THE ROYAL SOCIETY

'Small worlds' and the evolution of virulence: infection occurs locally and at a distance

Michael Boots[1,2*] **and Akira Sasaki**[1]

[1]*Laboratory of Mathematical Biology, Department of Biology, Faculty of Science, Kyushu University, Higashi-ku, Fukuoka-shi, Japan*
[2]*Laboratory of Medical Entomology, Institute of Tropical Medicine, Nagasaki University, 1–12–4 Sakamoto, Nagasaki 852, Japan*

Why are some diseases more virulent than others? Vector-borne diseases such as malaria and water-borne diseases such as cholera are generally more virulent than diseases spread by direct contagion. One factor that characterizes both vector- and water-borne diseases is their ability to spread over long distances, thus causing infection of susceptible individuals distant from the infected individual. Here we show that this ability of the pathogen to infect distant individuals in a spatially structured host population leads to the evolution of a more virulent pathogen. We use a lattice model in which reproduction is local but infection can vary between completely local to completely global. With completely global infection the evolutionarily stable strategy (ESS) is the same as in mean-field models while a lower virulence is predicted as infection becomes more local. There is characteristically a period of relatively moderate increase in virulence followed by a more rapid rise with increasing proportions of global infection as we move beyond a 'critical connectivity'. In the light of recent work emphasizing the existence of 'small world' networks in human populations, our results suggests that if the world is getting 'smaller'—as populations become more connected—diseases may evolve higher virulence.

Keywords: lattice model; parasite evolution; spatial structure; vector-borne disease; water-borne disease

1. INTRODUCTION

The study of the evolution of virulence in parasites, broadly defined to include pathogens such as viruses and bacteria, has become a central issue of modern evolutionary biology. Recent work has strongly challenged the old wisdom that parasites evolve to become harmless to their hosts (May & Anderson 1983), predicting a variety of outcomes under different conditions. One of the major challenges that remain is to explain the remarkable variation in the harm which infectious organisms inflict on their hosts. Here we consider the importance of the distance over which infection occurs in determining parasite virulence.

Classical parasite and disease models assume completely mixing host populations in which each infected individual is equally likely to infect each susceptible individual (Anderson & May 1979, 1991; Bowers *et al.* 1994; Boots & Haraguchi 1999). Under this assumption, selection of the parasite–disease will, under many circumstances, tend to increase the parasite's reproductive rate, i.e. the number of secondary infections caused by a single infected host (May & Anderson 1979; Bremermann & Pickering 1983). The reproductive rate is dependent on the parasite transmission rate and the length of the infectious period, which in turn is determined by the death rate (virulence) and rate of recovery of infected individuals. If there is no relationship between the transmission rate and virulence, theoretical models that assume completely mixing host populations (mean-field models) predict the evolution of infinite transmission and minimum virulence (May & Anderson 1979, 1983; Lenski & May 1994). Commonly, however, we expect a trade-off for the parasite where high transmission is associated with high virulence. Then the models predict high or ever increasing transmission and virulence unless virulence increases sublinearly with transmission (May & Anderson 1983). However, the parasite reproductive rate is not always maximized (Levin & Pimentel 1981; Bonhoffer & Nowak 1994; Lipsitch & Nowak 1995). For example, superinfection, where more than one parasite infects an individual host, leads to higher virulence (Axelrod & Hamilton 1981; Bremermann & Pickering 1983; Sasaki & Iwasa 1991; Frank 1992; Nowak & May 1994; Sasaki 1994; Van Baalen & Sabelis 1995; Mosquera & Adler 1998). This is a consequence of intrahost competition between strains favouring a more virulent parasite. It has also been shown that higher virulence will evolve in expanding host populations (Lenski & May 1995).

At present, there is a great deal of interest in the role of spatial structure in both ecology and evolution. All systems are to some degree spatially extended; however, the classical theory of the evolution of parasites ignores spatial effects with its assumption of homogeneous mixing. It is likely that local processes will play an important role in the majority of host–parasite interactions particularly when infection occurs through the direct contact of infected and susceptible individuals (Frank 1991; Dwyer 1992; Rand *et al.* 1995; Schinazi 1996; White *et al.* 1996; Keeling 1999*a*,*b*). As a consequence of this, there has recently been some attempt to take spatial structure explicitly into account when examining the

*Author for correspondence (mike@biology.kyushu-u.ac.jp).

