International Institute for
Applied Systems Analysis
Schlossplatz 1
A-2361 Laxenburg, Austria

Tel: +43 2236 807 342
Fax: +43 2236 71313
E-mail: publications@iiasa.ac.at
Web: www.iiasa.ac.at

Interim Report **IR-02-008**

Super- and Coinfection: The Two Extremes

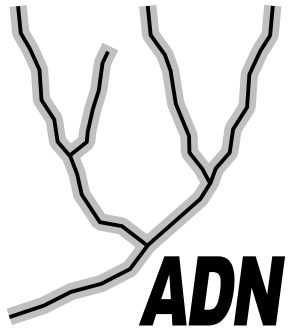
Martin A. Nowak (nowak@ias.edu)
Karl Sigmund (sigmund@univie.at)

Approved by

Ulf Dieckmann(dieckman@iiasa.ac.at)
Project Leader, Adaptive Dynamics Network

February 2002

IIASA STUDIES IN ADAPTIVE DYNAMICS NO. 60



The Adaptive Dynamics Network at IIASA fosters the development of new mathematical and conceptual techniques for understanding the evolution of complex adaptive systems.

Focusing on these long-term implications of adaptive processes in systems of limited growth, the Adaptive Dynamics Network brings together scientists and institutions from around the world with IIASA acting as the central node.

Scientific progress within the network is collected in the IIASA Studies in Adaptive Dynamics series.

No. 1 Metz JAJ, Geritz SAH, Meszéna G, Jacobs FJA, van Heerwaarden JS: *Adaptive Dynamics: A Geometrical Study of the Consequences of Nearly Faithful Reproduction.* IIASA Working Paper WP-95-099 (1995). van Strien SJ, Verduyn Lunel SM (eds): Stochastic and Spatial Structures of Dynamical Systems, Proceedings of the Royal Dutch Academy of Science (KNAW Verhandelingen), North Holland, Amsterdam, pp. 183-231 (1996).

No. 2 Dieckmann U, Law R: *The Dynamical Theory of Coevolution: A Derivation from Stochastic Ecological Processes.* IIASA Working Paper WP-96-001 (1996). Journal of Mathematical Biology 34:579-612 (1996).

No. 3 Dieckmann U, Marrow P, Law R: *Evolutionary Cycling of Predator-Prey Interactions: Population Dynamics and the Red Queen.* IIASA Preprint (1995). Journal of Theoretical Biology 176:91-102 (1995).

No. 4 Marrow P, Dieckmann U, Law R: *Evolutionary Dynamics of Predator-Prey Systems: An Ecological Perspective.* IIASA Working Paper WP-96-002 (1996). Journal of Mathematical Biology 34:556-578 (1996).

No. 5 Law R, Marrow P, Dieckmann U: *On Evolution under Asymmetric Competition.* IIASA Working Paper WP-96-003 (1996). Evolutionary Ecology 11:485-501 (1997).

No. 6 Metz JAJ, Mylius SD, Diekmann O: *When Does Evolution Optimize? On the Relation Between Types of Density Dependence and Evolutionarily Stable Life History Parameters.* IIASA Working Paper WP-96-004 (1996).

No. 7 Ferrière R, Gatto M: *Lyapunov Exponents and the Mathematics of Invasion in Oscillatory or Chaotic Populations.* Theoretical Population Biology 48:126-171 (1995).

No. 8 Ferrière R, Fox GA: *Chaos and Evolution.* IIASA Preprint (1996). Trends in Ecology and Evolution 10:480-485 (1995).

No. 9 Ferrière R, Michod RE: *The Evolution of Cooperation in Spatially Heterogeneous Populations.* IIASA Working Paper WP-96-029 (1996). The American Naturalist 147:692-717 (1996).

No. 10 van Dooren TJM, Metz JAJ: *Delayed Maturation in Temporally Structured Populations with Non-Equilibrium Dynamics.* IIASA Working Paper WP-96-070 (1996). Journal of Evolutionary Biology 11:41-62 (1998).

No. 11 Geritz SAH, Metz JAJ, Kisdi É, Meszéna G: *The Dynamics of Adaptation and Evolutionary Branching.* IIASA Working Paper WP-96-077 (1996). Physical Review Letters 78:2024-2027 (1997).

No. 12 Geritz SAH, Kisdi É, Meszéna G, Metz JAJ: *Evolutionary Singular Strategies and the Adaptive Growth and Branching of the Evolutionary Tree.* IIASA Working Paper WP-96-114 (1996). Evolutionary Ecology 12:35-57 (1998).

No. 13 Heino M, Metz JAJ, Kaitala V: *Evolution of Mixed Maturation Strategies in Semelparous Life-Histories: The Crucial Role of Dimensionality of Feedback Environment.* IIASA Working Paper WP-96-126 (1996). Philosophical Transactions of the Royal Society of London Series B 352:1647-1655 (1997).

No. 14 Dieckmann U: *Can Adaptive Dynamics Invade?* IIASA Working Paper WP-96-152 (1996). Trends in Ecology and Evolution 12:128-131 (1997).

No. 15 Meszéna G, Czibula I, Geritz SAH: *Adaptive Dynamics in a 2-Patch Environment: A Simple Model for Allopatric and Parapatric Speciation.* IIASA Interim Report IR-97-001 (1997). Journal of Biological Systems 5:265-284 (1997).

No. 16 Heino M, Metz JAJ, Kaitala V: *The Enigma of Frequency-Dependent Selection.* IIASA Interim Report IR-97-061 (1997). Trends in Ecology and Evolution 13:367-370 (1998).

No. 17 Heino M: *Management of Evolving Fish Stocks.* IIASA Interim Report IR-97-062 (1997). Canadian Journal of Fisheries and Aquatic Sciences 55:1971-1982 (1998).

No. 18 Heino M: *Evolution of Mixed Reproductive Strategies in Simple Life-History Models.* IIASA Interim Report IR-97-063 (1997).

No. 19 Geritz SAH, van der Meijden E, Metz JAJ: *Evolutionary Dynamics of Seed Size and Seedling Competitive Ability.* IIASA Interim Report IR-97-071 (1997). Theoretical Population Biology 55:324-343 (1999).

No. 20 Galis F, Metz JAJ: *Why Are There So Many Cichlid Species? On the Interplay of Speciation and Adaptive Radiation.* IIASA Interim Report IR-97-072 (1997). Trends in Ecology and Evolution 13:1-2 (1998).

No. 21 Boerlijst MC, Nowak MA, Sigmund K: *Equal Pay for all Prisoners/ The Logic of Contrition.* IIASA Interim Report IR-97-073 (1997). American Mathematical Society Monthly 104:303-307 (1997). Journal of Theoretical Biology 185:281-293 (1997).

No. 22 Law R, Dieckmann U: *Symbiosis Without Mutualism and the Merger of Lineages in Evolution.* IIASA Interim Report IR-97-074 (1997). Proceedings of the Royal Society of London Series B 265:1245-1253 (1998).

