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Epidemiological and evolutionary consequences of targeted vaccination

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Abstract

Recent theory has examined the way in which vaccination strategies are expected to influence the evolution of parasite virulence. Most of this work has assumed that vaccination is imposed on a homogeneous host population. However, host populations are typically composed of different types of individuals, with each type responding differently to infection. Moreover, actual interventions often focus treatment on those hosts that are likely to suffer the most ill effects of a particular disease. Here we consider the epidemiological and evolutionary consequences of interventions that focus vaccination on individuals expressing the greatest susceptibility to infection and/or the greatest vulnerability to mortality once infected. Our results indicate that predictions are very sensitive to the nature and degree of heterogeneity in susceptibility and vulnerability. They further suggest that accounting for realistic kinds of heterogeneity when contemplating targeted treatment plans and policies might provide a new tool in the design of more effective virulence management strategies.

Keywords: evolution, host heterogeneity, vaccination, virulence management

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Introduction

The host–parasite literature of the last decade or so bears witness to a growing interest in how ecological and epidemiological factors influence pathogen evolution (Galvani 2003). One of the key directions of recent research in this area is in determining how pathogen evolution might be most effectively managed through public-health interventions (Dieckmann *et al*. 2002). Perhaps the most studied intervention is the use of imperfect vaccines (McLean 1995; Gandon *et al*. 2001, 2003; Ganusov & Antia 2006), and much of the common intuition within this field has been shaped by the results of models that assume all hosts within a population respond identically to infection (Frank 1996; but see Regoes *et al*. 2000; Ganusov *et al*. 2002; Gandon 2004). A variety of theoretical results have now been derived from such models, and these clearly demonstrate that the epidemiological and evolutionary consequences of vaccination depend critically on what facets of the disease are altered by the vaccine (Gandon *et al*. 2001, 2003; Ganusov & Antia 2006; Gandon & Day 2007).

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In contrast, there has been remarkably little work done exploring the epidemiological and evolutionary consequences of vaccination in host populations that are heterogeneous. This is surprising, as susceptibility and vulnerability are often key determinants of public-health vaccination strategies when vaccine stocks are in short supply, or when the cost of universal coverage is prohibitive. In particular, groups with a high probability of becoming infected, and/or of dying once infected, are often preferentially targeted for treatment. For example, prior to seasonal flu and pneumonia outbreaks, public health agencies typically focus their efforts on protecting those individuals with naïve or compromised immune function (Spika *et al*. 1999; van Essen *et al*. 2003). While the immediate, mortality-reducing benefit of preferentially protecting high-risk individuals has been documented (Voordouw *et al*. 2004), and the population-level epidemiological consequences of such strategies studied to some degree (Longini *et al*. 1978; Patel *et al*. 2005; Weycker *et al*. 2005), the evolutionary consequences remain unexplored.

Multiple factors can contribute to within-population heterogeneity in susceptibility and vulnerability, including age (Ashman *et al*. 1999; Gomez *et al*. 2005), gender (Morales-Montor *et al*. 2004; Imahara *et al*. 2005), nutritional

status (Slater & Keymer 1988; Bhaskaram 2002) and concomitant infection with other pathogens (Cox 2001). Such factors structure populations into different risk classes, so that a given strain of pathogen will produce a range of transmission/virulence phenotypes across the different host types. Eventually, theoretical treatments of specific forms of heterogeneity tailored to specific diseases will be required if evolutionary biology is to contribute meaningful suggestions to public policy. Here, however, we intend to take a first pass at exploring the qualitative evolutionary consequences of targeted vaccination through the use of a simple generic 'toy' model.

The main results of this study are based on an extension of a standard *S-I (*susceptible-infected) epidemiological model to include two classes of hosts that differ in their susceptibility to infection and/or their vulnerability to mortality once infected. We consider the situation in which only a single class is vaccinated, but where coverage within that class is 100%. This is an extreme case, but it allows for a largely analytic treatment of the situation. Moreover, it does reflect plausible intervention policies for a number of diseases, which typically recommend blanket coverage within certain high-risk groups. (Center for Disease Control Website: http://www.cdc.gov/flu/professionals/vaccination/pdf/targetpopchart.pdf). We use this model to explore the epidemiological and evolutionary consequences of altering the efficacy of a vaccine that acts on various components of disease transmission and/or mortality. Our results demonstrate that heterogeneities in the host population with respect to disease susceptibility and vulnerability can be important determinants of evolutionary and epidemiological predictions.

Modelling host heterogeneities

Our model is of the *SIS*-type (presented in the expressions below) similar to that presented in Anderson & May (1991) wherein a host population, maintained by a constant inflow of uninfected individuals, is subjected to a microparasitic infection:

$$\dot{S}_1 = \Lambda_1 - (\lambda_{11}I_1 + \lambda_{12}I_2)S_1 - \delta_1 S_1 + \gamma_1 I_1 \quad (1a)$$

$$\dot{S}_2 = \Lambda_2 - (\lambda_{21}I_1 + \lambda_{22}I_2)S_2 - \delta_2 S_2 + \gamma_2 I_2 \quad (1b)$$

$$\dot{I}_1 = (\lambda_{11}I_1 + \lambda_{12}I_2)S_1 - \alpha_1 I_1 \quad (1c)$$

$$\dot{I}_2 = (\lambda_{21}I_1 + \lambda_{22}I_2)S_2 - \alpha_2 I_2 \quad (1d)$$

Here S_j, $j = 1, 2$, are two distinct susceptible host types that are maintained by the constant input rates, Λ_j, due to factors like reproduction and immigration. Given a sufficient contact with an infected host of class k, class j susceptible hosts become infected at a rate determined by the transmission coefficient λ_{jk}, where the double subscript is meant to indicate that this transmission probability generally depends on the risk-classes of both the susceptible and the infected hosts. Class j infected hosts die due to infection at rate ν_j and clear the infection at a per capita rate γ_j, after which they are no longer susceptible to the disease. Defining δ_j as the background mortality rate of host type j, that is, the rate of mortality experienced in the absence of infection with the pathogen of interest, the total exit rate from infected-class j is given by $\alpha_j = \delta_j + \nu_j + \gamma_j$ (Fig. 1). Note that by setting $\Lambda_1 = (1 - q)$, $\Lambda_2 = q\Lambda$ and $\delta_1 = \delta_2$, where q is the proportion of the population that is vaccinated, we recover a standard model in which vaccination is imposed on a homogeneous population (Gandon *et al*. 2001; Gandon & Day 2007). Conditions for the local stability of the endemic equilibrium of the system in expression 1 are given in Appendix I.

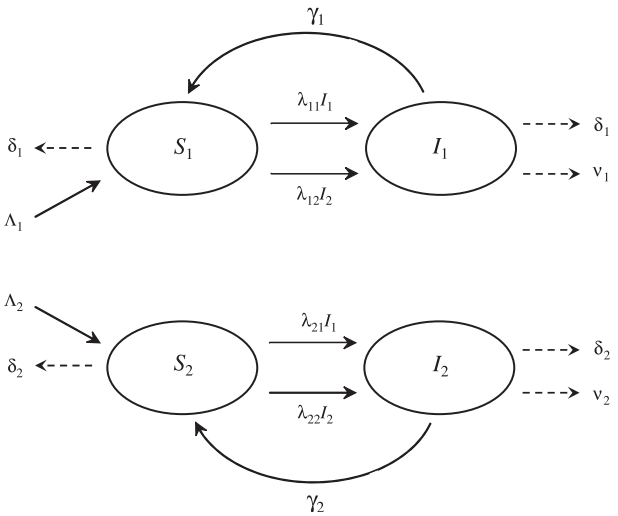

Fig. 1 Box diagram of the susceptible–infected–recovered (*S-I-S*) model with two host types. Solid arrows indicate transitions between susceptible and infected classes, while dotted arrows indicate per capita exit rates due to mortality.

In accordance with numerous theoretical works (e.g. Anderson & May 1979; 1982; Ewald 1983; Lenski & May 1994; Taylor *et al*. 1998; Day & Burns 2003), as well as a growing body of empirical evidence (Ebert 1994; Mackinnon & Read 1999; Messenger *et al*. 1999; Quinn *et al*. 2000; Ferguson *et al*. 2003; Van der Goot *et al*. 2003), we assume that parasite strains face a fitness trade-off between probability of transmission and transmission duration. Mechanistically, such a trade-off arises when both transmission and virulence covary positively with the degree to which a parasite strain exploits its hosts. We therefore assume that parasite strains are defined by a genetically determined exploitation strategy, ε, which in turn defines a given strain's transmission probability and virulence. We follow other standard works by modelling virulence as a linearly increasing function of the pathogen's host-exploitation strategy, $\nu_j = \omega_j\varepsilon$,

where $\omega_j > 0$. A single strain of parasite can therefore produce levels of virulence that differ across the two host types, reflecting the host types' differing abilities at resisting or repairing parasite-induced damage.