Received 3 June 1999 *Accepted* 12 July 1999

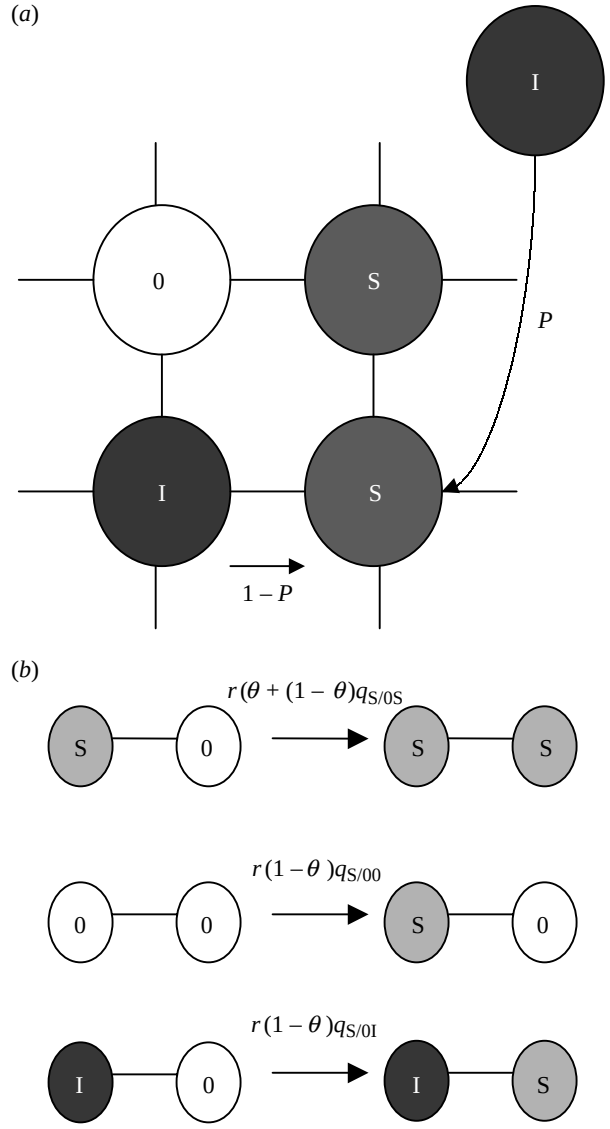

Figure 1. (*a*) The arrangement of part of the regular lattice where the sites can be one of three sites: empty (0), occupied by a susceptible (S) or occupied by an infected (I) individual. Each site has four nearest neighbours ($z=4$) with which it interacts. We illustrate the infection process of a susceptible individual who can be infected from a nearest-neighbour site at probability $1-P$ and globally from a distant site at probability P. (*b*) The reproductive process with possible pair states and their transmission probabilities.

evolution of parasites (Claessen & De Roos 1995; Rand *et al.* 1995). For example, when completely local, nearest-neighbour infection and host reproduction has been assumed (Rand *et al.* 1995; Haraguchi & Sasaki 1999) the parasite has been shown to evolve to a critical, finite transmission rate and a correspondingly lower virulence, independent of the shape of the trade-off curve chosen.

When all interactions are local, only suceptible individuals next to an infected individual can become infected. The completely local and completely global (mean-field) approximations provide the two extremes of what is in reality a continuum of different proportions of local and distant infection. Different host–parasite interactions will have different degrees of local, as opposed to global, random infection. For example, vector-borne or water-borne diseases may be spread over greater distances than those spread by direct contact. It has been suggested that high proportions of distant transmission may lead to the evolution of higher virulence (Ewald 1994). Here we consider the situation where host reproduction is local but infection can vary from completely local to completely global. The global infection may be a consequence of any number of general processes including water-borne and vector-borne transmission, as well as relatively rapid, distant movement of infected hosts. A simple generalized host–pathogen/parasite model is considered for clarity and general applicability to a wide range of hosts, parasites and diseases.