No. 23 Klinkhamer PGL, de Jong TJ, Metz JAJ: *Sex and Size in Cosexual Plants.* IIASA Interim Report IR-97-078 (1997). Trends in Ecology and Evolution 12:260-265 (1997).

No. 24 Fontana W, Schuster P: *Shaping Space: The Possible and the Attainable in RNA Genotype-Phenotype Mapping.* IIASA Interim Report IR-98-004 (1998). Journal of Theoretical Biology 194:491-515 (1998).

No. 25 Kisdi É, Geritz SAH: *Adaptive Dynamics in Allele Space: Evolution of Genetic Polymorphism by Small Mutations in a Heterogeneous Environment.* IIASA Interim Report IR-98-038 (1998). Evolution 53:993-1008 (1999).

No. 26 Fontana W, Schuster P: *Continuity in Evolution: On the Nature of Transitions.* IIASA Interim Report IR-98-039 (1998). Science 280:1451-1455 (1998).

No. 27 Nowak MA, Sigmund K: *Evolution of Indirect Reciprocity by Image Scoring/ The Dynamics of Indirect Reciprocity.* IIASA Interim Report IR-98-040 (1998). Nature 393:573-577 (1998). Journal of Theoretical Biology 194:561-574 (1998).

No. 28 Kisdi É: *Evolutionary Branching Under Asymmetric Competition.* IIASA Interim Report IR-98-045 (1998). Journal of Theoretical Biology 197:149-162 (1999).

No. 29 Berger U: *Best Response Adaptation for Role Games.* IIASA Interim Report IR-98-086 (1998).

No. 30 van Dooren TJM: *The Evolutionary Ecology of Dominance-Recessivity.* IIASA Interim Report IR-98-096 (1998). Journal of Theoretical Biology 198:519-532 (1999).

No. 31 Dieckmann U, O'Hara B, Weisser W: *The Evolutionary Ecology of Dispersal.* IIASA Interim Report IR-98-108 (1998). Trends in Ecology and Evolution 14:88-90 (1999).

No. 32 Sigmund K: *Complex Adaptive Systems and the Evolution of Reciprocation.* IIASA Interim Report IR-98-100 (1998). Ecosystems 1:444-448 (1998).

No. 33 Posch M, Pichler A, Sigmund K: *The Efficiency of Adapting Aspiration Levels.* IIASA Interim Report IR-98-103 (1998). Proceedings of the Royal Society London Series B 266:1427-1435 (1999).

No. 34 Mathias A, Kisdi É: *Evolutionary Branching and Coexistence of Germination Strategies.* IIASA Interim Report IR-99-014 (1999).

No. 35 Dieckmann U, Doebeli M: *On the Origin of Species by Sympatric Speciation.* IIASA Interim Report IR-99-013 (1999). Nature 400:354-357 (1999).

No. 36 Metz JAJ, Gyllenberg M: *How Should We Define Fitness in Structured Metapopulation Models? Including an Application to the Calculation of Evolutionarily Stable Dispersal Strategies.* IIASA Interim Report IR-99-019 (1999). Proceedings of the Royal Society of London Series B 268:499-508 (2001).

No. 37 Gyllenberg M, Metz JAJ: *On Fitness in Structured Metapopulations.* IIASA Interim Report IR-99-037 (1999). Journal of Mathematical Biology 43:545-560 (2001).

No. 38 Meszéna G, Metz JAJ: *Species Diversity and Population Regulation: The Importance of Environmental Feedback Dimensionality.* IIASA Interim Report IR-99-045 (1999).

No. 39 Kisdi É, Geritz SAH: *Evolutionary Branching and Sympatric Speciation in Diploid Populations.* IIASA Interim Report IR-99-048 (1999).

No. 40 Ylikarjula J, Heino M, Dieckmann U: *Ecology and Adaptation of Stunted Growth in Fish.* IIASA Interim Report IR-99-050 (1999). Evolutionary Ecology 13:433-453 (1999).

No. 41 Nowak MA, Sigmund K: *Games on Grids.* IIASA Interim Report IR-99-038 (1999). Dieckmann U, Law R, Metz JAJ (eds): The Geometry of Ecological Interactions: Simplifying Spatial Complexity, Cambridge University Press, Cambridge, UK, pp. 135-150 (2000).

No. 42 Ferrière R, Michod RE: *Wave Patterns in Spatial Games and the Evolution of Cooperation.* IIASA Interim Report IR-99-041 (1999). Dieckmann U, Law R, Metz JAJ (eds): The Geometry of Ecological Interactions: Simplifying Spatial Complexity, Cambridge University Press, Cambridge, UK, pp. 318-332 (2000).

No. 43 Kisdi É, Jacobs FJA, Geritz SAH: *Red Queen Evolution by Cycles of Evolutionary Branching and Extinction.* IIASA Interim Report IR-00-030 (2000).

No. 44 Meszéna G, Kisdi É, Dieckmann U, Geritz SAH, Metz JAJ: *Evolutionary Optimisation Models and Matrix Games in the Unified Perspective of Adaptive Dynamics.* IIASA Interim Report IR-00-039 (2000).

No. 45 Parvinen K, Dieckmann U, Gyllenberg M, Metz JAJ: *Evolution of Dispersal in Metapopulations with Local Density Dependence and Demographic Stochasticity.* IIASA Interim Report IR-00-035 (2000).

No. 46 Doebeli M, Dieckmann U: *Evolutionary Branching and Sympatric Speciation Caused by Different Types of Ecological Interactions.* IIASA Interim Report IR-00-040 (2000). The American Naturalist 156:S77-S101 (2000).

No. 47 Heino M, Hanski I: *Evolution of Migration Rate in a Spatially Realistic Metapopulation Model.* IIASA Interim Report IR-00-044 (2000). The American Naturalist 157:495-511 (2001).

No. 48 Gyllenberg M, Parvinen K, Dieckmann U: *Evolutionary Suicide and Evolution of Dispersal in Structured Metapopulations.* IIASA Interim Report IR-00-056 (2000).

No. 49 van Dooren TJM: *The Evolutionary Dynamics of Direct Phenotypic Overdominance: Emergence Possible, Loss Probable.* IIASA Interim Report IR-00-048 (2000). Evolution 54: 1899-1914 (2000).

No. 50 Nowak MA, Page KM, Sigmund K: *Fairness Versus Reason in the Ultimatum Game.* IIASA Interim Report IR-00-57 (2000). Science 289:1773-1775 (2000).

No. 51 de Feo O, Ferrière R: *Bifurcation Analysis of Population Invasion: On-Off Intermittency and Basin Riddling.* IIASA Interim Report IR-00-074 (2000). International Journal of Bifurcation and Chaos 10:443-452 (2000).

No. 52 Heino M, Laaka-Lindberg S: *Clonal Dynamics and Evolution of Dormancy in the Leafy Hepatic Lophozia Silvicola.* IIASA Interim Report IR-01-018 (2001). Oikos 94:525-532 (2001).