For transmission coefficients, we first note that the λ_{jk} are each the product of a between-host contact rate (assumed constant for all types and scaled to 1), and the probability of successful transmission. Transmission probability can be further partitioned into components governed by the susceptibility of the host receiving the infection, η_j, and the infectivity of the donor host, β_k, respectively. The per-capita rate of infection of class j-susceptible hosts can therefore be written as $\eta_j(\beta_1 I_1 + \beta_2 I_2)$. Here η_j is a positive constant that depends only on the state of the susceptible hosts, with larger values indicating a greater susceptibility to becoming infected. The parameters β_k quantify the relationship between the rate at which a parasite strain exploits a given host and the degree to which that host then becomes infectious. We again follow other works in supposing an increasing, but saturating, functional form for β_k given by $\theta_k\varepsilon/(\theta_k\varepsilon + c)$, $c > 0$. Here $\theta_k > 0$ is a constant that determines the rate at which a given host, infected with a parasite strain with exploitation strategy ε, produces infectious particles. For a given level of exploitation, a larger θ_k thus results in greater infectious particle production, perhaps reflecting a host's compromised ability to resist parasite replication (Table 1).

We further assume that background mortalities for the two types of host are similar, and set $\delta_1 = \delta_2 = \delta$. This implies that the factor responsible for the enhanced susceptibility and vulnerability of class 2 hosts causes very little mortality when acting alone, as is the case with, for example, infection with the protozoan *Toxoplasma gondii*, which usually poses a health risk only to those with compromised immunity (Pfaff & Candolfi 2003). Similarly, typically harmless infections with the Epstein-Barr virus can lead to Burkitt's lymphoma when hosts are co-infected with malaria (Burkitt 1969). It also reasonably approximates the interactions between some diseases of relevance to public health, including HIV-tuberculosis. In this case, primary infections by *Mycobacterium tuberculosis* in healthy individuals usually induce very mild and transient disease symptoms, with a yearly risk of reactivation of approximately 0.2%. In contrast, HIV co-infected hosts suffer greater rates of acute disease upon primary infection, as well as a 25- to 40-fold increase in the rate of disease reactivation (Dolin *et al*. 1994; Sepkowitz *et al*. 1995). Also fitting this model are syndromes of mild protein malnutrition and subclinical deficiencies in numerous vitamins and micronutrients, all of which can have little direct effect on mortality but which are known to exert a powerful influence on immune responses (Bhaskaram 2002; Field *et al*. 2002).

We use the system in expression 1 to model the situation in which class 2 hosts are more susceptible to infection, and/or more vulnerable to mortality once infected, than those in class 1. In particular, class 2 hosts can experience any combination of the following: (i) increased virulence (i.e. for a given level of exploitation, parasite-induced mortality is greater in I_2 than I_1 individuals); (ii) decreased rate of parasite clearance; increased probability of contracting the disease (given that contact with an infected host has occurred); and (iii) increased probability of transmitting the infection (due to the greater production of infectious particles for a given level of exploitation). One possible way to interpret this situation is to consider class 1 and 2 hosts as wealthy and poor, respectively, with the poor ones being exposed to the secondary disease-modifying factor. Given the aforementioned functional forms for virulence and transmission, these susceptibilities and vulnerabilities imply that the following inequalities all hold: $0 < \omega_1 \leq \omega_2$, $0 < \gamma_1 \leq \gamma_2$, $0 < \eta_1 \leq \eta_2$ and $0 < \theta_1 \leq \theta_2$.

In the following section, we use the model of expression 1 to explore the epidemiological and evolutionary consequences of altering the efficacy of an imperfect vaccine that is targeted at a particular host type. As with previous work (e.g. Gandon *et al*. 2001), we consider vaccines whose epidemiological effects are to: (i) reduce a host's probability of

Table 1 Notation and definitions of parameters and variables used

Parameter or variable	Definition
Λ_j	Constant input rate of susceptible hosts of type j
ε	Exploitation strategy of pathogen; determines virulence and infectiousness
η_j	Susceptibility of type j hosts to acquiring infection given contact with an infected host
β_j	Infectiousness of type j infected hosts given contact with a susceptible host
δ_j	Disease-independent background mortality rate experienced by type j hosts
γ_j	Per capita rate of clearing an infection by type j infected hosts
ν_j	Per capita rate of morality due to infection suffered by type j infected hosts (i.e. virulence)
α_j	Total per capita exit rate of type j infected hosts from infected class
ω_j	Host-specific parameter determining degree to which pathogen exploitation results in type j host mortality (i.e. $\nu_j = \omega_j\varepsilon$)
θ_j	Parameter determining degree to which pathogen exploitation results in type j host infectiousness (i.e. $\beta_j = \theta_j\varepsilon/(\theta_j\varepsilon + c)$)
f_j	Proportion of the total equilibrium force of infection that is due to type j infected hosts (i.e. $\beta_j\hat{I}_j/(\beta_1\hat{I}_1 + \beta_2\hat{I}_2)$)

becoming infected (infection–blocking treatment); (ii) reduce disease transmission from infected hosts (transmission-blocking treatment); (iii) diminish a pathogen's virulent effects given an infection occurs (antitoxin treatment); (iv) reduce a parasite strain's ability to replicate within host tissue (growth-suppressing treatment); and (v) enhance a host's ability to rid itself of infection via a successful immune response (clearance-augmenting treatment).

Targeted intervention strategies

Measuring intervention costs and benefits

Ideally, treatment strategies address the epidemiological interests of communities as well as the individuals that compose them. For rapidly evolving pathogens, this also includes accounting for evolutionary consequences at both these levels of population organization. Accurate assessment of the costs and benefits of a given intervention thus requires some collection of measures to determine when these organizational and/or temporal interests conflict. Protecting the most vulnerable hosts of a population has obvious benefits at the individual level over short timescales, but how do such interventions translate to the population or community level over intermediate, or epidemiological, timescales? Moreover, how does this influence parasite evolution over long timescales, which can alter both individual and population level effects of the intervention?

Epidemiological effects

Various epidemiological statistics can be used to measure the impact of a disease at the population level. Here we consider the effect of increased efficacy of the various vaccine types on the proportion of the total population that is infected, or disease prevalence. Letting the population equilibrium value of a variable X be indicated by $\hat{X}$, this is given by $\Omega = \hat{I}/\hat{N}$, where $\hat{N} = \hat{S} + \hat{I}$ is the total equilibrium population size, with $\hat{S} = \hat{S}_1 + \hat{S}_2$ and $\hat{I} = \hat{I}_1 + \hat{I}_2$.

As indicated in Table 2, infection-blocking, transmission-blocking and clearance-augmenting vaccines are all predicted to reduce disease prevalence, regardless of which host type is targeted. Such treatments act to diminish the spread of infection by reducing either the likelihood of host-to-host transmission (infection-blocking and transmission-blocking) or the mean transmission time of a given infection (clearance-augmenting). In either case, all three vaccine types increase equilibrium numbers of both susceptible host types while reducing the numbers of both infected types (Appendix II). Reduced prevalence then follows from the fact that $\partial\Omega/\partial p_j \propto \hat{S}\partial\hat{I}/\partial p_j - \hat{I}\partial\hat{S}/\partial p_j$, where p_j is the efficacy of the vaccine type of interest targeted at type j hosts.

Why does not a similar argument hold for antitoxin and growth-suppressing vaccines? The answer is most easily illustrated by noting that, by expressions 1c,d , the equilibrium number of type j-susceptible hosts can be written as $\hat{S}_j = \alpha_j f_j/\lambda_{jj}$, where $f_j = \beta_j \hat{I}_j/(\beta_1\hat{I}_1 + \beta_2\hat{I}_2)$ is the proportion of the (equilibrium) force of infection that is due to class j infected hosts. Virulence reduction in a particular type not only increases the equilibrium number of both types of infected hosts, but it also increases the proportion of the force of infection that is due to the targeted type (since infected hosts of this type increase the most; Appendix II). We thus have that $\partial f_j/\partial p_j > 0$, which in turn implies that $\partial\hat{S}_j/\partial p_k < 0$ for $k \neq j$. In other words, antitoxin vaccines targeted at a particular type always lead to a decrease in the number of susceptible hosts of the untargeted type.