2. THE MODEL

We represent space by considering a regular network of sites, each of which contains either a single host individual or is empty. There are three possible states to each site: empty (0), occupied by a susceptible host (S) or occupied by an infected host (I). Susceptible host individuals reproduce at rate r into neighbouring empty sites while infection occurs from the contact of an infected and susceptible locally at neighbouring sites and globally at sites chosen at random (P denotes the proportion of global infection where $0 \leqslant P \leqslant 1$; figure 1). Hosts do not move between sites and infected individuals have a higher death rate ($d+\alpha$) than that of susceptibles (d). There are a number of strains (i) of the parasite that differ in their transmission rate (β) (the probability of causing infection) and have correlated changes in the increased death rate (α) that infection causes in their hosts (virulence). Evolution occurs through small mutations (in any single time-step mutation to the strain with the next highest or next lowest transmission rate can occur). We initially assume that infected individuals do not reproduce.

When all the interactions are local—such that the pathogen is transmitted only to local, nearest-neighbouring individuals ($P=0$) and reproduction occurs to nearest-neighbour vacant sites—the parasite always evolves to a finite transmission rate and corresponding virulence (Haraguchi & Sasaki 1999). This occurs even when the mean-field model, in which all the interactions are global, predicts an infinite transmission rate and virulence. Here reproduction is local, but transmission can vary from completely local to completely global. We can determine the evolutionarily stable virulence for the parasite by invasion analysis from pair density dynamics (Sato *et al.* 1994).

The state of each site is included in $\boldsymbol{S}' \equiv \{0, \mathrm{S}, \mathrm{I}\}$. Let $\rho_\sigma(t)$ ($\sigma \in \boldsymbol{S}'$) be the probability that a randomly chosen site has state σ at time t, and $P_{\sigma\sigma'}$ be a probability that a randomly chosen site has state σ and one of its randomly chosen nearest neighbours has state σ' (σ and $\sigma' \in \boldsymbol{S}'$). Let $q_{\sigma/\sigma'}$ be a conditional probability that a randomly chosen nearest neighbour of a σ' site is a σ site. Let $q_{\sigma/\sigma'\sigma''}$ be a conditional probability that a randomly chosen nearest neighbour of a $\sigma'\sigma''$ pair is a σ site. Reproduction is local and, therefore, depends on the number of susceptibles around each site ($q_{\mathrm{S}/0\mathrm{S}}$, $q_{\mathrm{S}/0\mathrm{I}}$, $q_{\mathrm{S}/00}$). Here d is the death rate of susceptible hosts, α the increased death rate due to infection, r the reproductive rate of the susceptibles (in this scheme the infecteds do not reproduce) and β the

transmission rate of the pathogen. The pairs of states approximately change such that

$$\frac{dp_{SS}}{dt} = 2r\{\theta + (1-\theta)q_{S/0S}\}p_{S0} - \{2d + 2P\beta x_I + 2(1-P)\beta(1-\theta)q_{I/SS}\}p_{SS}, \quad (1)$$

$$\frac{dp_{S0}}{dt} = r(1-\theta)q_{S/00}p_{00} + dp_{SS} + (d+\alpha)p_{IS} - [d + r\{\theta + (1-\theta)q_{S/0S}\} + P\beta x_I + (1-P)\beta(1-\theta)q_{I/0S}]p_{S0}, \quad (2)$$

$$\frac{dp_{00}}{dt} = 2dp_{S0} + 2(d+\alpha)p_{I0} - 2r(1-\theta)q_{S/00}p_{00}, \quad (3)$$

$$\frac{dp_{II}}{dt} = 2P\beta x_I p_{IS} + 2\beta(1-P)\{\theta + (1-\theta)q_{I/IS}\}p_{IS} - 2(d+\alpha)p_{II}, \quad (4)$$

$$\frac{dp_{IS}}{dt} = r(1-\theta)q_{S/0I}p_{I0} + P\beta x_I p_{SS} + (1-P)\beta(1-\theta)q_{I/SS}p_{SS} - [2d + \alpha + P\beta x_I + (1-P)\beta\{\theta + (1-\theta)q_{I/SI}\}]p_{IS}, \quad (5)$$

$$\frac{dp_{I0}}{dt} = P\beta x_I p_{S0} + \beta(1-P)(1-\theta)q_{I/S0}p_{S0} + dp_{IS} + (d+\alpha)p_{II} - \{d + \alpha + r(1-\theta)q_{S/0I}\}p_{I0}, \quad (6)$$

where $x_I = p_{II} + p_{IS} + p_{I0}$ is the global density of the infecteds and $\theta = 1/z$ where z is the number of nearest neighbours for each site ($z=4$ for a regular two-dimensional lattice).

