction number, R_0, of the system is as follows:

$$R_0 = \frac{R^*}{X^*} = \frac{\lambda^* \int_0^1 p(z)x^*(z)\mathrm{d}z}{[\mu Y^* + k_y(1)y^*(1)]\int_0^1 x^*(z)\mathrm{d}z}. \tag{8}$$

Given the functions $p(z)$ and $q(z)$ are equal to the constants p and q, respectively, the formula for the basic reproduction number can be simplified to the following:

$$\left.\begin{aligned}
R_0 &= \frac{pq\beta}{\mu + \nu}\\
\nu &= \frac{k_y(1)y^*(1)}{\int_0^1 y^*(z)\mathrm{d}z}
\end{aligned}\right\}. \tag{9}$$

It should be noted that the rate of decay of immunity, $k_x(z)$, does not appear in the reduced formula (equations (9)), and the unreduced formula (equation (8)) is not expected to depend on it. The expansion of this formula, if analytically possible, would be cumbersome and unrevealing, although its value for specific parameters and functions ($k_x(z), k_y(z), \mu, b(z), p(z), q(z), \beta$) can be calculated. However, it is clear that this expression for R_0 represents a product of infectiousness (represented here by $pq\beta$) and duration of infectiousness (with removals due to death, μ and a loss of infectivity at $z=1$, ν), as in simpler models.

4. INFECTIOUS AND IMMUNE PERIODS

Much of the understanding of microparasite transmission dynamics is based on the parameters describing the average infectious and immune periods. However, in the proposed model, these parameters are derived from more mechanistic assumptions about the rates of gain and loss of immunity. In order to construct links between the two approaches, we show how various assumptions of rate of gain of immunity relate to average infectious periods.

(a) *Infectiousness*

In the current model the infectious period depends on the level of immunity that an individual has on infection, as well as the rate of development of immunity. In

order to derive a formula for the duration of infection, we consider the original PDE for y with zero transmission

$$\frac{\partial y(z,t)}{\partial t}+\frac{\partial[k_y(z)y(z,t)]}{\partial z}=-\mu y(z,t). \tag{10}$$

Solutions are divided by a boundary (the characteristic curve) in (z,t) space between y-values originating from the initial condition (at $t=0$) and those originating from the boundary flux condition $(k_y(0)y(0,t)=0)$ which means zero infections. This boundary satisfies the following:

$$\left.\begin{aligned} f_y(z)&=\int_0^z\frac{\mathrm{d}\omega}{k_y(\omega)}\\ f_y(z)&=t+f_y(0)\end{aligned}\right\}. \tag{11}$$

Since the time taken for all infected hosts at a given initial time to recover equals the time taken for the y-values of which the origins are the initial rather than the boundary conditions on y, the time from being fully infectious to fully recovered, T_R (i.e. the maximum infectious period), is given by the following:

$$T_R=\int_0^1\frac{\mathrm{d}z}{k_y(z)}. \tag{12}$$

If k_y is constant, then $T_R=1/k_y$, and this definition of the recovery time is analogous to that for the SIR model, i.e. the inverse of the recovery rate. But in this case, it represents the maximum rather than the mean of a negative exponential.

(b) *Immunity*

The immune period is much harder to define in the current framework. It depends on the rate of loss immunity, k_x, the susceptibility function, $p(z)$, and the equilibrium rate of infection, λ. Without any infection or death, the uninfected population all eventually occupy the lower boundary of immunity ($z=0$), so that the density of hosts at this point approaches infinity. In order to consider the time spent by hosts in the uninfected compartment, the following PDE was solved using the method of characteristics to model the fate of a cohort of uninfected individuals.

$$\frac{\partial x(z,t)}{\partial t}-\frac{\partial[k_x(z)x(z,t)]}{\partial z}=-[\lambda p(z)+\mu]x(z,t). \tag{13}$$

The force of infection, λ, was considered constant and the flux into the compartment was considered zero. The following solution was obtained for the number of uninfected hosts, $x(z,t)$, at any time, t, or level of immunity, z.

