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Imperfect vaccination: some epidemiological and evolutionary consequences

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An aim of some vaccination programmes is to reduce the prevalence of an infectious disease and ultimately to eradicate it. We show that eradication success depends on the type of vaccine as well as on the vaccination coverage. Vaccines that reduce the parasite within-host growth rate select for higher parasite virulence and this evolution may both increase the prevalence of the disease and prevent disease eradication. By contrast, vaccines that reduce the probability of infection select against virulence and may lead more easily to eradication. In some cases, epidemiological feedback on parasite evolution yields an evolutionary bistable situation where, for intermediate vaccination coverage, parasites can evolve towards either high or low virulence, depending on the initial conditions. These results have practical implications for the design and use of imperfect vaccines in public- and animal-health programmes.

Keywords: vaccination; virulence; eradication; epidemiology

1. INTRODUCTION

A handful of vaccines prevent the illness or death of millions of individuals every year (Plotkin & Orenstein 1999) and global vaccination has led to the eradication of smallpox. These successes are partly because the infectious diseases involved are the easier cases. The more difficult challenge for vaccination is to control diseases for which natural immunity is poorly effective. For example, the vaccines that are currently being developed against malaria are not expected to provide sterilizing immunity (Hoffman 1996). These imperfect vaccines may not completely prevent infection but could reduce the probability of being infected or reduce the consequences of being infected, thereby reducing the disease burden.

We explore the potential consequences of the use of imperfect vaccines. We derive a vaccination-coverage threshold, above which the use of imperfect vaccines could lead to the eradication of the disease. In addition to these epidemiological consequences, the use of these vaccines may drive the evolution of parasite virulence (Gandon *et al.* 2001*a*), which also has consequences for the eradication threshold. We base our predictions on the trade-off theory for the evolution of parasite virulence (Anderson & May 1982, 1991; Frank 1996) in which it is assumed that there are both benefits and costs associated with host exploitation. The exploitation of host tissues allows higher parasite transmission but such exploitation harms the host, reduces its life expectancy and thereby limits parasite transmission. Thus, virulence can be viewed as a pleiotropic life-history trait characterized by a trade-off between within-host reproduction and between-host transmission. Such a trade-off yields the prediction that parasites should evolve toward optimal host-exploitation strategies with intermediate levels of virulence.

Most of the theory on the evolution of parasite virulence is based on the assumption that the host population is homogeneous. Individual hosts, however, may differ and, from the parasite's point of view, they may constitute very different habitats. In particular, some habitats may provide more resources or be less vulnerable to parasite exploitation and, consequently, these different habitats may select for different virulence levels. The use of imperfect vaccines may generate this type of heterogeneity. The importance of heterogeneity for epidemiology has long been recognized (May & Anderson 1984; Anderson & May 1991), but how does the parasite population evolve in such heterogeneous environments?

Two different resistance components are considered: (i) resistance may decrease the probability of infection; and/or (ii) it may decrease the growth rate within the host. These different mechanisms are known to have different evolutionary consequences (Gandon & Michalakis 2000), which interact with the epidemiological dynamics to produce non-intuitive effects of vaccination on total disease burden (Gandon *et al.* 2001*a*). We explore these further in the context of disease eradication. First, we analyse the epidemiological effects of the use of such imperfect vaccines on the critical vaccination coverage, p_c, the proportion of people that need to be successfully vaccinated to achieve disease eradication (Anderson & May 1991). This eradication threshold is positively correlated with disease prevalence, so that, even for non-eradicable diseases, it is of interest to determine the effect of particular intervention measures on p_c. Second, we study the potential impact of different types of vaccines on the evolution of parasite virulence. In particular, we find that the use of anti-growth vaccines may yield an evolutionary bistability in parasite virulence, where virulence may evolve towards either a high or a low level, depending on the initial conditions. Thus, in some cases, vaccination may lead to sudden dramatic increases in virulence. Third, we analyse the implications of parasite evolution for disease eradication. In particular, we show that when higher virulence is selected for by vaccines, this may result in increased transmission rates and prevent eradication. These results have implications for the medium-term consequences of vacci-

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nation programmes, and we suggest possible ways in which to optimize vaccination strategies.