3. ANALYSIS

From the pair density dynamics (equations (1)–(6)), the global density of infecteds follows exactly as

$$\frac{dx_I}{dt} = [\beta\{Px_S + (1-P)q_{S/I}\} - (d+\alpha_I)]x_I. \quad (7)$$

If a mutant parasite strain J invades a population at endemic equilibrium with strain I, the growth rate of the mutant when rare is approximated as

$$\lambda(J|I) = \frac{1}{x_J}\frac{dx_J}{dt} = \beta_J\{P\hat{x}_S + (1-P)\hat{q}^0_{S/J}\} - (d+\alpha_J), \quad (8)$$

where $\hat{q}^0_{S/J}$ is the local density of susceptible individuals in the neighbourhood of the mutant parasite at a quasi-equilibrium (any conditional density including $q_{S/J}$ in the nearest neighbourhood of a rare mutant parasite J changes much faster than that of its global density x_J and, hence, it can be approximated by the quasi-equilibrium value—the equilibrium value for a fixed global density; Matsuda *et al.* 1992). Since

$$P\hat{x}_S + (1-P)\hat{q}_{S/I} = \frac{d+\alpha_I}{\beta_I} \quad (9)$$

holds at the endemic equilibrium of the resident strain I, therefore, the sign of

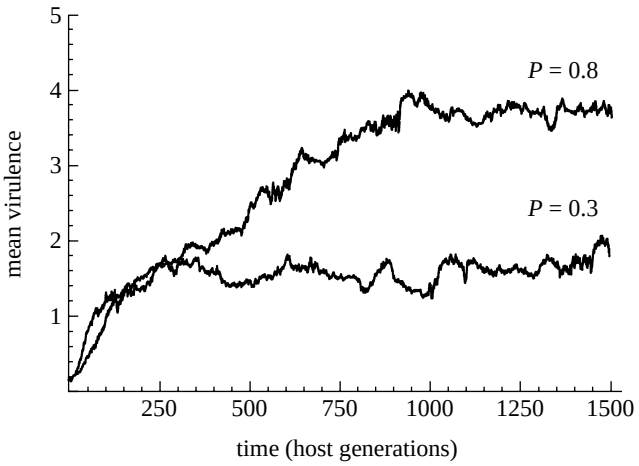

Figure 2. Simulations of the evolution of mean virulence of the disease population through time at two different levels of global infection: (*a*) $P=0.3$ and (*b*) $P=0.8$. The maximum virulence (α_{max}) is fixed at 4.767 and the reproduction rate (r) at 3, the mutation rate is 0.015, the disease-free death rate (d) is 0.01 and the lattice size is 100×100. The transmission rate (β) and the virulence (α) are linked such that $\beta = 3\alpha$. Selection is low as $P \to 1$ due to the linear trade-off function chosen.

$$\lambda(J|I) = \beta_J\left[\left(\frac{d+\alpha_I}{\beta_I} - \frac{d+\alpha_J}{\beta_J}\right) + (1-P)(\hat{q}^0_{S/J} - \hat{q}_{S/I})\right], \quad (10)$$

determines the invasibility of the mutant.

From equation (10) we can see that, when transmission is completely global ($P=1$), evolution maximizes the basic reproductive rate $R_0 = (d+\alpha)/\beta$. The ESS is therefore the same as when we completely ignore spatial structure. Otherwise ($P<1$) the ESS of the parasite is different from that in the completely mixing population and there is no simple quantity such as R_0 that is maximized. Local transmission ($P<1$) favours the pathogen that increases the local density of its nearest neighbours that are susceptible ($q_{S/I}$). This in turn implies that a parasite with a lower basic reproductive rate can overcome one with a higher basic reproductive rate.