On the other hand, such manipulations do not necessarily reduce susceptible host numbers of the focal host type. Since increasing the efficacy of an antitoxin vaccine changes the number of susceptible hosts of the targeted type according to the sign of $\partial S_j/\partial p_j = S_j(\partial f_j/\partial p_j/f_j + \partial\alpha_j/\partial p_j/\alpha_j)$, focal susceptible host numbers will increase when the term in the '( )' braces is positive, and decrease otherwise. Numerical calculations indicate that both outcomes are possible (Fig. 2a, c, e, g). In fact, it is possible for the total susceptible host population size to increase after the application of an antitoxin vaccine targeted at type 1 hosts (Fig. 2c). Such an outcome might initially seem counter-intuitive, as any reduction in the rate at which infections are terminated in a homogeneous population is predicted to decrease the total number of susceptible hosts, given by $\hat{S} = \alpha/\lambda$. This unexpected behaviour can be explained by noting that decreased virulence in type 1 hosts skews the proportion of infections more towards type 1 hosts

Table 2 The effects of increased efficacy of the various vaccine types on disease prevalence, Ω, (in the absence of parasite evolution) and the ESS level of host exploitation, ε^*. The leftmost column identifies the manipulated vaccine type, while the remaining columns give the predicted effect of an increase in the efficacy of the vaccine type in question on disease prevalence (middle column) or the ESS (rightmost column). Each of these remaining columns is partitioned into two sub-columns, separated by a dashed line, the leftmost of which gives the effect of increasing the efficacy of a vaccine that targets type 1 hosts. Similarly, the rightmost member of each pair identifies the effect that results from targeting type 2 hosts. A '↑' or '↓' symbol indicates that an increase or decrease, respectively, is predicted

Vaccine type	Disease prevalence		ESS exploitation	
Infection-blocking	↓	↓	↓	↑
Transmission-blocking	↓	↓	↓	↑
Anti-toxin	↑	↑	↑	↑↓
Growth-suppressing	↓	↓	↑↓	↑↓
Clearance-augmenting	↓	↓	↑↓	↑

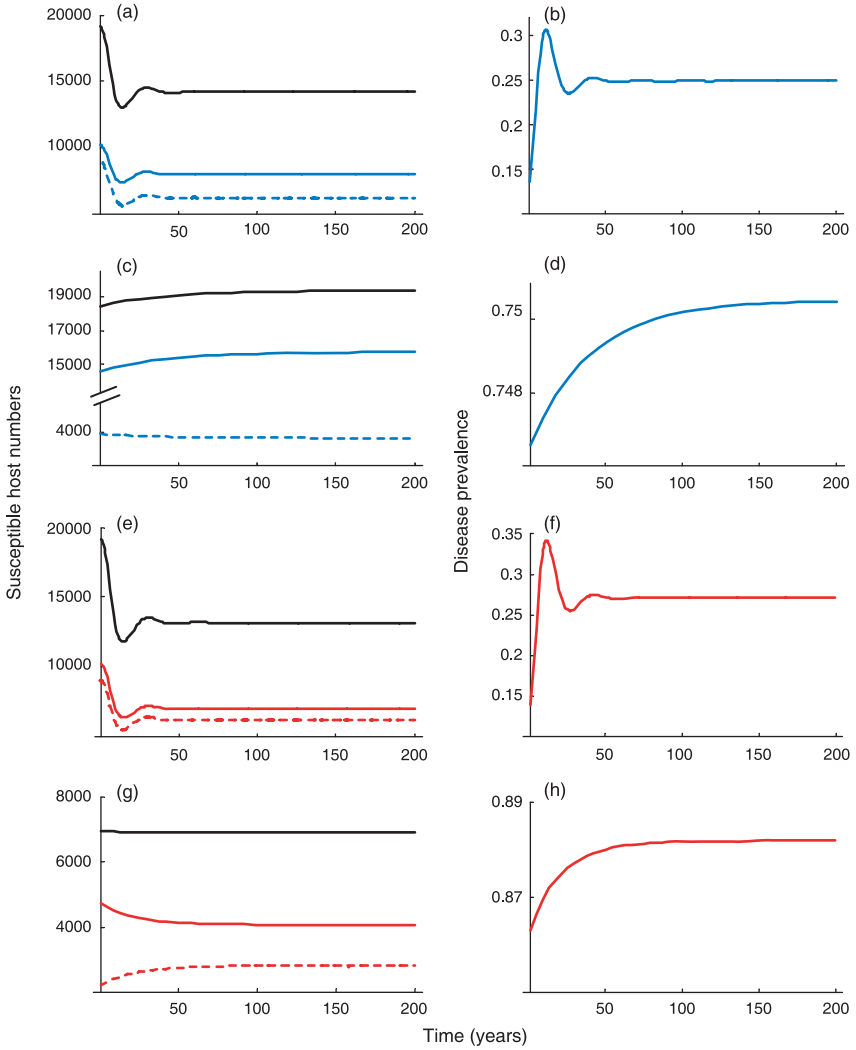

Fig. 2 Change in total numbers of different susceptible host types (a, c, e and g) and disease prevalence (b,d,f and h) after the application of an antitoxin vaccine with 50% efficacy targeted at type 1 (a–d; blue lines), or type 2 (e–h; red lines), hosts. Solid blue and red lines in (a, c) and (e, g), respectively, show the time evolution of type 1 susceptible host numbers after vaccination, with dashed lines showing type 2 susceptible hosts and solid black lines indicating total susceptible host numbers. Common prevaccination parameters for all calculations are $\Lambda_1 = \Lambda_2 = 1000$, $\beta_1 = \beta_2 = 0.003$, $\delta = 0.02$. Remaining prevaccination parameters are: (a,b) $\eta_1 = \eta_2 = 0.01$, $\nu_1 = 0.25$, $\nu_2 = 0.5$, $\gamma_1 = 0.1$ and $\gamma_2 = 0.01$; (c, d) $\eta_1 = \eta_2 = 0.05$, $\nu_1 = 0.005$, $\nu_2 = 0.01$, $\gamma_1 = 5$ and $\gamma_2 = 1$. (e, f) same as in (a, b), except that $\nu_1 = 0.5$ and $\nu_2 = 0.25$. (g, h) $\eta_1 = \eta_2 = 0.05$, $\nu_1 = 0.01$, $\nu_2 = 0.025$ and $\gamma_1 = \gamma_2 = 1$.

($\partial f_1/\partial p_1 > 0$), so that an increased number of infected type 1s clear the infection and recover their susceptible status. If this rate of clearance is sufficiently high, the production of susceptible hosts through recovery can outweigh the increased production of infected hosts due to the increased transmission time afforded by the antitoxin vaccine (Fig. 2c). Despite this effect, disease prevalence increases with antitoxin vaccine efficacy in all examples. Moreover, a similar effect cannot occur when type 2 hosts are targeted, since in that case $\partial f_1/\partial p_2 < 0$, but by assumption $\gamma_2 \leq \gamma_1$, so that increased recovery cannot occur (Fig. 2g).

The situation with growth-suppressing vaccines is more equivocal, as the two component's effects — reduction of virulence and reduction of transmission — can act in opposite directions on disease prevalence and can either increase (Fig. 3a) or decrease (Fig. 3c) susceptible host numbers. Nevertheless, such interventions, regardless of which type is targeted, typically act to reduce disease prevalence, although such reductions are typically quite moderate (Fig. 3b, d).

Evolutionary effects

We now move on to consider how targeted vaccination influences selection pressures on parasite exploitation strategies, and hence transmission and virulence traits. In a homogeneous host population, the ES (evolutionarily stable) level of exploitation by a parasite, ε^*, is given by the solution to $\beta'/\beta - \alpha'/\alpha = 0$, where the X' denotes the derivative of X with respect to exploitation strategy. This states that the marginal benefit, β'/β, and cost, α'/α, of an increase in host exploitation must be balanced at the ESS (evolutionarily stable strategy) (Frank 1996). In the heterogeneous setting determined by the system in 1 (a–d), an analogous expression is given by

$$E\left[\frac{\beta'}{\beta} - \frac{\alpha'}{\alpha}\right] = 0, \qquad (2)$$

where all terms are evaluated at the ES exploitation level, and $E[\,]$ denotes the expectation over the probability

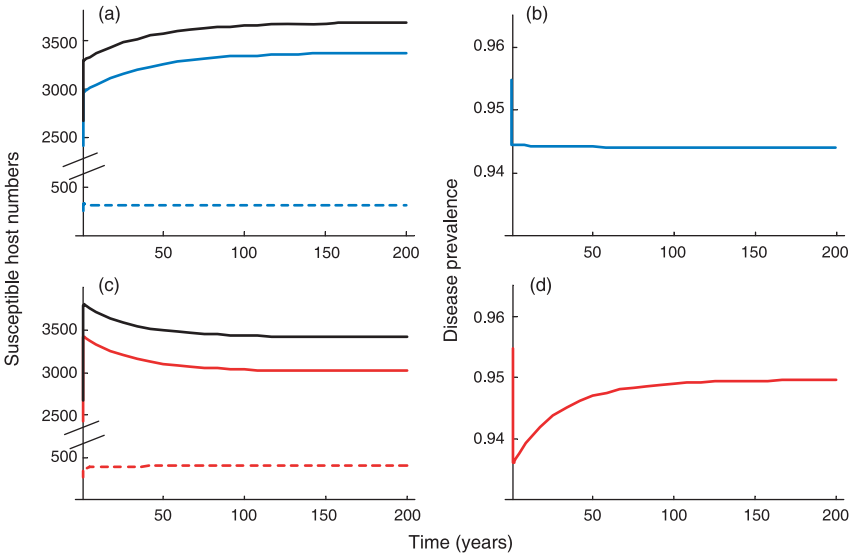

Fig. 3 Change in the total numbers of different susceptible host types (a and c) and disease prevalence (b and d) after the application of a growth-suppressing vaccine with 50% efficacy targeted at type 1 (a, b; blue lines), or type 2 (c, d; red lines), hosts. Solid blue and red lines in (a) and (c), respectively, show the time evolution of type 1 susceptible host numbers after vaccination, with dashed lines showing type 2 susceptible hosts and solid black lines indicating total susceptible host numbers. Common prevaccination parameters for all calculations are $\Lambda_1 = \Lambda_2 = 1000$, $\eta_1 = \eta_2 = 0.05$, $\gamma_1 = 1$, $\gamma_2 = 0.1$ and $\delta = 0.02$. Transmission parameters are given by $\beta_j = \nu_j/(\nu_j + 3)$. Remaining (prevaccination) parameters are: (a, b) $\nu_1 = 0.005$ and $\nu_2 = 0.02$; (c, d) $\nu_1 = 0.01$ and $\nu_2 = 0.01$.

distribution given by f_i. An incremental change in vaccine efficacy targeted at type j hosts, p_j, then causes the ES exploitation strategy to change according to

$$\frac{d\varepsilon^*}{dp_j} \propto f_j \partial \left(\frac{\beta_j'}{\beta_j} - \frac{\alpha_j'}{\alpha_j} \right) \Big/ \partial p_j + \frac{\partial f_1}{\partial p_j} \left\{ \left(\frac{\alpha_2'}{\alpha_2} - \frac{\alpha_1'}{\alpha_1} \right) - \left(\frac{\beta_2'}{\beta_2} - \frac{\beta_1'}{\beta_1} \right) \right\}, \tag{3}$$

where again all terms on the right-hand side are evaluated at ε^*.