$$x(z,t)=\begin{cases}x_0(\theta_x)\mathrm{e}^{g_x((z)-g_x(\theta_x))} & 0\leqslant z\leqslant \lim_x\\ 0 & \lim_x\leqslant z\leqslant 1\end{cases} \tag{14}$$

where

$$\left.\begin{aligned} x(z,0)&=x_0(z)\\ g_x(z)&=\mu f_x(z)-\ln(k_x(z))+\lambda\int\frac{p(z)}{k_x(z)}\\ f_x(z)&=\int\frac{1}{k_x(z)}\mathrm{d}z\\ \theta_x&=f_x^{-1}(t+f_x(z))\\ \lim_x&=f_x^{-1}(f_x(1)-t)\end{aligned}\right\}. \tag{15}$$

For the system solved, the functions have the following forms

$$\left.\begin{aligned} k_x(z)&=a_xz\\ p(z)&=1-z\end{aligned}\right\}. \tag{16}$$

The following result is obtained

$$x(z,t)=\begin{cases}x_0(z\mathrm{e}^{a_xt})\exp\left[\dfrac{a_x(a_x-\mu)\,t+\lambda(1-\mathrm{e}^{a_xt})z}{a_x}\right] & 0\leqslant z\leqslant \mathrm{e}^{-a_xt}\\ 0 & \mathrm{e}^{-a_xt}\leqslant z\leqslant 1\end{cases}. \tag{17}$$

This is shown in figure 2*a* and is the type of result for a vaccinated cohort in a largely unvaccinated population, i.e. when the level of vaccination does not greatly alter the rate of infection.

The total density of uninfected hosts over time, $X(t)$, can be calculated as follows:

$$X(t)=\int_0^1 x(z,t)\mathrm{d}z. \tag{18}$$

This survival curve is plotted in figure 2*b* where total numbers reduce over time due to death and infection.

5. EXAMPLE EQUILIBRIUM SOLUTIONS

This section deals with the numerical solution of the set of ordinary differential equations which describe the equilibrium distributions of uninfected and infected hosts with immunity (equations (4)). In order to demonstrate on a larger scale the model behaviour, the simplest functional forms were chosen for each quantity. The recovery rate, k_y, was considered constant; the rate of loss of immunity, k_x, was considered linear in order to satisfy the constraint on the system (equation (3)); susceptibility, $p(z)$, was assumed to alter linearly starting at its maximum at $z=0$ (totally susceptible) and decreasing to zero at $z=1$ (totally immune); and the births of hosts into the uninfected compartment were considered exponentially distributed over the level of immunity with the highest number of births entering the most susceptible parts of the uninfected class (i.e. no births into the infected class).

$$\left.\begin{aligned} k_x(z)&=a_xz\\ k_y(z)&=a_y\\ p(z)&=1-z\\ b(z)&=\frac{a\mathrm{e}^a}{\mathrm{e}^a-1}\mathrm{e}^{-az}\end{aligned}\right\}. \tag{19}$$