It should also be noted that, if $\beta_I < \beta_{ESS} < \beta_J$, the two strains may coexist under some circumstances. When this is the case, it follows that

$$\frac{1}{R_{0I}} - (1-P)q_{S/I} = \frac{1}{R_{0J}} - (1-P)q_{S/J} = Px_S. \quad (11)$$

Therefore, two strains with different basic reproductive rates may coexist when the one with the inferior basic reproductive rate compensates for this with a higher local density of susceptibles. This is not the case without spatial structure where R_0 is maximized.

Therefore, if infection is global ($P=1$), the highest attainable transmission rate is predicted for the pathogen, regardless of whether host reproduction is local (here with $P=1$) or global (classical mean-field approximation) (May & Anderson 1983). Simulation shows that, when a proportion of the infection is local and a proportion global, we obtain evolution of intermediate transmission rates between the two extremes. Figure 2 shows how an increased proportion of global infection leads to

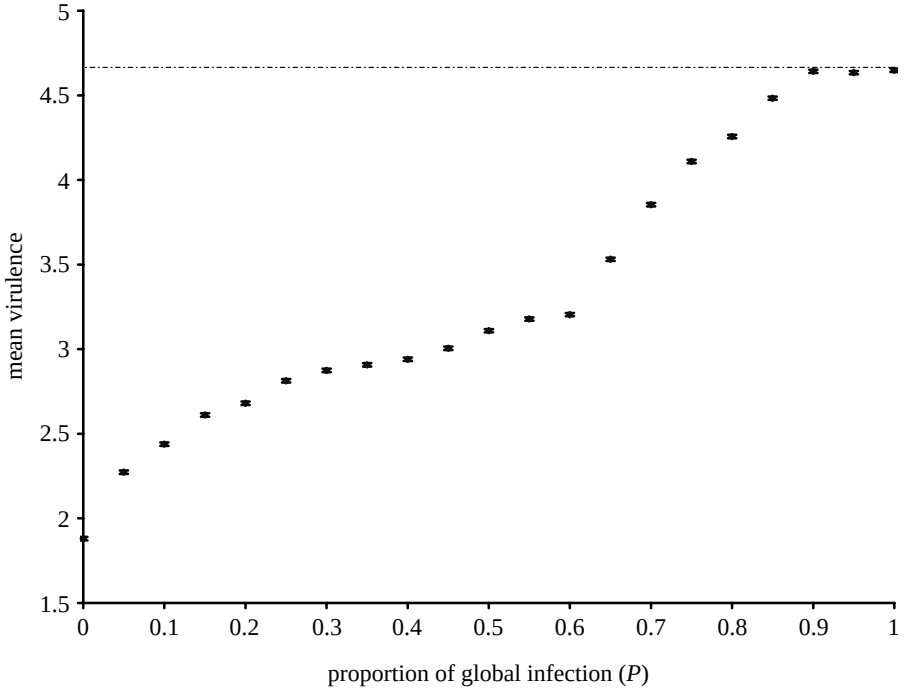

Figure 3. Long-term steady mean equilibrium virulence ($\pm$s.d.) at different levels of global infection. The equilibrium virulence is calculated by taking the mean of the long-term average once the steady state is reached. The maximum virulence (α_{max}) is fixed at 4.767, the mutation rate is 0.015, the reproduction rate (r) is 1.0, the disease-free death rate (d) is 0.01 and the lattice size is 150×150. The transmission rate (β) and the virulence (α) are linked such that $\beta = 3\alpha^2$. The shape of the trade-off curve leads to greater selection at higher values of P than the linear trade-off. For values of $P = 0.9$ or above virulence approaches the maximum value (dashed line) consistent with a mutation–selection balance. The analytical results (neglecting the mutation–selection balance) predict infinite virulence here for $P = 1.0$.