2. THE MODEL

(a) *Epidemiological dynamics*

We consider a heterogeneous host population with two types of host. The first is assumed to be fully susceptible to the parasite while the second is partially resistant to infection as a result of vaccination with an imperfect vaccine. Resistance may reduce the probability of being infected (resistance parameterized by r_1) and, if infection occurs, it may reduce the level of host exploitation by the parasite (resistance parameterized by r_2). Because of its effect on within-host growth rate, this latter type of resistance may also reduce both the virulence and the transmission of the parasite. For the sake of simplicity we further assume that new hosts are introduced into the population at a constant rate, λ, which covers both reproduction and immigration. Among these new hosts, a proportion, p, are resistant while the rest $(1-p)$ are fully susceptible to the parasite. One may consider that the input of resistant hosts results from host vaccination. In this case, the parameter p measures the vaccination coverage of the host population. Uninfected hosts have a death rate δ, while infected hosts incur an extra mortality rate (i.e. parasite virulence). The virulence is equal to α if the host is susceptible and it is equal to $\alpha' = (1-r_2)\alpha$ if the host is resistant. In the remainder of the paper, we refer to parasite *virulence* as the level of parasite-induced host mortality, α, measured in susceptible hosts. Note that, although the extra mortality induced by the parasites will vary between susceptible and vaccinated hosts (i.e. $\alpha' \leqslant \alpha$), we assume that the parasite strategy is not allowed to be conditional on the type of host.

The parasite is horizontally transmitted from susceptible and resistant hosts to uninfected susceptible hosts with rates β and β', respectively. Parasite transmission is assumed to depend on its host exploitation and, consequently, to correlate with its virulence (i.e. $\beta \equiv \beta[\alpha]$, $\beta' \equiv \beta[\alpha'] = \beta[(1-r_2)\alpha]$) as suggested by several empirical observations in different host–parasite systems (Lipsitch & Moxon 1997; Mackinnon & Read 1999; Messenger *et al.* 1999; Fenner & Fantini 1999; Weiss 2002). Moreover, this relationship is assumed to be the same in both susceptible and resistant hosts, as also supported by experiments in rodent malaria (Mackinnon & Read 2003) and in myxomatosis (Best & Kerr 2000). Superinfection of already-infected hosts may also occur. The parameter σ measures the susceptibility to superinfection (relative to uninfected hosts). For example, when $\sigma = 0$ only single infections occur (no superinfection) and when $\sigma = 1$ infected hosts are as susceptible as uninfected ones.

Host and parasite life cycles are formalized using the following set of differential equations (when the parasite population is monomorphic with virulence α):

$$\left.\begin{aligned} \mathrm{d}x/\mathrm{d}t &= (1-p)\lambda - (\delta + h)x \\ \mathrm{d}x'/\mathrm{d}t &= p\lambda - (\delta + h')x' \\ \mathrm{d}y/\mathrm{d}t &= hx - (\delta + \alpha)y \\ \mathrm{d}y'/\mathrm{d}t &= h'x' - (\delta + \alpha')y' \end{aligned}\right\}, \tag{2.1}$$

where y and x are the densities of infected and uninfected susceptible hosts, respectively (the prime refers to resistant hosts), and $h \equiv \beta y + \beta' y'$ and $h' \equiv (1-r_1)h$ are the forces of infection on susceptible and resistant hosts, respectively.