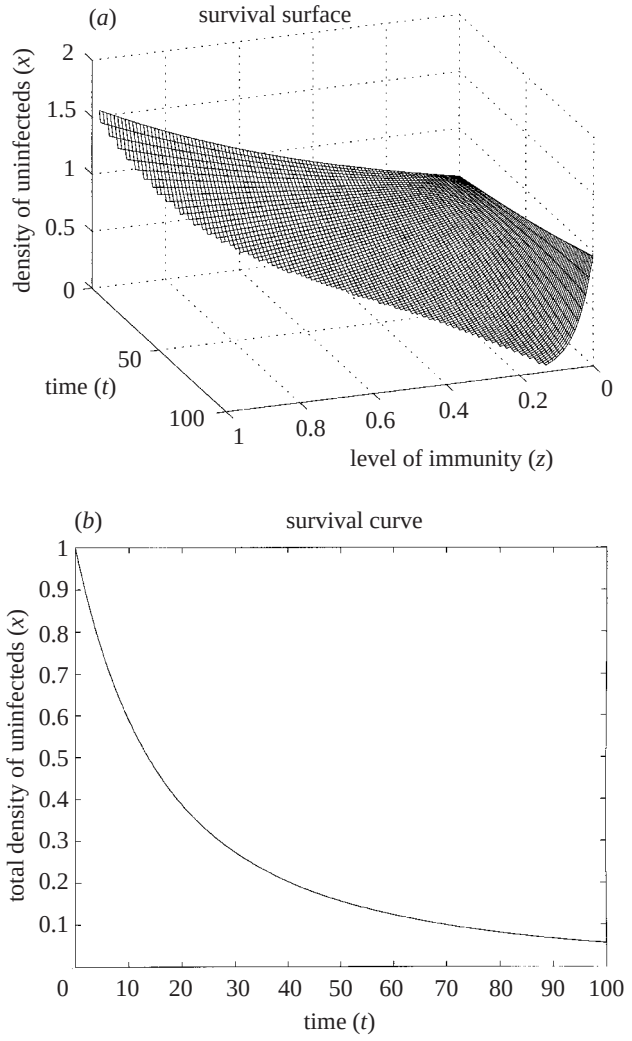

Figure 2. Immune period distributions. (*a*) The distribution of uninfected individuals over the level of immunity changing with time. Calculated using equation (17) with parameters $a_x=0.02$, $\lambda=0.09$ and life expectancy, $1/\mu=1/0.015$. At time zero, the hosts are distributed with a higher density at higher levels of immunity this distribution is situated on the 'back wall' of the three-dimensional plot. As time (plotted travelling out of the page) increases, the density of hosts at the higher levels of immunity decreases due to their loss of immunity, and the density of hosts at lower levels of immunity increases The final distribution shows higher densities of hosts at lower levels of immunity, with no hosts occupying the higher levels of immunity. The 'stepwise' structure is an artefact of the plotting procedure. (*b*) The total density of uninfected individuals changing over time. Calculated using equation (18) with parameters as in part (*a*).

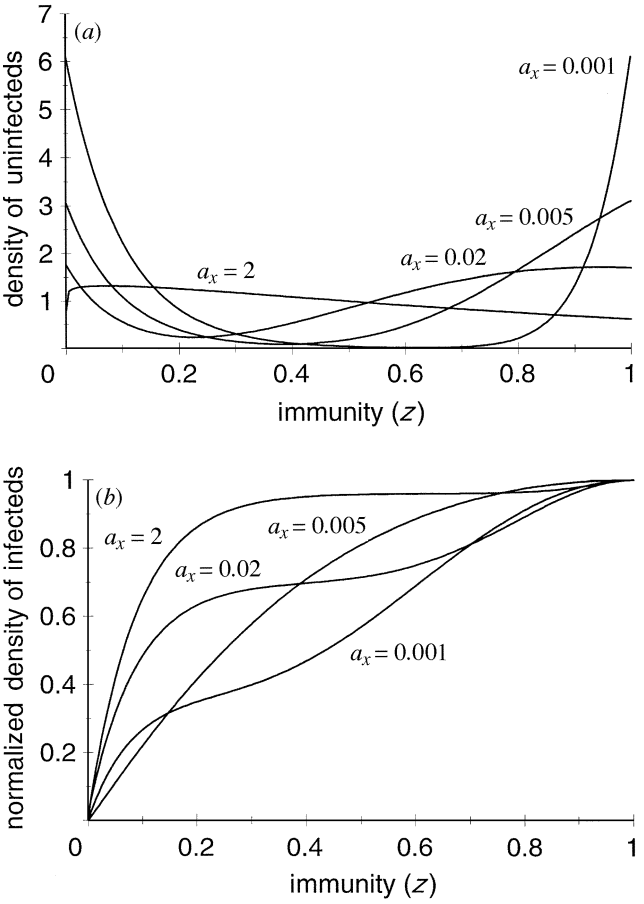

Figure 3. Equilibrium results. The figures show the equilibrium distributions (*a*) $x^*(z)$ (uninfecteds), and (*b*) $y^*(z)$ (infecteds) for four different values of a_x corresponding with equation (5). The values used are $(a_x, \lambda)=(0.001, 0.0105)$, (0.005, 0.039), (0.02, 0.09) and (2.0, 2.2), respectively. Life expectancy is 1/0.015, duration of infection is 1/52, the steepness of the birth distribution, $a=10$.

These functions are used in a numerical solution of equations (4) (ModelMaker, v. 3, Cherwell Scientific Publishing, Oxford, UK). The conditions on the boundary fluxes, equations (2), must be satisfied for a valid solution. The equations were rescaled using the transformation $z=1-s$ so that the $z=1$ condition could be fixed as initial conditions on x^* and y^*. Values of λ^* (a constant at equilibrium) and $x^*(1)$ are found by trial and improvement so that the two conditions for hosts not to 'leak' from the system (the total density of hosts is equal to unity and $y^*(0)=0$) are satisfied.