the evolution of higher virulence when there is a linear trade-off between the transmission rate and virulence ($\beta = \alpha$). These results do not depend on the details of the model chosen and are consistent for different trade-offs between transmission and virulence. Figure 3 emphazises this point, showing that virulence increases as the proportion of infection via global transmission increases when a trade-off function of the form $\beta = \alpha^2$ is chosen and infected individuals are allowed to reproduce. An equivalent mathematical analysis to the one above again shows that the ESS transmission rate is the same as in the completely mixed model when all the infection is random ($P = 1$) when infecteds reproduce. In simulations for intermediate values of P we find that, as P and, therefore, the actual proportion of global infections and, therefore, the overall connectivity of the population increase, there is a range of relatively moderate increase in virulence followed by a more rapid increase (around $P = 0.6$ in figure 3). Beyond this 'critical connectivity' as we approach $P = 1$ (where the ESS virulence is infinite) we find that we have the maximum virulence consistent with a mutation–selection balance.

The absolute virulence and transmission rate that is predicted depends on various parameters, such as the reproductive rate of the host. However, the role of the proportion of global infection is consistently that illustrated in figure 3. The critical connectivity may provide a basis for comparisons of the effect on virulence of various parameters, such as the reproductive rate, and complexities that capture particular disease characteristics, such as acquired immunity. Using this measure, we may be able to predict the general characteristics of diseases that lead to high virulence.

4. DISCUSSION

We have clearly shown that the degree of local and global transmission of a parasite is critical in determining its evolutionarily stable transmission rates and virulence. When infections occur predominantly locally we predict a lower virulence than when transmissions occur predominantly randomly throughout the population. The importance of spatial structure in a wide variety of evolutionary and ecological systems is being increasingly recognized. Our work demonstrates this importance in that considerable differences occur between the predictions of spatially explicit and mean-field models. However, the present study goes further in that it also emphasizes that 'local' and 'global' interactions are two extremes of a continuum. We show that the intermediate states between these two extremes are also important, with rapid increases in virulence occurring around a critical connectivity. Given that many if not most interactions in nature will fall within the two extremes of the standard 'spatial' and 'non-spatial' models, our approach may prove necessary for understanding the role of space in many ecological and evolutionary interactions.

The lower parasite transmission rates that are predicted in spatially viscous host populations may intuitively be understood to be due to two related processes. First, an invading mutant parasite that is on average surrounded by a higher proportion of susceptible hosts

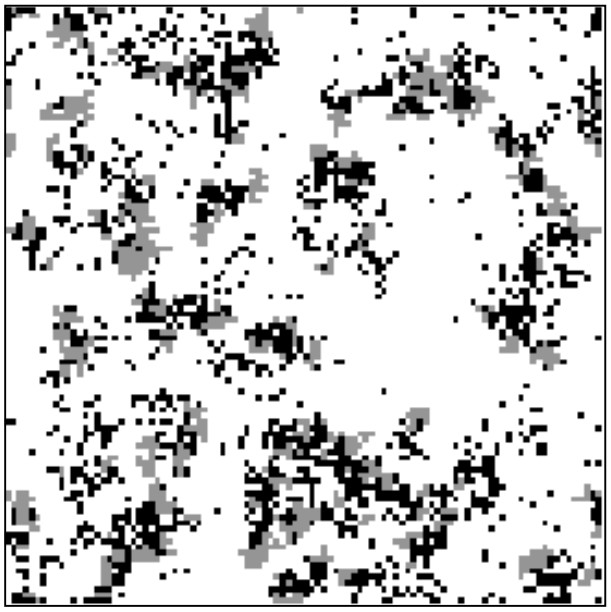

Figure 4. Snapshots of a 100×100 lattice equivalent to those in figure 2 with $P = 0.3$ and $r = 5$. Clusters of individuals can be seen with the grey dots representing susceptible individuals and black dots representing infected individuals.

than the resident parasites is able to invade the population. This can occur even if the invading mutant has a lower basic reproductive rate. Since a low transmission rate and low virulence tend to increase the local density of susceptible individuals around infected hosts, spatial structure within clusters of individuals favours a lower transmission rate and lower virulence. This process can be seen as 'self shading' by infected hosts, reducing their effective transmission rate. It should be noted that this first mechanism does not rely on any group selection argument. In addition, the spatial separation of the clusters also favours the evolution of lower transmission rates since parasites with high transmission rates and high virulence will tend to infect all the individuals in a cluster quickly. This in turn leads to relatively rapid local cluster extinction (figure 4) and, therefore, a low probability of transmission to another cluster. When there is an increasing proportion of global infection ($P \rightarrow 1$) these local processes break down. The rapid rise in ESS virulence beyond the critical connectivity may relate to the average spatial separation of the clusters. This will tend to determine the likelihood of virulent parasites 'jumping' to other clusters and the ESS transmission rate becomes a balance between local extinction and the probability of escaping to a fresh cluster.