No. 53 Sigmund K, Hauert C, Nowak MA: *Reward and Punishment in Minigames.* IIASA Interim Report IR-01-031 (2001). Proceedings of the National Academy of Sciences of the USA 98:10757-10762 (2001).

No. 54 Hauert C, De Monte S, Sigmund K, Hofbauer J: *Oscillations in Optional Public Good Games.* IIASA Interim Report IR-01-036 (2001).

No. 55 Ferrière R, Le Galliard J: *Invasion Fitness and Adaptive Dynamics in Spatial Population Models.* IIASA Interim Report IR-01-043 (2001).

No. 56 de Mazancourt C, Loreau M, Dieckmann U: *Can the Evolution of Plant Defense Lead to Plant-Herbivore Mutualism.* IIASA Interim Report IR-01-053 (2001). The American Naturalist 158: 109-123 (2001).

No. 57 Claessen D, Dieckmann U: *Ontogenetic Niche Shifts and Evolutionary Branching in Size-Structured Populations.* IIASA Interim Report IR-01-056 (2001).

No. 58 Brandt H: *Correlation Analysis of Fitness Landscapes.* IIASA Interim Report IR-01-058 (2001).

No. 59 Dieckmann U: *Adaptive Dynamics of Pathogen-Host Interacations.* IIASA Interim Report IR-02-007 (2002). Dieckmann U, Metz JAJ, Sabelis MW, Sigmund K (eds): Adaptive Dynamics of Infectious Diseases: In Pursuit of Virulence Management, Cambridge University Press, Cambridge, UK, pp. 39-59 (2002).

No. 60 Nowak MA, Sigmund K: *Super- and Coinfection: The Two Extremes.* IIASA Interim Report IR-02-008 (2002). Dieckmann U, Metz JAJ, Sabelis MW, Sigmund K (eds): Adaptive Dynamics of Infectious Diseases: In Pursuit of Virulence Management, Cambridge University Press, Cambridge, UK, pp. 124-137 (2002).

Issues of the IIASA Studies in Adaptive Dynamics series can be obtained at www.iiasa.ac.at/Research/ADN/Series.html or by writing to adn@iiasa.ac.at.

Contents

Abstract

This paper investigates simplified models of multiple infection. Its first part deals with superinfection: the more virulent strain quickly outcompetes its rivals. The second part deals with coinfection: the rate of new infections produced by one strain is unaffected by the presence of other strains. The two cases differ in expectations for the resultant range of strains within the host population; they are similar in that both predict a considerable increase in virulence. This underscores that mathematical arguments for the evolution of virulence based on optimizing the basic reproduction ratio of the pathogen do not work if several strains of pathogens compete within the host.

About the Authors

Martin A. Nowak
Institute for Advanced Study
Princeton University
Einstein Drive, Princeton, NJ 08540, U.S.A.

Karl Sigmund
Institute for Mathematics
University of Vienna
Strudlhofgasse 4, A-1090 Vienna, Austria
and
Adaptive Dynamics Network
International Institute for Applied Systems Analysis
Laxenburg, Austria

Super- and Coinfection: The Two Extremes

Martin A. Nowak
Karl Sigmund

1 Introduction

As is well known, the "conventional wisdom" that successful parasites have to become benign is not based on exact evolutionary analysis. Rather than minimizing virulence, selection works to maximize a parasite's reproduction ratio (see Box 1). If the rate of transmission is linked to virulence (defined here as increased mortality due to infection), then selection may in some circumstances lead to intermediate levels of virulence, or even to ever-increasing virulence (see Anderson and May 1991; Diekmann et al. 1990, and the references cited there).

A variety of mathematical models has been developed to explore theoretical aspects of the evolution of virulence (see, for instance, Chapters 2, 3, 11, and 16 in Dieckmann et al. 2002). Most of these models exclude the possibility that an already infected host can be infected by another parasite strain. They assume that infection by a given strain entails immunity against competing strains. However, many pathogens allow for multiple infections, as shown in Chapters 6, 12, and 25 in Dieckmann et al. 2002. The (by now classic) results on optimization of the basic reproduction ratio cannot be applied in these cases.

The mathematical modeling of multiple infections is of recent origin, and currently booming. Levin and Pimentel (1981) and Levin (1983a, 1983b) analyzed two-strain models in which the more virulent strain can take over a host infected by the less virulent strain. They found conditions for coexistence between the two strains. Bremermann and Pickering (1983) looked at competition between parasite strains within a host, and concluded that selection always favors the most virulent strain. Frank (1992a) analyzed a model for the evolutionarily stable level of virulence if there is a trade-off between virulence and infectivity, and if infection occurs with an ensemble of related parasite strains. In Adler and Brunet (1991), Van Baalen and Sabelis (1995a), Andreasen and Pugliese (1995), Lipsitch et al. (1995a), and Claessen and de Roos (1995), further aspects of multiple infection are discussed.

In this paper, following Nowak and May (1994) and May and Nowak (1994, 1995), we deal with two opposite extreme instances of multiple infection by several strains of a parasite. These simplified extreme cases, which are at least partly amenable to analytical understanding, seem to "bracket" the more general situation. The first case deals with *superinfection*. This approach assumes a competitive hierarchy among the different parasite strains, such that a more virulent parasite can infect and take over a host already infected by a less virulent strain. Multiply infected hosts transmit only the most virulent of their strains. The opposite scenario is that of *coinfection*. In this case, there is no competition among the different strains within the same host: each produces new infections at a rate that is unaffected by the presence of other strains in the host.

Both these extremes are amenable to analytical understanding, at least in some simplified cases. Mosquera and Adler (1998) produced a unified model for multiple infections (by two strains), which yields both superinfection and coinfection (as well as single infection) as special cases (see also Chapter 10 in Dieckmann et al. 2002). The long-term goal is, of course, to combine the full scenario of multiple infections in a single host with the adaptive dynamics for evolution within and among hosts. Such studies will mostly rely on computer simulations, but it is important to understand the basics first.

What happens when many different strains are steadily produced by mutation? Both for superinfection and for coinfection, the virulence will become much larger than the optimal value for the basic reproduction ratio. There are interesting differences, however, in the packing of the strains and in the increase of their diversity, depending on whether superinfection or coinfection holds. Furthermore, in the case of superinfection, removal of a fraction of the hosts implies a lasting reduction of the average virulence. This last fact has obvious implications for virulence management: it is quite conceivable that even an incomplete vaccination campaign will have a decisive impact on population health, not by eradicating the pathogen but by making it harmless.

2 Superinfection

In this section we expand the basic model for single infections (Box 1) to allow for superinfection. We consider a heterogeneous parasite population with a range of different strains j (with $1 \le j \le n$) having virulence α_j, with $\alpha_1 < \alpha_2 < \ldots < \alpha_n$. Furthermore, we assume that more virulent strains outcompete less virulent strains on the level of intra-host competition. For simplicity we assume that the infection of a single host is always dominated by a single parasite strain, namely that with maximal virulence. In our framework, therefore, superinfection means that a more virulent strain takes over a host infected by a less virulent strain. Only the more virulent strain is passed on to other hosts. The translation of these assumptions into mathematical terms is given in Box 2.