The case where $x = (1-p)\lambda/\delta$, $x' = p\lambda/\delta$ and the parasite is absent (i.e. $y = y' = 0$) is a trivial equilibrium of equations (2.1). The stability of this equilibrium depends on the ability of a parasite to invade a previously uninfected host population, which is given by the basic reproductive ratio of the parasite (Blower & McLean 1995; Dushoff 1996):

$$R_0 = (1-p)R_0^{\mathrm{S}} + pR_0^{\mathrm{V}}, \tag{2.2}$$

where

$$R_0^{\mathrm{S}} \equiv \beta\lambda/(\delta(\delta + \alpha))$$

and

$$R_0^{\mathrm{V}} \equiv (1-r_1)\beta'\lambda/(\delta(\delta + \alpha'))$$

are the basic reproductive ratios in unvaccinated and 100% vaccinated host populations, respectively. Parasite invasion will occur if $R_0 > 1$. This condition can be used to derive the critical vaccination coverage leading to disease eradication:

$$p_{\mathrm{c}} = 1 - \frac{1 - R_0^{\mathrm{V}}}{R_0^{\mathrm{S}} - R_0^{\mathrm{V}}}. \tag{2.3}$$

In the limit case of a perfect vaccine (i.e. when $r_1 = 1$ and/or $r_2 = 1$, yielding $R_0^{\mathrm{V}} = 0$) the threshold value of vaccination coverage leading to eradication reduces to the classical quantity (Anderson & May 1991):

$$p_{\mathrm{c}} = 1 - \delta(\delta + \alpha)/(\lambda\beta) = 1 - 1/R_0^{\mathrm{S}}.$$

Equation (2.3) shows that eradication may be impossible with some imperfect vaccines (Blower & McLean 1994). Indeed, even good imperfect vaccines ($r_1 = r_2 = 0.75$) will be unable to eradicate diseases with quite modest values of R_0 (figure 1). As expected, $R_0^{\mathrm{V}} < 1$ is a necessary condition for eradication to be possible for some level of vaccination coverage (i.e. $p_{\mathrm{c}} < 1$): in ecological terminology, vaccinated hosts have to be 'sink' habitats (Pulliam 1988; Dias 1996) for eradication to be feasible.

Not surprisingly, the level of vaccination required to eradicate the disease increases with increasing basic reproductive ratio in vaccinated hosts, R_0^{V}. In other words, the better the vaccine, the lower the vaccination coverage required for eradication. Since R_0^{V} is always a decreasing function of r_1, the critical eradication threshold is always a decreasing function of r_1. However, R_0^{V} can both decrease and increase with higher values of r_2. In the remainder of the paper, we focus on cases where parasite virulence is at an optimal level before the vaccine is introduced. In such cases, it can be shown that an increase in r_2 always decreases R_0^{V} and, consequently, the eradication threshold. We note in passing, however, that, where a parasite's virulence is higher than optimal, an increase in r_2 leads to an increase in R_0^{V} and hence an increase in the eradication threshold. This is because it alleviates the fitness cost of host mortality and, consequently, increases the duration of the infection and the basic reproductive ratio. This might be relevant if imperfect vaccines are ever