The first term on the right of expression 3 quantifies the direct effect of a change in p_j on the marginal benefits (β_j'/β_j) and costs (α_j'/α_j) of host exploitation. The second term is the indirect effect that arises from changes in the proportion of the force of infection due to type 1 hosts (the $\partial f_1/\partial p_j$ term) and a second component that quantifies existing variability across the different host types in transmission, virulence and clearance rates (the term in the '{ }' braces). Note that the inequalities that arise due to the unequal susceptibility and vulnerability of the different host types guarantee that this second component is positive, so that the sign of the indirect effect is given by the sign of $\partial f_1/\partial p_j$. Table 2 presents the predicted direction of evolution in ESS parasite exploitation given an increase in efficacy of a particular vaccine type, with some examples confirming the predictions presented in Fig. 4.

By expression 3, it is obvious that interventions that only multiplicatively affect transmission coefficients, that is infection- and transmission-blocking vaccines, have no direct effect on exploitation evolution, so that their effects are completely determined by the way that the intervention alters the equilibrium proportion of the force of infection that is due to class 1 infected hosts (i.e. the sign of $\partial f_1/\partial p_j$). For both vaccine types, targeting type 1 infected hosts reduces the contribution of type 1 hosts to the force of infection, skewing this proportion towards type 2 hosts and selecting for reduced exploitation (Appendix IV; blue lines in Fig. 4a, b). Similarly, targeting the most susceptible or vulnerable type 2 infected hosts enhances the value of type 1 hosts and thus selects for increased exploitation (red lines in Fig. 4a, b).

The remaining vaccine types all have positive direct effects that promote the evolution of more exploitative parasite strains (Appendix IV). However, under certain conditions, the indirect effects of these vaccines can be negative. When this occurs, a lower level of ES exploitation is favoured if the balance of the indirect and direct effects is also negative. For example, when type 2 hosts are targeted with an antitoxin vaccine, the resultant reduction in the death rate of the vulnerable type enhances the contribution of type 2 hosts to the force of infection which can result in selection for a reduced level of exploitation (dashed red line in Fig. 4c).

Similar arguments hold for growth-suppressing vaccines, although in this case reduced exploitation can result from targeting either type 1 (blue dashed line in Fig. 4d) or type 2 (red dashed line in Fig. 4d) hosts. This is made possible by the fact that the growth-suppressing vaccines act to reduce both virulence in, as well as transmission from, the targeted type. When targeting type 1 hosts, the effect of the vaccine on virulence selects for increased exploitation, while the transmission component effect acts to favour reduced exploitation. When the transmission effect outweighs the virulence effect, the total indirect effect selects for less exploitation. Of course, when indirect effects are too small compared to the direct ones, increased exploitation will result, regardless of the type targeted (solid lines in Fig. 4d).

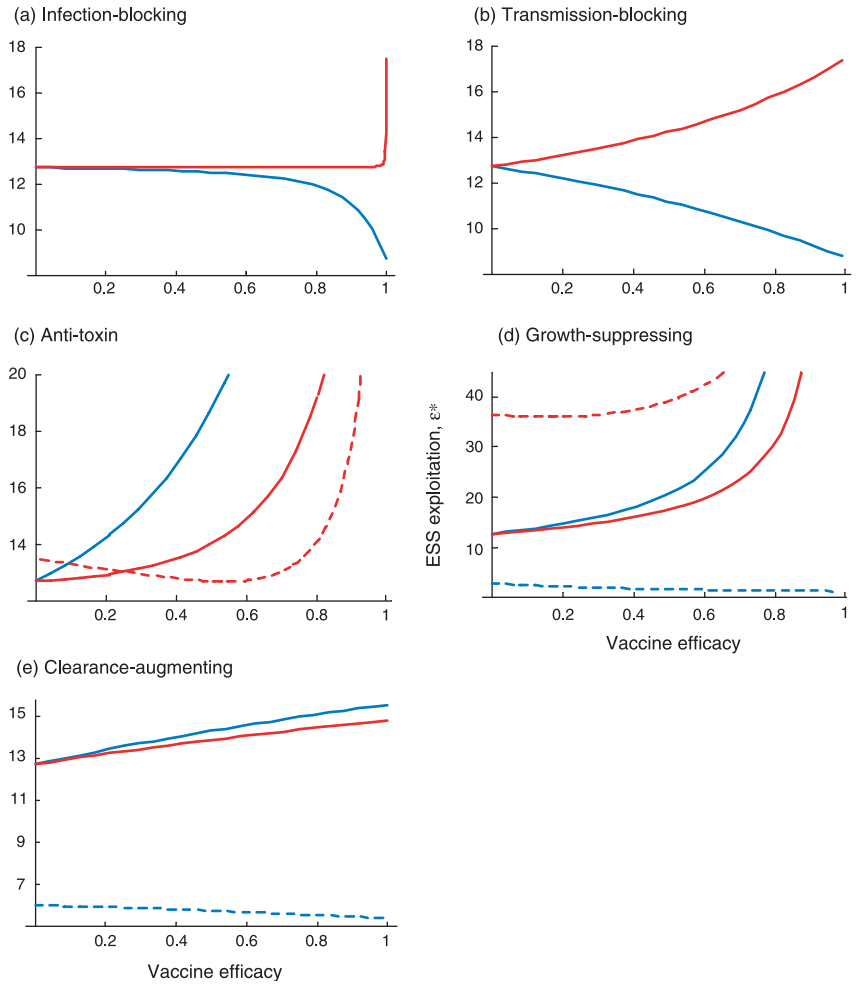

Fig. 4 ESS exploitation as a function of: (a) infection-blocking, (b) transmission-blocking, (c) antitoxin, (d) growth-suppressing and (e) clearance-augmenting vaccine efficacies. Blue lines indicate vaccines that target type 1 hosts and red lines type 2 hosts. Solid lines provide examples for one set of (prevaccination) parameters given by: $\Lambda_1 = \Lambda_2 = 1000$, $\theta_1 = 0.1$, $\theta_2 = 0.2$, $k = 3$, $\nu_1 = 0.1\varepsilon$, $\nu_2 = 0.2\varepsilon$, $\gamma_1 = \gamma_2 = 1$, $\eta_1 = 0.001$, $\eta_2 = 0.1$, $\delta = 0.02$. Examples exhibiting qualitatively different behaviours are shown by the dashed lines. The parameters used in these examples are the same as above except where noted: $\nu_2 = 0.5\varepsilon$ for type 2 antitoxin vaccine alternate example; $\theta_1 = 0.001$, $\nu_1 = 0.001\varepsilon$ and $\gamma_1 = \gamma_2 = 0$ for type 1 growth-suppressing vaccine alternate example; $\gamma_1 = 50$ and $\eta_1 = 0.1$ for type 2 growth-suppressing vaccine alternate example; and $\theta_2 = 0.5$, 1 and $\eta_1 = 0.001$ for type 1 clearance-augmenting alternate example.

Finally, clearance-augmenting vaccines basically have the opposite effect of antitoxin vaccines, and so induce opposite effects (Appendix IV). In this case, targeting a particular host type increases the relative contribution of the other type to the force of infection. Targeting type 1 hosts can therefore select for either increased (solid blue line in Fig. 4e) or decreased exploitation (dashed blue line in Fig. 4e), while targeting type 2 hosts must always increase the ES exploitation level (solid red line in Fig. 4e).

Discussion

Natural host populations, including humans, are subject to a diverse array of both biotic and abiotic stressors that can greatly alter susceptibility and vulnerability to infection by pathogens. Here we have considered some of the epidemiological and evolutionary consequences that such heterogeneity can have by analysing a model in which the host population is composed of two types that differ in these traits. Our results indicate that targeting a particular host-type for treatment produces outcomes that depend critically on the nature of pre-existing host heterogeneities, as well as the effect that altering disease parameters has on the frequencies of the different infected host types.