To arrive at an analytic understanding, we consider the special case that all parasite strains have the same infectivity, β, and differ only in their degree of virulence, α_j. For the relative frequencies i_j of hosts infected by strain j we obtain from Equation (c) in Box 1 the Lotka–Volterra equation

$$i_j' = i_j(r_j + \sum_{k=1}^{n} a_{jk} i_k) \ , \tag{1}$$

on the positive orthant R_+^n, with $r_j = \beta - \alpha_j - d$ (here, d is the background mortality of uninfected hosts) and $A = (a_{jk})$, given by

$$A = -\beta \begin{pmatrix} 1 & 1+\sigma & 1+\sigma & \ldots & 1+\sigma \\ 1-\sigma & 1 & 1+\sigma & \ldots & 1+\sigma \\ 1-\sigma & 1-\sigma & 1 & \ldots & 1+\sigma \\ \vdots & \vdots & \vdots & \ddots & \vdots \\ 1-\sigma & 1-\sigma & 1-\sigma & \ldots & 1 \end{pmatrix} \ , \tag{2}$$

where the parameter σ describes the vulnerability of an already infected host to infection by another strain (with higher virulence). In the extreme case $\sigma = 0$, infection confers complete immunity to all other strains (an effect similar to vaccination); for $\sigma = 1$, an infected individual is as vulnerable as an uninfected one; for $\sigma > 1$, infection weakens the immune system so that invasion by another strain becomes more likely.

Box 1 Population dynamics of pathogen diversity in SI models

We consider the model of Box 2.1 in Dieckmann et al. 2002 with the recovery rate γ set equal to zero,

$$\frac{dS}{dt} = B - dS - \beta SI \ ,$$
$$\frac{dI}{dt} = I(\beta S - d - \alpha) \ . \qquad \text{(a)}$$

The basic reproduction ratio of the parasite for this model is

$$R_0 = \frac{\beta}{d+\alpha}\frac{B}{d} \ . \qquad \text{(b)}$$

If R_0 is larger than one, then the parasite will spread in an initially uninfected population, and damped oscillations lead to the stable equilibrium

$$S^* = \frac{d+\alpha}{\beta} \ , \qquad I^* = \frac{\beta B - d(d+\alpha)}{\beta(d+\alpha)} \ . \qquad \text{(c)}$$

To understand parasite evolution, consider a number of parasite strains competing for the same host. The strains differ in their infectivity β_j and their degree of virulence α_j. If I_j denotes the density of hosts infected by strain j, and excluding the possibility of infection by two strains at once, then

$$\frac{dS}{dt} = B - dS - S\sum_j \beta_j I_j \ ,$$
$$\frac{dI_j}{dt} = I_j(\beta_j S - d - \alpha_j) \ . \qquad \text{(d)}$$

For a generic choice of parameters there is no interior equilibrium, and coexistence between any two strains in the population is not possible. To see this, consider two strains, which, without loss of generality, are called 1 and 2. Now $h_{1,2} = \beta_1^{-1}\ln I_1 - \beta_2^{-1}\ln I_2$ is introduced, which gives

$$\frac{dh_{1,2}}{dt} = \frac{d+\alpha_2}{\beta_2} - \frac{d+\alpha_1}{\beta_1} \ . \qquad \text{(e)}$$

So $h_{1,2}$ goes to $-\infty$ or $+\infty$ depending on which of the two terms is the larger. Since the model does not allow I_j to go to infinity, the conclusion is that strain 2 always outcompetes strain 1 if

$$\frac{\beta_2}{d+\alpha_2} > \frac{\beta_1}{d+\alpha_1} \ . \qquad \text{(f)}$$

This is exactly the condition that the transversal eigenvalue $\lambda_2 = \partial I_2'/\partial I_2$ at the two-species equilibrium $E_1 = (S^*, I_1^*, I_2 = 0)$ is positive, while the transversal eigenvalue $\lambda_1 = \partial I_1'/\partial I_1$ at the two-species equilibrium $E_2 = (S^*, I_1 = 0, I_2^*)$ is negative; that is, strain 2 can invade 1, but 1 cannot invade 2. Applying Condition (f) to any pair of two strains shows that ultimately, out of the full diversity, only one strain remains, which is the one with the highest value of R_0.

If there is no relation between infectivity and virulence, then the evolutionary dynamics will increase β and reduce α. In general, however, there is some relationship between α and β, see Box 5.1 in Dieckmann et al. 2002. This can lead to an intermediate degree of virulence prevailing, corresponding to the maximum value of R_0. Other situations allow evolution toward ever higher or lower virulences. The detailed dynamics depends on the shape of β as a function of α.

In Nowak and May (1994) it is shown that Equation (1) has one globally stable fixed point, that is, one equilibrium that attracts all orbits from the interior of the positive orthant. If this equilibrium lies on a face of the positive orthant, then it also attracts all orbits from the interior of that face. In Nowak and May (1994) this equilibrium is computed.

Box 2 SI models accounting for superinfection

In this box the simple model of Box 1 is modified to cope with superinfection. We now have to deal with a number of different strains of parasite, which will be labeled with the index j. If I_j denotes the density of hosts infected with strain j, then we obtain

$$\frac{dS}{dt} = B - dS - S\sum_{j=1}^{n}\beta_j I_j \ ,$$

$$\frac{dI_j}{dt} = I_j(\beta_j S - d - \alpha_j + \sigma\beta_j\sum_{k=1}^{j-1} I_k - \sigma\sum_{k=j+1}^{n}\beta_k I_k) \ , \quad j = 1,\ldots,n \ . \tag{a}$$

Here α_j denotes the virulence of strain j. Without restricting generality, we assume $\alpha_1 < \alpha_2 < \ldots < \alpha_n$. In our model a more virulent strain can superinfect a host already infected with a less virulent strain. The parameter σ describes the rate at which infection by a new strain occurs, relative to infection of uninfected hosts. If either the host or the parasite has evolved mechanisms to make superinfection more difficult, then σ would be smaller than one. If already-infected hosts are more susceptible to acquiring a second infection (with another strain), then $\sigma > 1$, that is, superinfection occurs at increased rates. The case $\sigma = 0$ corresponds to the single-infection model discussed in Box 1.