The theoretical pattern that we have observed can explain the observed virulence of many diseases. For example, it neatly explains the well-known correlation between virulence and the degree of water-borne transmission of diarrhoeal diseases caused by pathogenic bacteria of the gastrointestinal tract (Ewald 1991, 1994). Diseases with a high proportion of water-borne transmission, such as the classical biotype of *Vibrio cholerae* and *Shigella dysenteriae* type 1, cause higher mortality in untreated hosts than diseases such as non-typhoid *Salmonella* and *Campylobacter jejuni* with a higher non-water-borne transmission (Ewald 1991). Here high proportions of water-borne transmission correspond to a relatively high P and, therefore, we would predict the evolution of higher virulence. On a more basic level it can help to explain why vector-borne diseases are characteristically more virulent than diseases spread by local contact (Ewald 1994). Vectors will tend to increase the number of distant infections due to their own movement and, therefore, increase P and the ESS virulence of the disease.

Of great additional interest is the relevance of this study to the 'small world' phenomena (Kochen 1989) that were recently examined in a number of contexts by models of static networks with a high degree of clustering and characteristically short path lengths between sites (Watts & Strogatz 1998). Our model differs from those of Watts & Strogatz (1998) in that the connections between the different sites are dynamic. However, since we are studying systems in evolutionary time, it is more realistic to adopt our dynamic approach (see also Keeling (1999*a*,*b*) for an alternative approach with a partly irregular connection). In terms of infection, when $P \rightarrow 1$ we approach the smallest most connected world, while $P \rightarrow 0$ approximates to the least connected 'big world'. Modern social networks (Wasserman & Faust 1994) are known to be small worlds (Watts & Strogatz 1998) and it follows that infection networks may also show 'small world' connections in modern societies. It seems reasonable to assume that human societies in the past were often much larger worlds with interactions more localized within more isolated communities. At that time most infections and diseases spread by contact would have occurred locally ($P \rightarrow 0$). The present study suggests that these diseases would therefore have evolved a relatively low virulence. Connectivity in modern populations has undoubtedly increased and seems likely to continue to increase, not least through improved transportation. As connectivity increases and the world becomes 'smaller', more infections will occur at a distance ($P \rightarrow 1$) and, therefore, diseases may evolve to be more virulent. Therefore, if human societies become more connected as the world gets 'smaller', we may be at an increasing risk from virulent diseases and parasites.

This work was funded by the European Union and the Japanese Ministry of Education, Science and Technology.

REFERENCES

Anderson, R. M. & May, R. M. 1979 Population biology of infectious diseases. I. *Nature* **280**, 361–367.

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

Axelrod, R. & Hamilton, W. D. 1981 The evolution of cooperation. *Science* **211**, 1390–1396.

Bonhoffer, S. & Nowak, M. 1994 Mutation and the evolution of virulence. *Proc. R. Soc. Lond.* B **258**, 133–140.

Boots, M. & Haraguchi, Y. 1999 The evolution of costly resistance in host–parasite systems. *Am. Nat.* **153**, 359–370.

Bowers, R. G., Boots, M. & Begon, M. 1994 Life-history tradeoffs and the evolution of pathogen resistance: competition between host strains. *Proc. R. Soc. Lond.* B **257**, 247–253.

Bremermann, H. J. & Pickering, J. 1983 A game-theoretical model of parasite virulence. *J. Theor. Biol.* **100**, 411–426.

Claessen, D. & De Roos, A. 1995 Evolution of virulence in a host–pathogen system with local pathogen transmission. *Oikos* **74**, 401–413.

Dwyer, G. 1992 On the spatial spread of insect pathogens—theory and experiment. *Ecology* **73**, 479–494.