Quite generally, all of the treatments considered here have a non-negative direct effect on ESS exploitation and thus favour either no evolutionary change or increased virulence. However, various targeted strategies (see Table 2) can increase the relative contribution of the vulnerable/susceptible class to the total force of infection, producing a negative indirect effect. The total selective effect of a given vaccine then depends on the balance of these positive and negative components, and can sometimes resolve in favour of reduced exploitation. For example, analytic work (Appendix III) suggests that selection for reduced exploitation when targeting vulnerable type 2 hosts with antitoxin vaccines is most likely to occur when the direct effects of such an intervention are small, which occurs when virulence in such hosts is relatively large. This expectation is borne out in one of the numerical examples presented (dashed red line in Fig. 4c).

Furthermore, even if the net evolutionary outcome of a vaccination programme is inevitably increased virulence,

these results demonstrate that host heterogeneity can be exploited through targeted vaccination to minimize these detrimental effects. For instance, with antitoxin or growth-suppressing vaccines, the indirect effect resulting from targeting the vulnerable population is always negative. Such a targeting strategy is therefore predicted to always ameliorate the detrimental effects of pathogen evolution, whereas targeting the robust population will always exacerbate them (Appendix IV).

It is worthwhile comparing some of the findings here with those of some earlier models. Previous studies based on imposing vaccination on an initially homogeneous population have found that infection- and transmission-blocking treatments leave ESS exploitation unchanged (or generally select for its decrease if superinfection occurs), while antitoxin and growth-suppressing vaccines typically select for increased exploitation (Gandon *et al*. 2001, 2003; Gandon & Day 2007). These results follow from expression 3 above, since for an initially homogeneous population, the indirect effects term vanishes so that selection is completely determined by direct effects.

In contrast, the results of the present model suggest that these vaccine types can produce very different predictions when imposed in a targeted fashion on a host population heterogeneous in vulnerability and susceptibility. Of particular note is the possibility for antitoxin vaccines to select for reduced exploitation when targeted at the most vulnerable type (Appendix III; dashed red line in Fig. 4c). This suggests the intriguing possibility that such vaccine types can still be usefully employed even when virulence management is a major concern. Similarly, by focusing on the most robust class with infection- or transmission-blocking vaccines, virulence escalation can be averted (Appendix III; Fig. 4a, b) while still enjoying the positive epidemiological benefits offered by this kind of intervention.

That increased clearance selects for increased ESS host exploitation is a standard finding from models without host heterogeneity (May & Anderson 1983; Kakehashi & Yoshinaga 1992; Lenski & May 1994; Frank 1996; Ebert & Weisser 1997; Day & Proulx 2004; Porco *et al*. 2005). This is typically understood in terms of the costs and benefits of host exploitation: increased clearance reduces the cost of virulence to the parasite, resulting in selection for increased exploitation (but see Day & Proulx 2004; Day & Gandon 2005). Again, under certain circumstances (for example, little variation between host types in virulent effects of the pathogen), targeting the least-susceptible type of host with a clearance-augmenting vaccine might provide beneficial epidemiological results while avoiding undesirable evolutionary consequences (dashed blue line in Fig. 4e).

One final general finding of this analysis is that none of the vaccine types unequivocally promote the evolution of more benign parasite strains when the most vulnerable and/or susceptible class of host is targeted for treatment. Indeed, increasing the efficacy of three of the five vaccine types considered (infection-blocking, transmission-blocking and clearance-augmenting) leads to the evolution of a higher ES exploitation strategy. Such evolutionary outcomes can considerably undermine the benefits, obtained at the level of the individual host, of protecting the most vulnerable and/or susceptible host types.

Epidemiology and evolution

The total influence that a particular intervention has on epidemiology must take into account both initial epidemiological effects as well as the long-term effects that result due to parasite evolution. Again looking at disease prevalence, Ω, this total effect is given by

$$\frac{d\Omega}{dp_j} = \frac{\partial\Omega}{\partial\varepsilon}\frac{d\varepsilon^*}{dp_j} + \frac{\partial\Omega}{\partial p_j}, \tag{4}$$

where p_j is vaccine efficacy, $(\partial\Omega/\partial\varepsilon)(d\varepsilon^*/dp_j)$ is the evolutionary effect and $\partial\Omega/\partial p_j$ the initial epidemiological effect. An ideal intervention is one that provides benefits across the different levels of host population organization and across different timescales. This occurs when it induces: (i) an initially beneficial epidemiological effect, $\partial\Omega/\partial p_j < 0$; (ii) an evolutionary benefit at the level of individual hosts, $d\varepsilon*/dp_j < 0$; and (iii) an epidemiological benefit at the population level after accounting for evolutionary change, $\partial\Omega/\partial\varepsilon > 0$, so that the total evolutionary epidemiological effect is negative.

In the present case, it is easy to find examples where this last condition fails to be met (Appendix IV). When this occurs, interventions with beneficial evolutionary effects at the individual level will lead to an evolutionary increase in disease prevalence, which diminishes any initial epidemiological benefit of the treatment. Such conflicts can have important implications for disease management schemes. For example, while targeting either host type with infection- or transmission-blocking vaccines reduces disease prevalence, evolutionary effects are opposed: $d\varepsilon^*/dp_j$ is negative if treatment targets type 1 hosts and positive if type 2 hosts are targeted (Table 1). If $\partial\Omega/\partial\varepsilon > 0$, then the direction of the evolutionary effect of these vaccines on disease prevalence is simply given by the sign of $d\varepsilon^*/dp_j$, or by the sign of $-d\varepsilon^*/dp_j$ if $\partial\Omega/\partial\varepsilon < 0$. In either case, targeting one host type will lead to an evolutionary reduction in parasite exploitation but an erosion of the initial epidemiological benefit of the treatment, while targeting the other host type will produce the opposite effect of increased exploitation with a concomitant evolutionary reduction in disease prevalence. Under these kinds of circumstances, determining which host type should be targeted requires a more precise quantitative analysis of which treatment type presents the lesser of two evils.

Alternative model interpretations

The heterogeneities considered here assume that one host type is most susceptible to becoming infected, most infectious when infected, least likely to clear the infection and most vulnerable to the mortality effects of the infection. While this is quite plausible for a broad class of clinically relevant situations (e.g. Cox 2001), other cases of importance require that the enhanced vulnerabilities and susceptibilities be shared across host types. For example, it is well known that young children both acquire and shed the influenza virus at greater rates than other age groups, and are thus the primary drivers of disease transmission (Longini *et al*. 1982). On the other hand, the age group comprising those over 65 years typically suffers the greatest degree of morbidity and mortality due to influenza (Thompson *et al*. 2003). Evolutionary analysis of this type of situation then leads to an expression identical to expression 3 of the text, with type 1 hosts having the higher transmission rates and type 2s suffering the highest mortality. The major difference is that the inequalities that guaranteed that the sign of the indirect effects term is given by the sign of $\partial f_1/\partial p_j$ no longer hold. This is because increased vulnerability of type 2 hosts still gives $(\alpha_2'/\alpha_2 - \alpha_1'/\alpha_1) > 0$, but the greater infectiousness of type 1 hosts now means that $-(\beta_2'/\beta_2 - \beta_1'/\beta_1) < 0$. The sign of the sum of these two quantities is therefore no longer obvious and nothing definite can be said regarding the sign of the indirect effects term, so that evolutionary predictions are equivocal in this case.

However, it may well often be the case that the secondary factor responsible for disease heterogeneity (age in the influenza example) is associated with an increased risk of mortality even in the absence of the focal disease, which implies that $\delta_2 > \delta_1$. If this added risk is big enough, it will overwhelm the effect of increased disease-induced mortality in the type 2 hosts, so that the inequality $(\alpha_2'/\alpha_2 - \alpha_1'/\alpha_1) < 0$ will then hold. In turn, this implies that the sign of the indirect effect will be given by the sign of $-\partial f_1/\partial p_j$, reversing all the predictions of the main text. When this occurs, the epidemiologically sensible strategy of targeting type 1 hosts with transmission–blocking vaccines or type 2 hosts with antitoxin vaccines are both predicted to lead to the evolution of higher pathogen exploitation rates. In any case, the contrasting results of this section with the findings of the main text strongly argue that accurate forecasting of the evolutionary consequences of various disease interventions will likely require intimate knowledge of the heterogeneities to disease effects present in host populations.

The work and predictions presented here also come with a number of important caveats. First, for simplicity, all analyses here have focused on evolutionary equilibria, although it should be noted that the transient dynamics of parasite exploitation strategies can differ significantly from their eventual ES values as equilibria are approached (Gandon *et al*. 2001; Day & Proulx 2004; Day & Gandon 2005; Gandon & Day 2007). Moreover, the time required to achieve an evolutionary equilibrium can be extremely long, so that shorter-term evolutionary effects may have major implications for public-health issues (Mackinnon & Read 2004). This necessitates a perspective that incorporates these away-from-equilibrium effects into assessments of disease impact in order to formulate comprehensive management schemes. Recent progress along these lines has been achieved through the reformulation of virulence evolution theory within a framework based on Price's equation (Day & Proulx 2004; Gandon & Day 2007). This work has revealed some interesting qualitative aspects of virulence evolution in response to different parameter changes. A potentially quite informative extension of this approach would be to include the different types of host heterogeneity considered here.