To arrive at an analytical understanding we make the simplifying assumption that the immigration of uninfected hosts exactly balances the death of uninfected or infected hosts, $B = dS + dI + \sum_{j=1}^{n}\alpha_j I_j$. In that case we can divide through by $N = S + \sum_{j=1}^{n} I_j$ to obtain an equation for the relative frequencies

$$\frac{di_j}{dt} = i_j[\beta_j(1-i) - d - \alpha_j + \sigma(\beta_j\sum_{k=1}^{j-1} i_k - \sum_{k=j+1}^{n}\beta_k i_k)] \ , \quad j = 1,\ldots,n \ , \tag{b}$$

where $i = \sum_{j=1}^{n} i_j$. This is a Lotka–Volterra system of equations,

$$\frac{di_j}{dt} = i_j(r_j + \sum_{k=1}^{n} a_{jk} i_k) \ , \quad j = 1,\ldots,n \ , \tag{c}$$

with $r_j = \beta_j - \alpha_j - d$ and the matrix $A = (a_{jk})$ is given by

$$A = -\begin{pmatrix} \beta_1 & \beta_1+\sigma\beta_2 & \beta_1+\sigma\beta_3 & \ldots & \beta_1+\sigma\beta_n \\ \beta_2(1-\sigma) & \beta_2 & \beta_2+\sigma\beta_3 & \ldots & \beta_2+\sigma\beta_n \\ \beta_3(1-\sigma) & \beta_3(1-\sigma) & \beta_3 & \ldots & \beta_3+\sigma\beta_n \\ \vdots & \vdots & \vdots & \ddots & \vdots \\ \beta_n(1-\sigma) & \beta_n(1-\sigma) & \beta_n(1-\sigma) & \ldots & \beta_n \end{pmatrix} \ . \tag{d}$$

The important special case $\sigma = 1$ offers a quick solution. The unique stable equilibrium is then given recursively in the following way,

$$i_n^* = \max\{0, 1 - \frac{\alpha_n + d}{\beta}\} \ , \tag{3a}$$

$$i_{n-1}^* = \max\{0, 1 - \frac{\alpha_{n-1} + d}{\beta} - 2i_n^*\} \ , \tag{3b}$$

$$i_{n-2}^* = \max\{0, 1 - \frac{\alpha_{n-2} + d}{\beta} - 2(i_n^* + i_{n-1}^*)\} \ , \tag{3c}$$

$$\vdots$$

$$i_1^* = \max\{0, 1 - \frac{\alpha_1 + d}{\beta} - 2(i_n^* + i_{n-1}^* + \ldots + i_2^*)\} \ , \tag{3d}$$

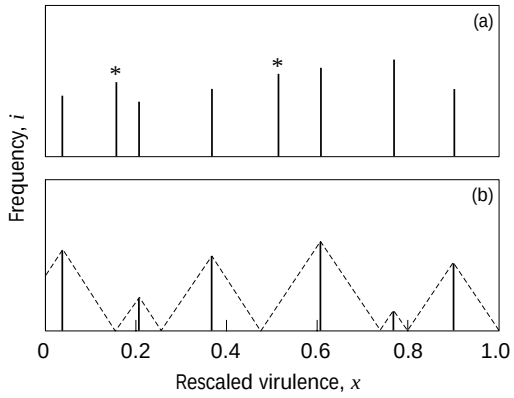


Figure 1 For $\sigma = 1$ there is a simple geometric method to construct the equilibrium configuration. Suppose there are n strains, given by their virulences $\alpha_1, \ldots, \alpha_n$, and let i_j^* be their relative frequencies. We set $x_j = (\alpha_j + d)/\beta$. (a) We only have to consider strains with $0 < x_1 < \ldots < x_n < 1$ and their corresponding frequencies. (b) Draw verticals with abscissae x_j and construct a polygonal line with 45° slopes, starting on the horizontal axis at abscissa 1, at first to the north-west until the first vertical is reached, from there to the south-west until the horizontal axis is reached, then to the north-west until the next vertical is reached, then south-west again, etc. The vertices on the verticals correspond to the i_j^* values that are positive. The strains with other virulences, marked by a star in (a), are eliminated. *Source*: Nowak and May (1994).

This fixed point is saturated, that is, no missing species can grow if it is introduced in a small quantity. Indeed, for each parasite strain j with equilibrium frequency $i_j^* = 0$ we obtain $\partial i_j'/\partial i_k < 0$ for a generic choice of parameters, see Hofbauer and Sigmund (1998). Hence this fixed point is the only stable fixed point in the system.

Equations (3) correspond to a very simple and illuminating geometric method for constructing the equilibrium (see Figure 1).

For a given σ, one can estimate $\alpha_{\max}$, the maximum level of virulence present in an equilibrium distribution. Assuming equal spacing (on average), that is, $\alpha_j = j\alpha_1$, Nowak and May (1994) derive

$$\alpha_{\max} = \frac{2\sigma(\beta - d)}{1 + \sigma} \ . \tag{4}$$

For $\sigma = 0$, we have $\alpha_{\max} = 0$, that is, only the strain with the lowest virulence survives, which for our scenario (with all transmission rates equal) is also the strain with the highest basic reproduction ratio [see Equation (c) in Box 1]. For $\sigma > 1$, strains can be maintained with virulences above $\beta - d$. These strains by themselves are unable to invade an uninfected host population, because their basic reproduction ratio is less than one.

From Equation (4) it can be deduced that the equilibrium frequency of infected hosts $\sum_{j=1}^{n} i_j$ is given by

$$i = \frac{\beta - d}{\beta(1 + \sigma)} \ . \tag{5}$$

Hence, with greater susceptibility to superinfection (larger σ) one obtains fewer infected hosts!

Let us now return to the model with different strains having different infectivities, β_j, as given by Equation (c) in Box 2. Here the solutions need not always converge to a stable equilibrium. For $n = 2$, either coexistence (i.e., a stable equilibrium between the two strains of parasites) or bistability (in which either one or the other strain vanishes, depending on the initial conditions) is possible. An interesting situation can occur if $\sigma > 1$,

and strain 2 has a virulence that is too high to sustain itself in a population of uninfected hosts ($R_0 < 1$), whereas strain 1 has a lower virulence with $R_0 > 1$. Since $\sigma > 1$, infected hosts are more susceptible to superinfection, and thus the presence of strain 1 can effectively shift the reproduction ratio of strain 2 above one. In this way, superinfection allows the persistence of parasite strains with extremely high levels of virulence.

For three or more strains of parasite we may observe oscillations with increasing amplitude and period, tending toward a heteroclinic cycle on the boundary of R_+^n, that is, a cyclic arrangement of saddle equilibria and orbits connecting them (comparable to those discussed in May and Leonard 1975, and Hofbauer and Sigmund 1998). Accordingly, for long stretches of time the infection is dominated by one parasite strain (and hence only one level of virulence), until suddenly another strain takes over. This second strain is eventually displaced by the third, and the third, after a still longer time interval, by the first. Such dynamics can, for example, explain the sudden emergence and re-emergence of pathogen strains with dramatically altered levels of virulence.

To explore the case of nonconstant infectivities, Nowak and May (1994) assume a specific relation between virulence and infectivity, $\beta_j = c_1\alpha_j/(c_2 + \alpha_j)$ for some constants c_1 and c_2. For low virulence, infectivity increases linearly with virulence; for high virulence the infectivity saturates. For the basic reproduction ratio this means that, for strain j

$$R_{0,j} = \frac{c_1 B \alpha_j}{d(c_2 + \alpha_j)(d + \alpha_j)} \ . \tag{6}$$

The virulence that maximizes R_0 is given by $\alpha_{\text{opt}} = \sqrt{dc_2}$. For $\sigma = 0$ (no multiple infection), the strain with largest R_0 is, indeed, selected. For $\sigma > 0$, selection leads to the coexistence of an ensemble of strains with a range of virulences between two boundaries $\alpha_{\min}$ and $\alpha_{\max}$, with $\alpha_{\min} > \alpha_{\text{opt}}$.