Epidemiological characteristics of different micro-parasite infections can be incorporated into the functional forms. For example, some childhood viral infections tend to have a fast recovery rate (high k_y) and a slow rate of loss of immunity (low k_x). Figure 3 shows the distribution (across z) for uninfected and infected individuals. In figure 3*a*, the distributions of the uninfected hosts over z for the highest and lowest values of the waning immunity rate parameter, a_x, have characteristics which could be associated with the profiles expected for SIS and SIR type infections. In the first case, uninfected hosts are concentrated at the lower values of z, implying that at equilibrium most uninfected hosts are susceptible. In the second case, it is possible to distinguish two peaks in the distribution of uninfected individuals: essentially the susceptible and resistant. The other distributions on the graph show profiles for possible intermediate stages between the SIS and SIR types of infection.

The form of the distribution of x (uninfecteds) is characterized by the presence or absence of a single maximum or minimum. In the case of a low rate of loss of immunity, there is a single minimum that essentially divides the uninfected population between those that have been infected (and are immune) and those that are susceptible to infection. In other words the SIR frame-

work is recovered. As the rate of loss of immunity is increased, a maximum appears and the two groups of uninfected individuals become increasingly merged. At high rates, the minimum is lost and the maximum appears at lower levels of immunity therefore approximating an SIS framework. Due to the existence of a short period of immunity, the distribution for the SIS case is not as concentrated as that for the SIR case.

The distribution of infected individuals (as shown in figure 3*b*) is always monotonically increasing. The principal effect of reducing the average period of immunity is to increase the equilibrium proportion of the population that are infected. Infected individuals with low levels of immunity are considered highly infectious and symptomatic, whereas those with high levels of immunity are considered asymptomatic with a low capacity for transmission. The shapes of the distributions imply that as a_x (the rate of loss of immunity) increases, the ratio of symptomatic to asymptomatic infecteds decreases. Therefore, implying a significant role for asymptomatic infections in SIS type infections.

6. DISCUSSION

We have developed a framework for microparasite transmission dynamics that permits individual hosts to exhibit immunity on a continuous dimension. Different levels of immunity can be associated with different susceptibilities to infection and disease, and with different levels of infectiousness. We have demonstrated that the equilibrium, with respect to time, shows similar results to those expected from SIR and SIS models, suggesting that this framework fills the gap between these two extremes.

This model provides a framework for the inclusion of results from models of immune responses to specific infections in the form of the functions for increasing and decreasing immunity (k_x and k_y, respectively). Consequently, the model provides a potential link between models describing the interaction between infection and immunity, and infection dynamics.

We propose an arbitrary scale for immunity level. It only becomes meaningful for a particular infection when the appropriate functions are defined in relation to some measurable quantity relating to immune protection. The most obvious candidate is some measure of antibody titre, which is already commonly used in seroepidemiological research as an approach to defining susceptibility/immunity for many viral infections (Chen *et al.* 1990). Part of the motivation for the current model is the desire to relate measured antibody levels to the degree of immunity in infections where reinfection is common (Cox *et al.* 1998*a*,*b*), so that we choose to include an upper bound for immunity (rather than allowing immunity to develop infinitely) as measures of immunity are bounded (Hutber & Kitching 1996).

Although potentially important, this framework requires some development before it can be applied profitably. In particular, the dynamics and existence and stability of equilibria with respect to time are important. These can be investigated through numerical solution, and we are currently addressing this problem. However, numerical solution of this type of system is very prone to the accumulation of errors, especially through the integral required to calculate the rate of infection (Sulsky 1993; Milner & Rabbio 1992). Consequently, analytical results for the existence and form of the equilibrium are ideally required.

Using the most simple forms for processes such as recovery, loss of immunity and altered susceptibility, the model has demonstrated a variety of behaviours, some of which are not easily categorized as SIR or SIS types. We are currently developing a numerical solution for the system which will allow us to further explore the possibility that important information is being discarded in the process of converting an antibody titre to a binary measure. It will also be possible, at this stage, to use the abundance of serological data and intra-host models available when modelling the transmission of a specific disease.