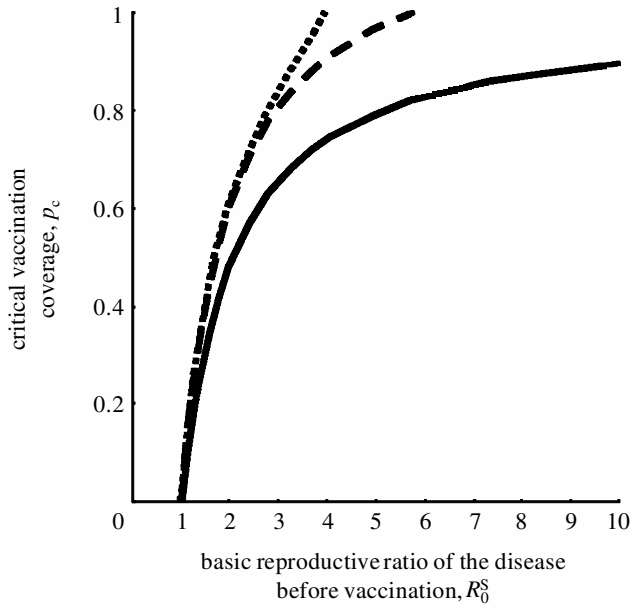

Figure 1. Critical vaccination coverage to achieve eradication, p_c, as a function of the basic reproductive ratio of the disease before vaccination, R_0^S. The solid line is for a perfect vaccine (i.e. when $r_1 = 1$ and/or $r_2 = 1$, yielding $R_0^V = 0$). The dashed line is for a partially effective (imperfect) vaccine with $r_1 = r_2 = 0.75$. In these two cases (the solid line and the dashed line) the virulence of the parasite is assumed to have reached its ES equilibrium in the absence of vaccination and is not allowed to evolve away from this. The dotted line shows what happens with the same type of imperfect vaccine when pathogen virulence is allowed to evolve. As vaccine efficacy increases, the vaccination threshold always decreases and virulence evolution always increases the critical vaccination threshold. The following transmission function has been used: $\beta[\alpha] = b(1 - e^{-2\alpha})$. We used variable values of b to produce a range in R_0^S. Other parameter values: $\lambda = 100$, $\delta = 0.09$, $\sigma = 0$.

used against a highly pathogenic emergent disease that is far above its evolutionarily stable (ES) virulence.

(b) *Evolutionary dynamics*

The change in the host population (the habitat of the parasite) induced by vaccination may drive the evolution of the parasite. In accordance with Gandon *et al.* (2001*a*), we will assume that no escape mutants (i.e. antigenic variants that could avoid being cleared by vaccine-induced immunity) emerge in the parasite population. Only life-history traits such as host exploitation, virulence and transmission are allowed to evolve. These different traits, however, will evolve under the constraints set by the relationships between them (we assume that virulence and transmission are pleiotropic effects of host exploitation). To determine the ES virulence in a population of vaccinated hosts, we need to focus on the invasion of a mutant parasite with a virulence strategy α^* appearing in a parasite population dominated by a resident strategy α at the epidemiological equilibrium. The direction of evolution and, ultimately, the ES virulence, depend on the fate of a rare-mutant strategy given by

$$R[\alpha^*,\alpha] = v_S[\alpha^*,\alpha]\hat{N} + v_V[\alpha^*,\alpha]\hat{N}', \tag{2.4}$$

with $\hat{N} \equiv \hat{x} + \sigma\hat{y}$ and $\hat{N}' \equiv (1 - r_1)(\hat{x}' + \sigma\hat{y}')$, where the hats refer to the epidemiological equilibrium;

$$v_S[\alpha^*,\alpha] \equiv \beta[\alpha^*]/(\delta + \alpha^* + \sigma\hat{h})$$

and

$$v_V[\alpha^*,\alpha] \equiv \beta[(1 - r_2)\alpha^*]/(\delta + (1 - r_2)\alpha^* + \sigma\hat{h}')$$

are the reproductive values of the parasite in a susceptible and in a resistant host, respectively (Gandon *et al.* 2001*a*). When $R[\alpha^*,\alpha] > 1$ the mutant strain will invade the resident population; hence, the ES virulence strategy can be found by maximizing $R[\alpha^*,\alpha]$ at $\alpha^* = \alpha$.

The optimum virulence differs between susceptible and vaccinated hosts. The different components of the vaccines (anti-infection and anti-growth components) have different evolutionary consequences for virulence evolution (Gandon *et al.* 2001*a*). First, vaccines with an anti-growth component (i.e. $r_2 > 0$) reduce the cost of virulence (i.e. the death of the infected host) and, consequently, select for higher virulence. Second, when superinfections occur, the anti-infection component may select for lower virulence because parasite strains in vaccinated hosts have a lower risk of being excluded by incoming strains. The consequent reduction in within-host competition favours milder exploitation strategies and lower virulence (Eshel 1977; Bremermann & Pickering 1983; Sasaki & Iwasa 1991; Nowak & May 1994; van Baalen & Sabelis 1995; Frank 1996).