Thus superinfection has two important effects:

- It shifts parasite virulence to higher levels, beyond the level that would maximize the parasite reproduction ratio;
- It leads to the coexistence of a number of different parasite strains within a range of virulences.

We note from Figure 2 that strains have a higher equilibrium frequency if the strains with slightly larger virulences have low frequencies. Conversely, if a strain has a high frequency, strains with slightly lower virulence are extinct or occur at very low frequencies. This implies a "limit to similarity," that is, a spacing of the coexisting strains, which agrees well with the construction of the equilibrium in the special case of constant β and $\sigma = 1$, see Figure 1.

Limits to similarity are well-known in ecology and, indeed, the epidemiological model above turns out to be equivalent to a metapopulation model introduced independently, and in an altogether different context, by Tilman (1994). The different strains play the role of distinct species and the hosts play the role of ecological patches. This is further analyzed in Nowak and May (1994) and Tilman et al. (1994); also see Nee and May (1992) for a related analysis.

If mutation keeps generating new strains with altered levels of virulence, then there will be an ever-changing parasite population, in which the virulences are restrained by selection to a range between $\alpha_{\min}$ and $\alpha_{\max}$. Indeed, there will always be new strains capable of invading the polymorphic population. Some of the old strains may then become extinct, and many of those surviving strains with lower virulence than the newcomer will have altered frequencies.

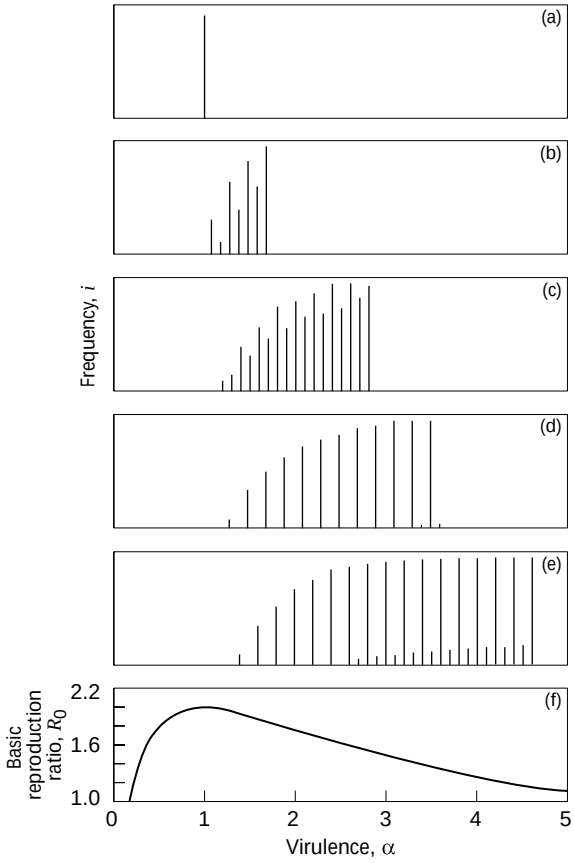


Figure 2 (a) to (e) Equilibrium distribution of parasite virulence for the superinfection model. The horizontal axis denotes virulence, and the vertical axis indicates equilibrium frequencies (always scaled to the same largest value). The simulation is performed according to Equation (b) in Box 2 with $B = 1$, $d = 1$, $n = 50$, $\beta_j = 8\alpha_j/(1 + \alpha_j)$ and $\sigma = 0, 0.1, 0.5, 1$, or 2 [in (a) to (e)]. The individuals α_j are assumed to be regularly spaced between 0 and 5. Thus $\alpha_1 = 0.1, \alpha_2 = 0.2, \ldots, \alpha_{50} = 5$. For $\sigma = 0$ (the single-infection case) the strain with maximum basic reproduction ratio, R_0 [displayed in (f)], is selected. With $\sigma > 0$ we find coexistence of many different strains with different virulences, α_j, within a range $\alpha_{\min}$ and $\alpha_{\max}$, but the strain with the largest R_0 is not selected; superinfection does not maximize parasite reproduction. For increasing σ, the values of $\alpha_{\min}$ and $\alpha_{\max}$ also increase. *Source*: Nowak and May (1994).

If this evolutionary dynamics is iterated for a very long time, then one can define a distribution function $i(\alpha)$ that describes the long-term equilibrium frequencies of strains as a function of their virulence, α. A semi-rigorous argument suggests that $i(\alpha)$ is given by a uniform distribution over the interval $[\alpha_{\min}, \alpha_{\max}]$. Extensive numerical experiments suggest that this distribution is globally stable for the mutation–selection process.

3 Coinfection

We now turn to the case of coinfection, and assume therefore that the infectivity of a strain is unaffected by the presence of other strains in the same host. Again, we derive a simple model and investigate it first analytically (after further simplifications) and then by means of numerical simulations.

As before, we denote by i_j the fraction of the host population infected by strain j, and assume that the strains are numbered in order of virulence: $\alpha_1 < \ldots < \alpha_n$. Several parasites can be present in the same host, and so $\sum_{j=1}^{n}$ can exceed the fraction of all hosts that are infected.

Box 3 SI models accounting for coinfection

With i_j denoting the fraction of individuals harboring strain j (possibly in addition to various other strains), a simple model for coinfection is

$$\frac{di_j}{dt} = i_j[\beta_j(1-i_j) - d - \overline{\alpha}_j], \qquad j = 1, \ldots, n \ . \tag{a}$$

The total population size of hosts is assumed to be held constant, and is normalized to one. The infectivity (transmission rate) of strain j is denoted by β_j. Strain j can invade any host that is not already infected by strain j. Thus $\beta_j i_j(1-i_j)$ is the rate at which new infections with strain j occur.

There is a natural death rate d and a disease induced death rate $\overline{\alpha}_j$ which denotes the average death rates of hosts infected by strain j, and is assumed to be given by the strain with the highest virulence in the host. We define p_j as the probability that a host is not infected with a strain *more* virulent than j. That is,

$$p_j = \prod_{k=j+1}^{n} (1-i_k) \ . \tag{b}$$

Note that $p_n = 1$ and $p_i = (1-i_{j+1})p_{j+1}$. The fraction of hosts that are uninfected is given by $p_0 = \prod_{k=1}^{n}(1-i_k)$. The probability that k is the most virulent strain found in a host is $i_k p_k$, and

$$\overline{\alpha}_j = \alpha_j p_j + \sum_{k=j+1}^{n} \alpha_k i_k p_k \ . \tag{c}$$

This coinfection model is completely defined by Equations (a) to (c). We note that infection and death rules are devised such that if the strains are randomly assorted relative to each other, this continues to be the case, so that Equation (a) remains correct.