Another interesting aspect of this framework is that the rate of recovery from infection, determined by k_y, can be made a function of z such that the distribution of infectious periods need not be negatively exponential. The recovery of hosts before reaching full immunity may also be included in the framework by adding a flow from infected to uninfected states (similar to the transmission term), the magnitude of which would depend on the level of immunity of the infected host. By increasing the rate of recovery with increasing immunity, the length of the tail of the distribution will reduce. Our current results do not emphasize this effect, as we have to fix the rate of infection. Alternative model assumptions could include removing the upper bound for immunity. However, including an upper bound introduces a maximum infectious period which is more appropriate than allowing a small proportion of hosts to have an infinitely long infectious period (Keeling & Grenfell 1996).

Likewise, the effect of waning immunity due to vaccination has been demonstrated to be important, and a determinant of vaccination programme success (Edmunds *et al.* 1996; Mossong *et al.* 1998). Immunity as a function of time since recovery from infection or vaccination, can naturally be included in this framework by appropriate choices of the rate of loss of immunity.

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REFERENCES

Anderson, R. M. & May, R. M. 1991 *Infectious diseases of humans: dynamics and control*. Oxford University Press.

Andreassen, V., Lin, J. & Levin, S. A. 1997 The dynamics of cocirculating influenza strains conferring partial cross-immunity. *J. Math. Biol.* **35**, 825–842.

Calvert, N., Cutts, F., Irving, R., Brown, D., Marsh, J. & Miller, E. 1996 Measles immunity and response to revaccination among secondary school children in Cumbria. *Epidemiol. Infect.* **116**, 65–70.

Castillo-Chavez, C., Wenzhang, H. & Li, J. 1997 The effects of females' susceptibilty on the coexistence of multiple pathogen strains of sexually transmitted diseases. *J. Math. Biol.* **35**, 503–522.

Chen, R. T., Markowitz, L. E., Albrecht, P., Stewart, J. A., Mofenson, L. M., Preblud, S. R. & Orenstein, W. A. 1990 Measles antibody: reevaluation of protective titres. *J. Infect. Dis.* **62**, 1036–1042.

Cox, M. J., Azevedo, R. S., Nokes, D. J., Beards, G. M., McCrae, M. A., Massad, E. & Medley, G. F. 1998*a* Seroepidemiology of group A rotavirus in suburban São Paulo, Brazil. *Epidemiol. Infect.* (In the press.)

Cox, M. J., Azevedo, R. S., Massad, E., Cane, P. A. & Medley, G. F. 1998*b* Seroepidemiological study of respiratory syncytial virus in São Paulo State, Brazil. *J. Med. Virol.* **55**, 234–239.

Edmunds, W. J., Medley, G. F. & Nokes, D. J. 1996 Vaccination against hepatitis B virus (HBV) in highly endemic areas: waning vaccine immunity and the need for booster doses. *Trans. R. Soc. Trop. Med. Hyg.* **90**, 436–440.

Gay, N. J. 1996 Analysis of serological surveys using mixture models: application to a survey of parvovirus B19. *Statist. Med.* **15**, 1567–1573.

Hutber, A. M. & Kitching, R. P. 1996 The use of vector transmission in the modelling of intraherd foot-and-mouth disease. *Environ. Ecol. Statist.* **3**, 245–255.

Keeling, M. J. & Grenfell, B. T. 1997 Disease extinction and community size: modelling the persistence of measles. *Science* **275**, 65–67.

Kermack, W. O. & McKendrick, A. G. 1927 A contribution to the mathematical theory of epidemics. *Proc. R. Soc. Lond.* A **722**, 700–721.

Milner, F. A. & Rabbio, G. 1992 Rapidly converging numerical algorithms for models of population dynamics. *J. Math. Biol.* **30**, 733–753.

Mossong, J., Nokes, D. J., Edmunds, W. J., Cox, M. J., Ratnam, S. & Miller, C. P. 1998 Modelling the impact of sub-clinical measles transmission in vaccinated populations with waning immunity. *Am. J. Epidemiol.* (Submitted.)

Offit, P. A. 1994 Rotaviruses: immunological determinants protection against infection and disease. *Adv. Virus Res.* **44**, 161–202.

Sulsky, D. 1993 Numerical solution of structured population models. I. Age structure. *J. Math. Biol.* **31**, 817–839.

White, L. J., Cox, M. J. & Medley, G. F. 1998 Cross-immunity and vaccination against multiple pathogen strains. *IMA J. Math. Appl. Med. Biol.* (In the press.)

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