In a heterogeneous population (i.e. $0 < p < 1$), the relative importance of selection occurring in susceptible and vaccinated hosts is weighted by the availability of these different types of host, measured by $\hat{N}$ and $\hat{N}'$, respectively (see equation (2.4)). A condition for evolutionary equilibrium derived from the maximization of $R[\alpha^*,\alpha]$ at $\alpha^* = \alpha$ (see also Regoes *et al.* 2000) is

$$\frac{dv_V}{dv_S} = -\frac{\hat{N}}{\hat{N}'}. \tag{2.5}$$

Both local and global evolutionary stability of these equilibria can be checked through the analysis of pairwise invasibility plots (see electronic Appendices A and B available on The Royal Society's Publications Web site).

The above condition yields a geometric view of parasite evolution. As shown in figure 2, the parasite's fitness set (Levins 1962) can be obtained by plotting the reproductive value in resistant hosts against the reproductive value in susceptible hosts for variable levels of virulence. The specific location of the ES phenotype is where the tangent to the fitness set has a slope equal to $-\hat{N}/\hat{N}'$. This point thus depends on the relative abundance of the different types of host in the population.

This geometrical view is also useful to show that, depending on the shape of the fitness set, several ES strategies (ESSs) may exist (figure 2*b*). Here, the shape of the fitness set is governed both by the relationship between virulence and transmission and by the level of resistance. When the relationship between transmission and virulence is very steep and when r_2 increases, the fitness set can become convex (see figure 2*b*). Whether or not multiple evolutionary equilibria do exist also depends on the number of each host type and hence on the vaccination coverage (figure 3). As shown in figure 3*g* and *h* (i.e. when $r_2 = 0.6$), as vaccination coverage increases, the system switches sequentially from: (i) a situation where there is a single evolutionary equilibrium; to (ii) a situation with