If we assume that the death rate is determined by the most virulent strain harbored by the host, we obtain a simple dynamic model presented in Box 3.

The equilibria of Equation (a) in Box 3 must satisfy, for all j, either

$$i_j = 0 \ , \tag{7a}$$

or

$$i_j = 1 - (\overline{\alpha}_j + d)/\beta_j \ . \tag{7b}$$

Using Equations (b) and (c) in Box 3, the equilibrium values of i_j can be computed in a recursive way, starting from $i_n = 1 - (\alpha_n + d)/\beta_n$.

If the transmission rates β_i are all equal to some value β, then, as shown in May and Nowak (1995), the following expressions for the average virulence $\overline{\alpha}$ and the fraction s^* of uninfected hosts are approximately valid (see Figure 3)

$$\overline{\alpha} = \beta - d - \sqrt{2\beta(\beta-d)/n} \ , \tag{8a}$$

and

$$s^* = 4\exp[-\sqrt{2n(\beta-d)/\beta}] \ . \tag{8b}$$

One can similarly investigate coinfection if the transmission rate is not constant, but an increasing function of virulence, for instance

$$\beta_j = c_1\alpha_j/(c_2 + \alpha_j) \ , \tag{9}$$

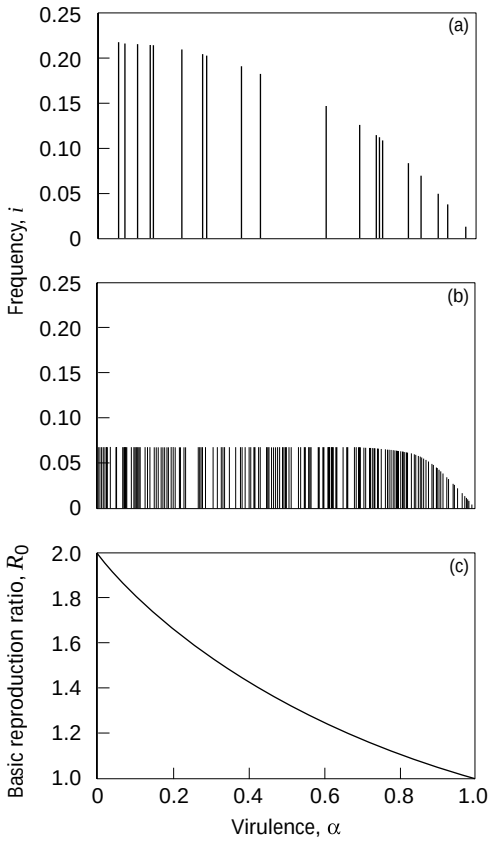


Figure 3 Equilibrium distribution of parasite virulence for the coinfection model given by Equations (a) to (c) in Box 3 with uniform transmission rate $\beta = 2$ and $d = 1$. The individual parasite strains have randomly assigned levels of virulence ranging from 0 to 1. For different numbers of strains n the equilibrium population structure is computed according to Equation (7b). (a) $n = 20$ parasite strains. (b) $n = 200$ parasite strains. For large n there is excellent agreement between the numerical calculations and the theoretical curve, given by Equation (8a). (c) The basic reproduction ratio R_0 as a function of virulence. *Source*: May and Nowak (1995).

with constants c_1 and c_2. The basic reproduction ratio for strain j is given by

$$R_{0,j} = \frac{c_1 \alpha_j}{(c_2 + \alpha_j)(d + \alpha_j)} \ . \tag{10}$$

R_0 is thus maximized by the strain with virulence $\alpha = \sqrt{dc_2}$, and takes the value $c_1/(\sqrt{d}+\sqrt{c_2})^2$. The minimum and maximum virulence values for strains that have the potential to maintain themselves within the host population, α_- and α_+, respectively, are given by

$$\alpha_\pm = \frac{1}{2}\left[c_1 - d - c_2 \pm \sqrt{(c_1 - d - c_2)^2 - 4dc_2}\right] \ . \tag{11}$$

In Figure 4 the results for coinfection are illustrated for transmission rates that increase with virulence.

4 Discussion

Multiple infections cause intra-host competition among strains and thus lead to an increase in the average level of virulence above the maximal growth rate for a single parasitic strain.

The simple models for superinfection (transmission only of the most virulent strain within a host) and for coinfection (all strains transmit independently of other strains

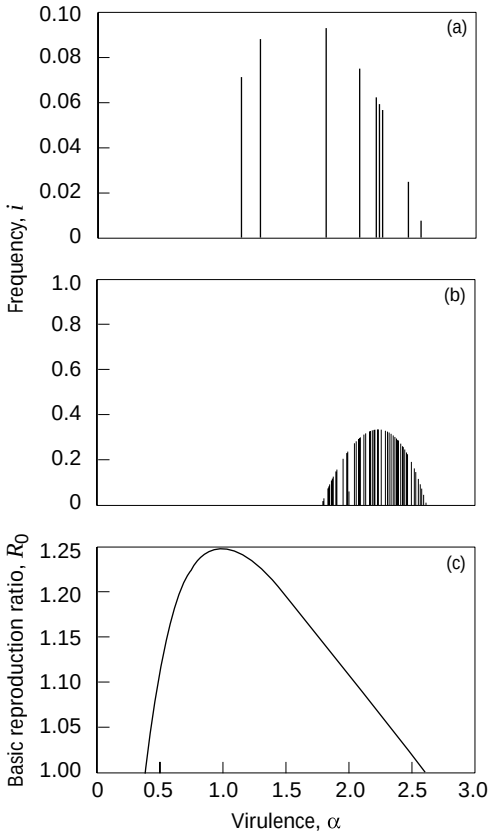


Figure 4 Equilibrium distribution of parasite virulence for the coinfection model with a trade-off between transmission rate β_j and virulence α_j given by $\beta_j = 5\alpha_j/(1+\alpha_j)$. The natural death rate is again $d = 1$, and the parasites have levels of virulence uniformly distributed between 0 and 3. The virulences of the persisting strains are between $\alpha_{\min}$ and the maximum level of virulence that corresponds to $R_0 = 1$, i.e., $\alpha_+ = (3+\sqrt{5})/2$. (a) $n = 20$ parasite strains. The average virulence is $\overline{\alpha} = 1.9246$ and the fraction of uninfected hosts is $s^* = 0.5716$. (b) $n = 200$ parasite strains. Here $\overline{\alpha} = 2.3039$ and $s^* = 0.1952$. (c) The basic reproduction ratio, R_0, as a function of virulence. *Source*: May and Nowak (1995).

present in the host) represent extremes that are likely to bracket the reality of polymorphic parasites. In both cases, we find the expected tendency toward the predominance of strains with a virulence significantly higher than that maximizing reproduction success of parasites in the single-infection case. The number of persisting strains and the range of their virulence, however, differ in the two cases of super- and coinfection. The latter allows for a larger number of coexisting strains, more closely grouped around the virulence level with the maximal reproduction ratio, than does the former.