Ewald, P. W. 1991 Waterborne transmission and the evolution of virulence among gastrointestinal bacteria. *Epidemiol. Infect.* **106**, 83–119.

Ewald, P. W. 1994 *Evolution of infectious disease*. Oxford University Press.

Frank, S. A. 1991 Spatial variation in coevolutionary dynamics. *Evol. Ecol.* **5**, 193–217.

Frank, S. A. 1992 A kin selection model for the evolution of virulence. *Proc. R. Soc. Lond.* B **250**, 195–197.

Haraguchi, Y. & Sasaki, A. 1999 The evolution of virulence in viscous populations. *J. Theor. Biol.* (Submitted.)

Keeling, M. J. 1999*a* Correlation equations for endemic diseases: externally imposed and internally generated heterogeneity. *Proc. R. Soc. Lond.* B **266**, 953–961.

Keeling, M. J. 1999*b* The effects of local spatial structure on epidemiological invasions. *Proc. R. Soc. Lond.* B **266**, 859–869.

Kochen, M. (ed.) 1989 *The small world*. Norwood, NJ: Ablex.

Lenski, R. & May, R. M. 1994 The evolution of virulence in parasites and pathogens: reconciliation between two competing hypotheses. *J. Theor. Biol.* **169**, 253–265.

Lenski, R. & May, R. M. 1995 The evolution of virulence: a reconciliation between two conflicting hypotheses. *J. Theor. Biol.* **169**, 253–265.

Levin, S. A. & Pimentel, D. 1981 Selection of intermediate rates of increase in parasite–host systems. *Am. Nat.* **117**, 308–315.

Lipsitch, M. & Nowak, M. A. 1995 The evolution of virulence in sexually transmitted HIV/AIDS. *J. Theor. Biol.* **174**, 427–440.

Matsuda, H., Ogita, A., Sasaki, A. & Sato, K. 1992 Statistical mechanics of population—the lattice Lotk–Volterra model. *Prog. Theor. Phys.* **88**, 1035–1049.

May, R. M. & Anderson, R. M. 1979 Population dynamics of infectious diseases. II. *Nature* **280**, 455–461.

May, R. M. & Anderson, R. M. 1983 Epidemiology and genetics in the coevolution of parasites and hosts. *Proc. R. Soc. Lond.* B **219**, 281–313.

Mosquera, J. & Adler, F. R. 1998 Evolution of virulence: a unified framework for coinfection and superinfection. *J. Theor. Biol.* **195**, 293–313.

Nowak, M. A. & May, R. 1994 Superinfection and the evolution of parasite virulence. *Proc. R. Soc. Lond.* B **255**, 81–89.

Rand, D. A., Keeling, M. & Wilson, H. B. 1995 Invasion, stability and evolution to criticality in spatially extended, artificial host–pathogen ecology. *Proc. R. Soc. Lond.* B **259**, 55–63.

Sasaki, A. 1994 Evolution of antigen drift/switching: continuously evading pathogens. *J. Theor. Biol.* **168**, 291–308.

Sasaki, A. & Iwasa, Y. 1991 Optimal growth schedule of pathogens within a host: switching between lytic and latent cycles. *Theor. Popul. Biol.* **39**, 201–239.

Sato, K., Matsuda, H. & Sasaki, A. 1994 Pathogen invasion and host extinction in lattice structured populations. *J. Math. Biol.* **32**, 251–268.

Schinazi, R. 1996 On an interacting particle system modeling an epidemic. *J. Math. Biol.* **34**, 915–925.

Van Baalen, M. & Sabelis, M. 1995 The dynamics of multiple infection and the evolution of virulence. *Am. Nat.* **146**, 881–910.

Wasserman, S. & Faust, K. 1994 *Social network analysis: methods and applications*. Cambridge University Press.

Watts, D. J. & Strogatz, S. H. 1998 Collective dynamics of 'small-world' networks. *Nature* **393**, 440–442.

White, A., Begon, M. & Bowers, R. G. 1996 Host–pathogen systems in a spatially patchy environment. *Proc. R. Soc. Lond.* B **263**, 325–332.