A second issue is that the analytic evolutionary analysis presented (Appendix III) is strictly valid only locally, so that the derived predictions only hold for small perturbations near vaccine efficacies of zero. Although these local predictions can, and often do (see Fig. 4), extend to larger perturbations, they can also fail (e.g. dashed red line in Fig. 4d). A more complete analytic treatment would thus need to consider higher-order terms in the expansion of the ESS exploitation as a function of the various vaccine efficacies.

It should also be noted that the purpose of the model presented here is to demonstrate some of the generic epidemiological and evolutionary implications of host heterogeneities in susceptibility to infection and/or vulnerability to mortality. More detailed models of particular types of heterogeneity would need to consider such details as vaccine-induced changes in age structure when susceptibility and vulnerability vary with age, or the ways that multiple diseases affect the equilibrium densities of one another, and how these are influenced by the various vaccine types.

A final point of importance concerns the types of situations under which the results reported here might be applicable. Although we have used the language of vaccination strategies throughout this work, many of the results obtained extend to other types of disease-influencing interventions. For example, reduced susceptibility of a targeted host type could equally well be achieved through mechanical means, as is the case with the use of bed nets in malaria prevention programmes. Again using malaria as an example, the administration of oral prophylactics might reasonably approximate the effects of exploitation-reducing or clearance-augmenting vaccines. Similarly, behavioural interventions, like the quarantining of infected hosts, could be viewed as analogues of transmission-blocking vaccines, while various types of medical attention might be equivalent to virulence reduction.

In many cases, these various interventions will be administered in an effectively targeted fashion. For example, depending on the disease and geographical region, those groups most at risk of health complications might be given the highest priority access to treatment. Alternatively, treatment may only be available to individuals in the highest socio-economic groups. Moreover, for many important human diseases in developing nations, access to medical treatment and/or disease prophylaxis typically varies between populations as well (Brentlinger *et al*. 2007). Together, these circumstances allow for a potentially useful experimental component to investigations of the evolutionary effects of targeted interventions. An increasingly popular practice in evolutionary ecology studies is to utilize extant geographical variation in some environmental parameters predicted to influence the evolution of a trait of interest (e.g. Endler 1995). If the trait also varies across populations, this then provides the impetus for further investigations into a possible causal relationship between the two. The application of this template to the present context would thus require a comparison of the virulence of pathogen strains collected from across a region characterized by differential availability of medical resources. Such comparisons are made simpler by the existence of localized genomic regions encoding for proteins that facilitate host exploitation. Candidate genes responsible for such virulence factors have been identified in numerous pathogens (Levin 1996), including the malaria parasite *Plasmodium falciparum* (Jensen *et al*. 2004), allowing for the direct assay of virulence differences between clones.

An added virtue of this approach is that it would require minimal adaptation of already established molecular techniques and community-level protocols commonly used in epidemiological studies of infectious diseases (Conway 2007). Given the insights that this method has yielded in other evolutionary studies (Reznick & Ghalambor 2005), it is reasonable to hope that valuable information might also be gleaned in this setting as well. The importance of formulating public-health policies that include effective virulence management programmes, in conjunction with the widespread practice of targeting the most vulnerable hosts for disease intervention, suggests that this idea at least warrants further consideration.

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Appendix I

Setting expressions 1(*a-d*) equal to zero and solving the resulting equalities gives

$$\hat{S}_j = \frac{\alpha_j}{\lambda_{jj}} f_j \text{ and } \hat{I}_j = \frac{\Lambda_j}{\alpha_j - \gamma_j} - \frac{\delta_j}{\beta_j y_j} f_j, \tag{A1-1}$$

for $j = 1, 2$, as implicit expressions for the endemic equilibrium values of susceptible and infected hosts. Here $f_j = \beta_j \hat{I}_j / (\beta_1 \hat{I}_1 + \beta_2 \hat{I}_2)$ is the proportion of the force of infection, at equilibrium, that is due to class j infected hosts. This can be expressed in terms of model parameters by solving the quadratic equation $f_1^2 - (A_1 + A_2 + 1) f_1 + A_1 = 0$, which gives

$$f_1 = \frac{(A_1 + A_2 + 1) - \frac{x}{\sqrt{x^2}} \sqrt{(A_1 + A_2 + 1)^2 - 4A_1}}{2}, \tag{A1-2}$$

where $A_j = \Lambda_j \lambda_{jj} y^{j-1} / \alpha_j x$, $x = \delta_1 - y\delta_2$, $y = y_1 / y_2$ and $y_j = \eta_j (\alpha_j - \gamma_j) / \alpha_j$, as the only admissible root.

Local stability of this endemic equilibrium is established when the system in expression 1, linearized about the equilibrium, has all eigenvalues with the negative real parts. To determine the conditions under which this holds we utilize the Liénard-Chipart (L-C) stability criterion (Jury 1982). Since the system in expression 1 is four-dimensional, the characteristic polynomial of the linearized system has the form $z^4 + a_3 z^3 + a_2 z^2 + a_1 z + a_0$. The L-C criterion then states that necessary and sufficient conditions for local stability are that all the a_j as well as the term $M = a_1 a_2 a_3 - a_0 a_3^2 - a_1^2$ be positive.

Evaluating the Jacobian, J, of the system in expression 1 at the above equilibrium, gives

$$J = \begin{bmatrix} -\left(\delta_1 + \frac{\eta_1}{y_1} q\right) & 0 & \gamma_1 - \alpha_1 f_1 & -\frac{\beta_2}{\beta_1} \alpha_1 f_1 \\ 0 & -\left(\delta_2 + \frac{\eta_2}{y_1} q\right) & -\frac{\beta_1}{\beta_2} \alpha_2 f_2 & \gamma_2 - \alpha_2 f_2 \\ \frac{\eta_1}{y_1} q & 0 & -\alpha_1 f_2 & \frac{\beta_2}{\beta_1} \alpha_1 f_1 \\ 0 & \frac{\eta_2}{y_1} q & \frac{\beta_1}{\beta_2} \alpha_2 f_2 & -\alpha_2 f_1 \end{bmatrix}, \tag{A1-3}$$

where $q = \beta_1 y_1 \hat{I}_1 / f_1$. From this the coefficients of the characteristic polynomial can be calculated as

$$a_3 = \alpha_1 f_2 + \alpha_2 f_1 + \delta_1 + \delta_2 + \left(\frac{\eta_1 + \eta_2}{y_1}\right) q \tag{A1-4a}$$

$$a_2 = T(\delta_1 + \delta_2) + \delta_1 \delta_2 + \left(\frac{\alpha_1 y_1 + \alpha_2 y_2}{y_1} + \frac{\delta_1 \eta_2 + \delta_2 \eta_1}{y_1} + \frac{\alpha_1 f_2 \eta_2 + \alpha_2 f_1 \eta_1}{y_1} + \frac{\eta_1 \eta_2}{y_1^2} q\right) q, \tag{A1-4b}$$

$$a_1 = T\delta_1\delta_2 + \left(\frac{\alpha_1\alpha_2(f_1 y_1 + f_2 y_2)}{y_1} + \frac{\alpha_1 f_2 \delta_1 \eta_2 + \alpha_2 f_1 \delta_2 \eta_1}{y_1} + \frac{\alpha_1 \delta_2 y_1 + \alpha_2 \delta_1 y_2}{y_1} + \left(\frac{\alpha_1 \eta_2 y_1 + \alpha_2 \eta_1 y_2}{y_1^2}\right) q\right) q, \tag{A1-4c}$$

and

$$\alpha_0 = \alpha_1 \alpha_2 \left(\frac{\delta_1 f_2 y_2 + \delta_2 f_1 y_1}{y_1} + \frac{y_2}{y_1} q\right) q, \tag{A1-4d}$$

where $T = a_1 f_2 + a_2 f_1$. Since $q > 0$ whenever the endemic equilibrium exists, all these terms are positive. Substituting these expressions into M and expanding the resulting expression in powers of q shows that the second condition of the L-C criterion also holds.