The basic reproduction ratio is not maximized. With superinfection, the strain with highest R_0 may even become extinct, and strains with very high levels of virulence can be maintained (even strains so virulent that they could not persist on their own in an otherwise uninfected host population). Both superinfection and coinfection lead to polymorphisms of parasites with many different levels of virulence within a well-defined range.

Superinfection can lead to very complicated dynamics, with sudden and dramatic changes in the average level of virulence. The higher the rate σ of superinfection the smaller the number of infected hosts.

It is particularly interesting to investigate evolutionary chronicles. What happens if mutation, from time to time, introduces a new strain? In the case of superinfection, according to the "limit to similarity" principle, only those mutants sufficiently different from the resident strain with next-higher virulence can invade; they then affect the equilibrium

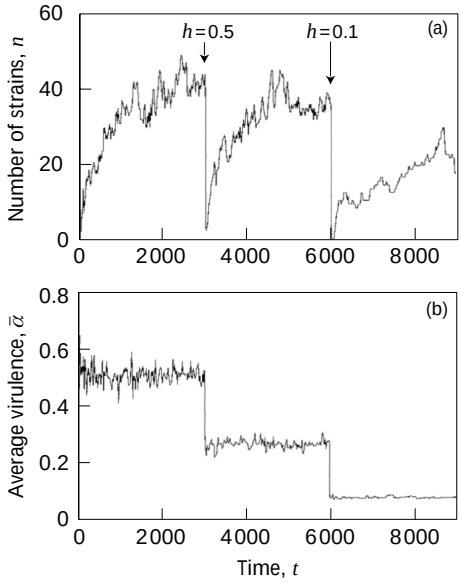


Figure 5 (a) The number n of pathogen strains present at time t, in the superinfection model, with mutations arising uniformly in the interval $0 \leq \alpha \leq 1$. At time $t = 3\,000$, the total number of hosts h is decreased by 50%. The number $n(t)$ subsequently increases again. At $t = 6\,000$ the number of hosts is reduced to 10% (since the rate of new mutants able to invade is 10% of the former value, the growth in n proceeds at a slower rate). (b) Corresponding average values of the virulence as a function of time. Removal of a fraction of the hosts permanently reduces the average virulence by that same fraction. *Source*: May and Nowak (1994).

frequencies of the resident strains with lower virulence, possibly eliminating some of them. The average total number of strains increases slowly (logarithmically in time). On the other hand, these limits to similarity result in a wide range of virulence values persisting in the system.

By contrast, coinfection models have no limits to similarity, and surviving strains are packed ever closer as time goes on, constrained to a narrow band of virulence values. If we assume again that mutants are produced at a constant rate, we find that, asymptotically, the total number of persisting strains increases with the square root of time.

In the superinfection case, removing a certain percentage of potential hosts (for instance by vaccination) results in a sharp drop in the number of strains, eliminating the most virulent strains. Indeed, if there are fewer hosts, then the overall incidence of infection is lower, and fewer hosts are superinfected; thus strains favored by their within-host advantage do less well than those favored by their between-host advantage. After the onset of vaccination, the total number of strains slowly recovers again, but not the average virulence (see Figure 5). Thus even if vaccination eliminates only a fraction of the potential hosts, and therefore has little long-term effect on the number of strains, it produces a lasting effect by reducing the average virulence.

At present, many instances of multiple infections are known, but there are disappointingly few data on the coinfection function (the actual rate of invasion by a more virulent strain). Mosquera and Adler (1998) make the point that many previous models are based on the assumption that this coinfection function is discontinuous: even a marginally more virulent strain will immediately, and certainly, displace its less virulent predecessor (see, e.g., May and Nowak 1994, 1995; Van Baalen and Sabelis 1995a). Continuous coinfection functions produce different results. Individual-based modeling and clinical research are needed to test the implications of the current superinfection models on the evolution and management of virulence.

References

Adler FR & Brunet RC (1991). The dynamics of simultaneous infections with altered susceptibilities. *Theoretical Population Biology* **40**:369–410

Anderson RM & May RM (1991). *Infectious Diseases of Humans*. Oxford, UK: Oxford University Press

Andreasen V & Pugliese R (1995). Pathogen coexistence induced by density-dependent host mortality. *Journal of Theoretical Biology* **177**:159–165

Bremermann HJ & Pickering J (1983). A game-theoretical model of parasite virulence. *Journal of Theoretical Biology* **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

Dieckmann U, Metz JAJ, Sabelis MW, Sigmund K, eds. (2002). *Adaptive Dynamics of Infectious Diseases: In Pursuit of Virulence Management*. Cambridge, UK: Cambridge University Press.

Diekmann O, Heesterbeek JAP & Metz JAJ (1990). On the definition and the computation of the basic reproductive ratio R_0 in models for infectious diseases in heterogeneous populations. *Journal of Mathematical Biology* **28**:365–382

Frank SA (1992). A kin selection model for the evolution of virulence. *Proceedings of the Royal Society of London B* **250**:195–197

Hofbauer J & Sigmund K (1998). *Evolutionary Games and Population Dynamics*. Cambridge, UK: Cambridge University Press

Levin SA (1983a). Coevolution. In *Population Biology*, eds. Freedman H & Stroeck C, pp. 328–334. Lecture Notes in Biomathematics **52**, Berlin, Germany: Springer-Verlag

Levin SA (1983b). Some approaches to modelling of coevolutionary interactions. In *Coevolution*, ed. Nitecki M, pp. 21–65. Chicago, IL, USA: University of Chicago Press

Levin S & Pimentel D (1981). Selection of intermediate rates of increase in parasite–host systems. *The American Naturalist* **117**:308–315

Lipsitch M, Herre E & Nowak MA (1995). Host population structure and the evolution of virulence: A 'law of diminishing returns'. *Evolution* **49**:743–748

May RM & Leonard W (1975). Nonlinear aspects of competition between three species. *SIAM Journal of Applied Mathematics* **29**:243–252

May RM & Nowak MA (1994). Superinfection, metapopulation dynamics, and the evolution of diversity. *Journal of Theoretical Biology* **170**:95–114

May RM & Nowak MA (1995). Coinfection and the evolution of parasite virulence. *Proceedings of the Royal Society of London B* **261**:209–215

Mosquera J & Adler F (1998). Evolution of virulence: A unified framework for coinfection and superinfection. *Journal of Theoretical Biology* **195**:293–313

Nee S & May RM (1992). Dynamics of metapopulations: Habitat destruction and competitive coexistence. *Journal of Animal Ecology* **61**:37–40

Nowak MA & May RM (1994). Superinfection and the evolution of virulence. *Proceedings of the Royal Society of London B* **255**:81–89

Tilman D (1994). Competition and biodiversity in spatially structured habitats. *Ecology* **75**:2–16

Tilman D, May RM, Lehman CL & Nowak MA (1994). Habitat destruction and the extinction debt. *Nature* **371**:65–66

Van Baalen M & Sabelis M (1995). The dynamics of multiple infection and the evolution of virulence. *The American Naturalist* **146**:881–910