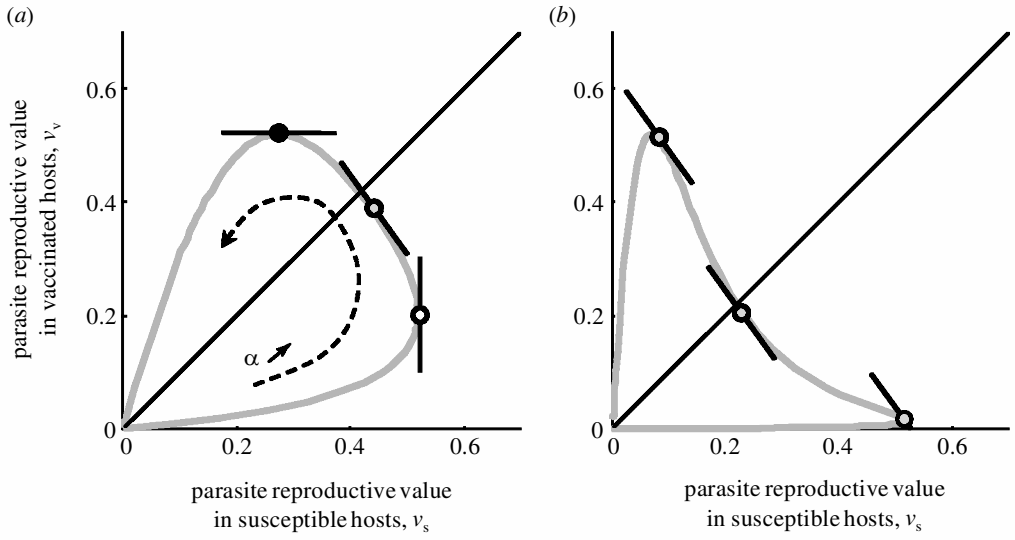

Figure 2. Graphical representation of the ES parasite virulence. The parasite fitness set is defined by parasite reproductive values in vaccinated (v_V) and susceptible (v_S) hosts for variable levels of parasite virulence. The point on the fitness set moves in an anticlockwise direction (indicated by the dashed arrow in (*a*)) as virulence increases. The fitness sets are derived using the transmission function $\beta[\alpha] = (1 - e^{-4\alpha})^2$ with (*a*) $r_2 = 0.75$ and (*b*) $r_2 = 0.95$. The ES parasite virulence is obtained by finding the tangent of the fitness set with slope equal to $-\hat{N}/\hat{N}'$ (see equation (2.5)). When all the hosts are resistant (i.e. $\hat{N} = 0$), the tangent must be horizontal, yielding the virulence that maximizes the reproductive value in resistant hosts (the black dot in (*a*)). When all the hosts are susceptible (i.e. $\hat{N}' = 0$), the tangent must be vertical, yielding the virulence that maximizes the reproductive value in susceptible hosts (the white dot in (*a*)). The case where the host population is heterogeneous lies between these two extremes. When the fitness set is convex (a set of points such that the straight line joining any two points of the set lies entirely within that set) there is only one point that satisfies the above ESS condition (the grey dot in (*a*)). However, when the fitness set is concave three different points may satisfy the above ESS condition (the grey dots in (*b*)), yielding an evolutionary bistability since the intermediate equilibrium is always unstable. Note that (*a*) and (*b*) differ only in the level of r_2.

three equilibria; and, finally, to (iii) a situation with a single equilibrium. The analysis of the three-equilibria case shows that the intermediate equilibrium is always evolutionarily unstable (since a mutant with a higher or lower virulence can always invade) and the system is therefore bistable. Again, the geometrical view presented in figure 2 is useful to explain these results since vaccination coverage strongly affects the slope $-\hat{N}/\hat{N}'$. In particular, this geometrical view explains why bistability can be observed only for intermediate values of vaccination coverage. Extreme values of the slope $-\hat{N}/\hat{N}'$ (i.e. either vertical or horizontal) always yield a single ESS whatever the shape of the fitness set.

In the bistable situation, the equilibrium to which evolution yields depends on the initial conditions (i.e. the virulence of the resident population). In the absence of any alteration of the epidemiological equilibrium, the transition from the lower equilibrium to the higher one may occur only if the vaccination coverage is sufficiently large. There is indeed a vaccination-coverage threshold, p_b (for *bistability* threshold), above which there may be a sharp rise in virulence towards the higher equilibrium (figure 3*g*,*h*). Note that the actual position of the vaccination-coverage threshold leading to the higher-virulence equilibrium depends on whether evolution proceeds in small steps through small-effect mutations. Figure 3 indicates both the *local* and the *global* stability of each evolutionary equilibrium. Locally stable equilibria can be globally unstable: thus, the switch from the lower-virulence optimum towards the higher one may occur for lower vaccination coverages if mutations with a large effect on virulence can occur (see electronic Appendices A and B).

In this instance, we are studying the effects of vaccination, but, as an aside, we note that any source of heterogeneity in the host population may yield different selective pressures on parasites infecting different host individuals and hence there may be different optima in different habitats (host types). The reproductive-value approach used above can be used to analyse more formally the level of adaptation of a given parasite strategy to a particular host type. Indeed, a higher reproductive value in one type of host could be viewed as an adaptation to this particular type of host. The ratio between reproductive values could also be used as a measure of the level of specialization of the parasite (the farther the equilibrium is from the diagonal in figure 2, the more specialized is the strategy). Interestingly, in the bistable situation, different specialization strategies may exist. Figure 2*b* shows that the two ES virulence strategies correspond to two specialization strategies on the different hosts.

(c) *Parasite evolution and eradication*

Virulence evolution will affect other parasite life-history traits and in particular transmission. This may have a strong impact on the critical vaccination coverage, p_c. Figure 1 shows the effects of different vaccines on p_c, with or without virulence evolution. Parasite evolution always leads to higher values of the critical vaccination coverage. In other words, evolution allows the parasite population