Appendix II

Using expression (A1-2), an increase in the efficacy of a vaccine targeted at type j hosts, p_j, alters f_1 according to

$$\frac{\partial f_1}{\partial p_j} = f_1 \frac{f_1 \partial A_2/\partial p_j - f_2 \partial A_1/\partial p_j}{(f_1^2 - A_1)}, \tag{A2-1}$$

where

$$\frac{\partial A_1}{\partial p_j} = A_1 \left(\frac{\partial \eta_1/\partial p_j}{\eta_1} + \frac{\partial \beta_1/\partial p_j}{\beta_1} - \frac{\partial \alpha_1/\partial p_j}{\alpha_1} + \frac{\delta_1 y}{x} \frac{\partial y/\partial p_j}{y} \right), \tag{A2-2a}$$

$$\frac{\partial A_1}{\partial p_j} = A_1 \left(\frac{\partial \eta_1/\partial p_j}{\eta_1} + \frac{\partial \beta_1/\partial p_j}{\beta_1} - \frac{\partial \alpha_1/\partial p_j}{\alpha_1} + \frac{\delta_1 y}{x} \frac{\partial y/\partial p_j}{y} \right), \tag{A2-2b}$$

$$\frac{\partial y}{\partial p_j} = (-1)^{j+1} y \left[\frac{\partial \eta_j/\partial p_j}{\eta_j} - \frac{\gamma_j}{\alpha_j - \gamma_j} \left(\frac{\partial \gamma_j/\partial p_j}{\gamma_j} - \frac{\partial \alpha_j/\partial p_j}{\alpha_j} \right) \right], \tag{A2-2c}$$

and it is straightforward to show that the $(f_1^2 - A_1)x$ term is negative. How changes in the various efficacies alter f_1 can then be derived from (A2-1) by substituting $(1 - \tau_j)\eta_j$, $(1 - \infty_j)\beta_j$, $(1 - \rho_j)\nu_j$, $(1 - \psi_j)\nu_j$, and $\beta_j((1 - \psi_j)\varepsilon)$, or $(1 + \sigma_j)\gamma_j$, for η_j, β_j, ν_j, ν_j and β_j, or γ_j, respectively, according to whether vaccination is infection-blocking, transmission-blocking, antitoxin, growth-suppressing or clearance-augmenting, and replacing p_j, with the efficacy of interest. This gives:

1 Infection-blocking vaccine

$$\frac{\partial f_1}{\partial \tau_j} = \frac{(-1)^{j+1}}{(1 - \tau_j)} \frac{f_1^2 f_2 y^{j-1} \delta_j}{(f_1^2 - A_1)x} \begin{matrix} < 0 \\ > 0 \end{matrix} \text{ for } \begin{matrix} j = 1 \\ j = 2 \end{matrix} \tag{A2-3a}$$

2 Transmission-blocking vaccine

$$\frac{\partial f_1}{\partial \infty_j} = \frac{(-1)^{j+1}}{(1 - \infty_j)} \frac{f_1 (1 - f_j) A_j}{(f_1^2 - A_1)} \begin{matrix} < 0 \\ > 0 \end{matrix} \text{ for } \begin{matrix} j = 1 \\ j = 2 \end{matrix} \tag{A2-3b}$$

3 Anti-toxin vaccine

$$\frac{\partial f_1}{\partial \rho_j} = (-1)^{j+1} \frac{f_1 (1 - f_j) y^{j-1}}{(f_1^2 - A_1)x} (f_j \delta_j + \lambda_{jj} \hat{I}_j) \frac{\partial \alpha_j/\partial \rho_j}{\alpha_j} \begin{matrix} > 0 \\ < 0 \end{matrix} \text{ for } \begin{matrix} j = 1 \\ j = 2 \end{matrix} \tag{A2-3c}$$

4 Growth-suppressing vaccine

$$\frac{\partial f_1}{\partial \psi_j} = (-1)^{j+1} \frac{f_1 (1 - f_j) y^{j-1}}{(f_1^2 - A_1)x} \left[(f_j \delta_j + \beta_j y_j \hat{I}_j) \left(\frac{\partial \alpha_j/\partial \psi_j}{\alpha_j} - \frac{\partial \beta_j/\partial \psi_j}{\beta_j} \right) + \frac{\partial \alpha_j/\partial \psi_j}{\alpha_j} \frac{\gamma_j}{\alpha_j} \lambda_{jj} \hat{I}_j \right] \begin{matrix} >< 0 \\ < 0 \end{matrix} \text{ for } \begin{matrix} j = 1 \\ j = 2 \end{matrix} \tag{A2-3d}$$

5 Clearance-augmenting vaccine

$$\frac{\partial f_1}{\partial \sigma_j} = (-1)^{j+1} \frac{f_1^2 f_2 \delta_j y^{i-1}}{(f_1^2 - A_1)x} \frac{\gamma_j}{\alpha_j} \begin{matrix} < 0 \\ > 0 \end{matrix} \text{ for } \begin{matrix} j = 1 \\ j = 2 \end{matrix} \tag{A2-3e}$$

How the different intervention types alter the equilibrium numbers of the different susceptible and infected host types can then be calculated by differentiating the equilibrium expressions of (A1-1), giving

$$\frac{\partial \hat{S}_j}{\partial p_j} = \hat{S}_j \left(\frac{\partial f_j/\partial p_j}{f_j} + \frac{\partial \alpha_j/\partial p_j}{\alpha_j} - \frac{\partial \eta_j/\partial p_j}{\eta_j} - \frac{\partial \beta_j/\partial p_j}{\beta_j} \right) \tag{A2-4a}$$

and

$$\frac{\partial \hat{I}_j}{\partial p_j} = \frac{-\partial \nu_j/\partial p_j}{\alpha_j - \gamma_j} \hat{I}_j - \frac{\delta_j \partial \hat{S}_j/\partial p_j}{\alpha_j - \gamma_j}, \tag{A2-4b}$$

and substituting the efficacy of interest for p_j.

Appendix III

Here we derive the criteria that a parasite exploitation strategy must satisfy to be both evolutionarily (ESS) and convergence stable (CS). We consider the fate of a rare mutant parasite strain, characterized by its exploitation strategy, $\tilde{\varepsilon}$ (with transmission and virulence rates given by $\lambda_{jk}(\tilde{\varepsilon}) = \tilde{\lambda}_{jk}$ and $\nu_j(\tilde{\varepsilon}) = \tilde{\nu}_j$, $j, k = 1, 2$), when introduced into a population at equilibrium with a parasite strain with exploitation strategy ε. The initial dynamics of such a rare parasite strain will be governed by the system

$$\dot{\tilde{I}}_1 = (\tilde{\lambda}_{11}\tilde{I}_1 + \tilde{\lambda}_{12}\tilde{I}_2)\hat{S}_1 - \tilde{\alpha}_1\tilde{I}_1 \tag{A3–1a}$$

$$\dot{\tilde{I}}_2 = \hat{S}_2(\tilde{\lambda}_{21}\tilde{I}_1 + \tilde{\lambda}_{22}\tilde{I}_2) - \tilde{\alpha}_2\tilde{I}_2, \tag{A3–1b}$$

where $\tilde{\alpha}_j = \alpha_j = \delta_j + \tilde{\nu}_j + \gamma_j$ and $\hat{S}_j$ is the equilibrium density of type j susceptible hosts calculated in the absence of the mutant (such equilibria are always stable when they exist). Linearizing this system about the equilibrium $(\hat{I}_1, \hat{I}_2) = (0, 0)$ describes the dynamics of the mutant when initially rare. Invasion occurs when mutant densities increase when rare, implying that the (0,0) equilibrium is unstable. This is indicated when the dominant eigenvalue of the Jacobian, J, of (A3-1), evaluated at (0,0), is positive. Since (A3-1) is two-dimensional this results in two eigenvalues, χ_+ and χ_-, given by $\chi_{+,-} = [TrJ \pm \sqrt{(TrJ)^2 - 4DetJ}]/2$, where $TrJ = \tilde{\lambda}_{11}\hat{S}_1 + \tilde{\lambda}_{22}\hat{S}_2 - (\tilde{\alpha}_1 + \tilde{\alpha}_2)$ and $DetJ = \tilde{\alpha}_1\tilde{\alpha}_2 - (\tilde{\lambda}_{11}\hat{S}_1\tilde{\alpha}_2 + \tilde{\lambda}_{22}\hat{S}_2\tilde{\alpha}_1)$. Moreover, the term under the radical sign is positive, since $(TrJ)^2 - 4DetJ = [(\tilde{\lambda}_{11}\hat{S}_1 - \tilde{\lambda}_{22}\hat{S}_2) + (\tilde{\alpha}_2 - \tilde{\alpha}_1)]^2 + 4\tilde{\lambda}_{11}\tilde{\lambda}_{22}\hat{S}_1\hat{S}_2 > 0$, and the dominant eigenvalue is χ_+.

We can therefore define the fitness of a mutant parasite strain, with exploitation strategy $\tilde{\varepsilon}$, in a host population at equilibrium with a resident parasite strain, with exploitation strategy ε, as $W(\tilde{\varepsilon}, \varepsilon) = 2\chi_+$. It is then straightforward to show that local conditions for an exploitation strategy ε^* to be an ESS are given by the first and second order conditions

$$\left.\frac{\partial DetJ}{\partial\tilde{\varepsilon}}\right|_{\tilde{\varepsilon}=\varepsilon=\varepsilon^*} = 0 \tag{A3-2a}$$

and

$$\left.\frac{\partial^2 DetJ}{\partial\tilde{\varepsilon}^2}\right|_{\tilde{\varepsilon}=\varepsilon=\varepsilon^*} > 0, \tag{A3-2b}$$

respectively. A further condition given by

$$\left.\frac{\partial^2 DetJ}{\partial\tilde{\varepsilon}^2} + \frac{\partial^2 DetJ}{\partial\varepsilon\partial\tilde{\varepsilon}}\right|_{\tilde{\varepsilon}=\varepsilon=\varepsilon^*} > 0, \tag{A3-3}$$

is required in order to guarantee that the ESS is evolutionarily attainable [i.e. that ε^* is convergence stable (CS) (Bulmer 1994)]. Evaluating (A3-2a) gives expression 2 of the text, while (A3-2b) gives

$$\left.-E\left[\frac{\beta''}{\beta}\right] + E\left[\frac{\alpha''}{\alpha}\right] + 2\left\{\mathrm{cov}\left[\frac{\beta'}{\beta}, \frac{\alpha'}{\alpha}\right] - \mathrm{var}\left[\frac{\alpha'}{\alpha}\right]\right\}\right|_{\tilde{\varepsilon}=\varepsilon=\varepsilon^*} > 0, \tag{A3-4}$$

where, cov[X,Y] is the covariance between the variables X and Y, $E[X]$ and var[X] the mean and variance of the variable X, and all expectations are taken with respect to the equilibrium proportions of the force of infection that are due to class j infected hosts, $f_j = \beta_j\hat{I}_j/(\beta_1\hat{I}_1 + \beta_2\hat{I}_2)$.

Using (A3-2a) the second term in the CS condition (A3-3) can be written as

$$\left.\frac{\partial^2 DetJ}{\partial\varepsilon\partial\tilde{\varepsilon}}\right|_{\tilde{\varepsilon}=\varepsilon=\varepsilon^*} = -\alpha_1\alpha_2\frac{f_1\beta_1 y_1\hat{I}_1}{(f_1^2 - A_1)x}\left[\left(\frac{\beta_1'}{\beta_1} - \frac{\alpha_1'}{\alpha_1}\right)\frac{y'}{y}\right]\Bigg|_{\tilde{\varepsilon}=\varepsilon=\varepsilon^*} \tag{A3-5}$$

where $(y'/y) = [\gamma_1/(\alpha_1 - \gamma_1)](\alpha_1'/\alpha_1) - [\gamma_2/(\alpha_2 - \gamma_2)](\alpha_2'/\alpha_2)$. Note that the inequalities that characterize the greater susceptibility and vulnerability of type 2 hosts imply both that $\gamma_1/(\alpha_1 - \gamma_1) \geq \gamma_2/(\alpha_2 - \gamma_2)$ and $\alpha_1'/\alpha_1 \leq \alpha_2'/\alpha_2$ so that no general claim can be made regarding the sign of y'/y.

The change in ESS exploitation given a change in some efficacy, p_j, is calculated by implicitly differentiating (A3-2*a*) to get

$$\frac{d\varepsilon^*}{dp_j} = \alpha_1\alpha_2 \frac{\partial^2}{\partial p_j \partial \tilde{\varepsilon}}\left[\frac{\tilde{\lambda}_{11}\hat{S}_1}{\tilde{\alpha}_1} + \frac{\tilde{\lambda}_{22}\hat{S}_2}{\tilde{\alpha}_2} - 1\right] \Bigg/ \frac{d}{d\varepsilon}\left[\frac{\partial DetJ}{\partial \tilde{\varepsilon}}\bigg|_{\tilde{\varepsilon}=\varepsilon}\right]\Bigg|_{\tilde{\varepsilon}=\varepsilon=\varepsilon^*}. \tag{A3-6}$$

Assuming the denominator of (A3-6) is positive, as it will be if the ESS is convergence stable, the direction of change in the ESS is governed by the sign of the numerator, which can be evaluated to give

$$\frac{d\varepsilon^*}{dp_j} \propto E\left[\frac{\partial(\beta_j'/\beta_j)}{\partial p_j}\right] - E\left[\frac{\partial(\alpha_j'/\alpha_j)}{\partial p_j}\right] + \frac{\partial f_1}{\partial p_j}\left\{\left(\frac{\alpha_2'}{\alpha_2} - \frac{\alpha_1'}{\alpha_1}\right) - \left(\frac{\beta_2'}{\beta_2} - \frac{\beta_1'}{\beta_1}\right)\right\}, \tag{A3-7}$$

resulting in expression 3 of the main text.

The evolutionary results of the main text can then be derived from (A3-7) by replacing p_j with the efficacy of interest. This gives:

1 Infection-blocking vaccine

$$\frac{d\varepsilon^*}{d\tau_j} \propto (-1)^j\left\{\left(\frac{\alpha_2'}{\alpha_2} - \frac{\alpha_1'}{\alpha_1}\right) - \left(\frac{\beta_2'}{\beta_2} - \frac{\beta_1'}{\beta_1}\right)\right\} \begin{matrix} <0 \\ >0 \end{matrix} \text{ for } \begin{matrix} j=1 \\ j=2 \end{matrix} \tag{A3-8}$$

2 Transmission-blocking vaccine

$$\frac{d\varepsilon^*}{d\alpha_j} \propto (-1)^j\left\{\left(\frac{\alpha_2'}{\alpha_2} - \frac{\alpha_1'}{\alpha_1}\right) - \left(\frac{\beta_2'}{\beta_2} - \frac{\beta_1'}{\beta_1}\right)\right\} \begin{matrix} <0 \\ >0 \end{matrix} \text{ for } \begin{matrix} j=1 \\ j=2 \end{matrix} \tag{A3-9}$$

3 Anti-toxin vaccine

$$\frac{d\varepsilon^*}{d\rho_j} \propto f_j\frac{\delta+\gamma_j}{\alpha_j} + \frac{(-1)^j f_1(1-f_j)y^{j-1}\varepsilon}{(f_1^2 - A_1)x} \times (f_j\delta_j + \lambda_{jj}\hat{I}_j)\left\{\left(\frac{\alpha_2'}{\alpha_2} - \frac{\alpha_1'}{\alpha_1}\right) - \left(\frac{\beta_2'}{\beta_2} - \frac{\beta_1'}{\beta_1}\right)\right\} \begin{matrix} >0 \\ <>0 \end{matrix} \text{ for } \begin{matrix} j=1 \\ j=2 \end{matrix} \tag{A3-10}$$

4 Growth-suppressing vaccine

$$\frac{d\varepsilon^*}{d\psi_j} \propto f_j\left[\beta_j' + \frac{\alpha_j'}{\alpha_j}\frac{(\delta+\gamma_j)}{\alpha_j}\right] + \frac{(-1)^j f_1(1-f_j)y^{j-1}\varepsilon}{(f_1^2 - A_1)x} \times \left[(f_j\delta_j + \beta_j y_j\hat{I}_j)\left(\frac{\alpha_j'}{\alpha_j} - \frac{\beta_j'}{\beta_j}\right) + \frac{\alpha_j'}{\alpha_j}\frac{\gamma_j}{\alpha_j}\lambda_{jj}\hat{I}_j\right] \left\{\left(\frac{\alpha_2'}{\alpha_2} - \frac{\alpha_1'}{\alpha_1}\right) - \left(\frac{\beta_2'}{\beta_2} - \frac{\beta_1'}{\beta_1}\right)\right\} \begin{matrix} <>0 \\ <>0 \end{matrix} \text{ for } \begin{matrix} j=1 \\ j=2 \end{matrix} \tag{A3-11}$$

5 Clearance-augmenting vaccine

$$\frac{d\varepsilon^*}{d\sigma_j} \propto \frac{\alpha_j'}{\alpha_j} + \frac{(-1)^{j+1} f_1(1-f_j)y^{j-1}\delta}{(f_1^2 - A_1)x}\left\{\left(\frac{\alpha_2'}{\alpha_2} - \frac{\alpha_1'}{\alpha_1}\right) - \left(\frac{\beta_2'}{\beta_2} - \frac{\beta_1'}{\beta_1}\right)\right\} \begin{matrix} <>0 \\ >0 \end{matrix} \text{ for } \begin{matrix} j=1 \\ j=2 \end{matrix} \tag{A3-12}$$

Appendix IV

Since $\Omega = \hat{I}/(\hat{S}+\hat{I})$, this implies that $\partial\Omega/\partial\varepsilon \propto \partial\hat{I}/\partial\varepsilon/\hat{I} - \partial\hat{S}/\partial\varepsilon/\hat{S}$. This can be used calculate

$$\frac{\partial\Omega}{\partial\varepsilon} \propto -\left(\frac{\alpha_1'}{\alpha_1-\gamma_1}f_1 + \frac{\alpha_2'}{\alpha_2-\gamma_2}f_2\right) + \bar{\beta}\frac{f_1 f_2 y_1}{(f_1^2 - A_1)x}\frac{y'}{y} \times \left\{\delta\left[\frac{\hat{S}_2}{\alpha_2-\gamma_2} - \frac{\hat{S}_1}{\alpha_1-\gamma_1}\right] + \frac{\hat{I}}{\hat{S}}[\hat{S}_2 - \hat{S}_1]\right\}, \tag{A4-1}$$

where $\bar{\beta} = \beta_1 g_1 + \beta_2 g_2$ and $g_j = \hat{I}_j/(\hat{I}_1 + \hat{I}_2)$. While it is unclear whether or not this quantity might be positive for any parameter values, it is clear that situations exist for which it will be negative. This will occur, for example, when both $y'/y \leq 0$ and $\hat{S}_1 \geq \hat{S}_2$.