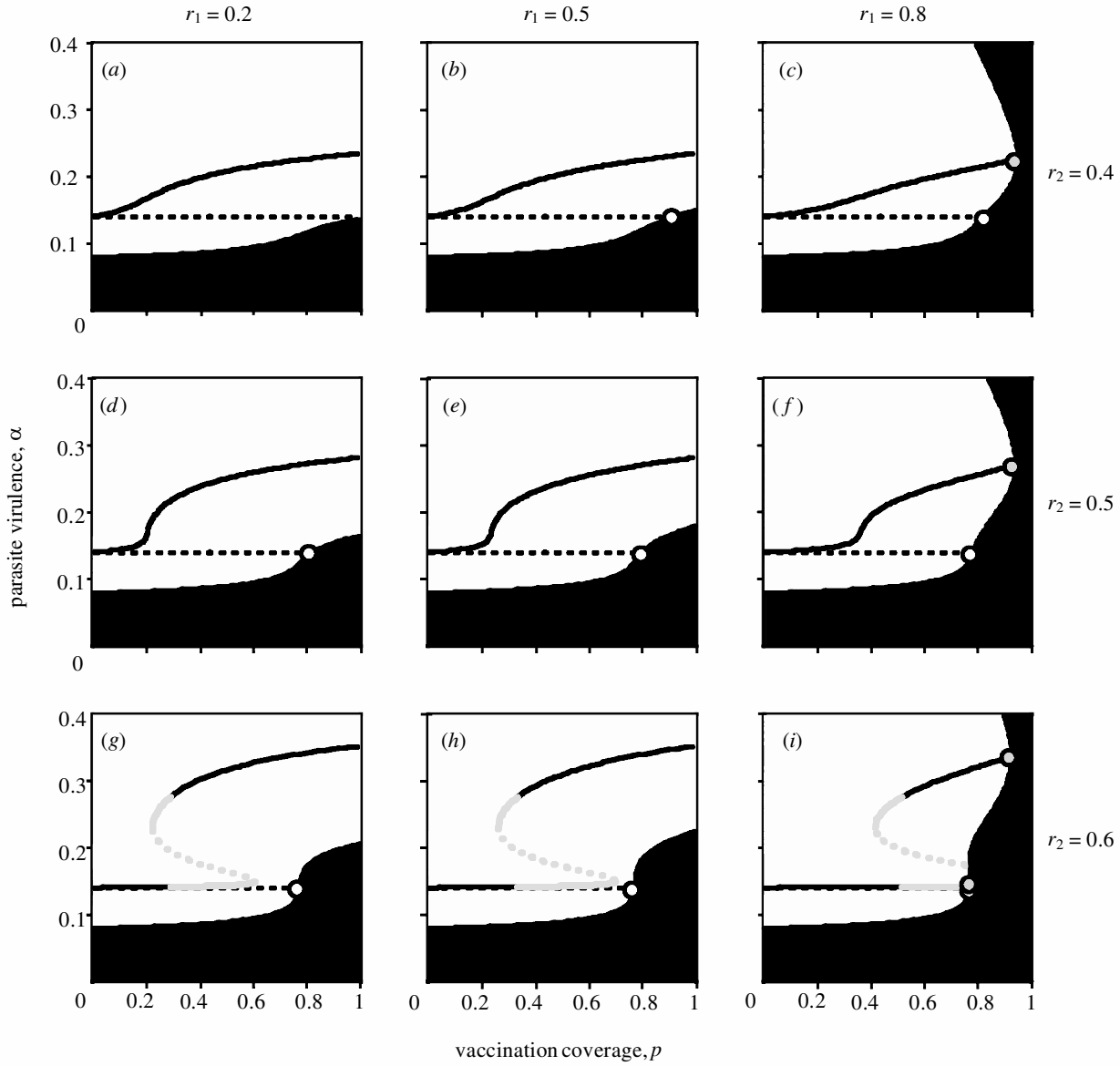

Figure 3. The effect of vaccination coverage on the evolution of parasite virulence for different types of vaccine ($r_1 = 0.2$, 0.5, 0.8 and $r_2 = 0.4$, 0.5, 0.6). The dashed black line shows the ES virulence strategy in the absence of a vaccine. The solid black line presents the virulence strategies, α^*, that are both locally and globally ES. In figure (*g–i*), the solid grey line refers to locally ES but globally unstable equilibria, while the dashed grey line shows equilibria that are both locally and globally evolutionarily unstable (see electronic Appendices A and B). The actual position of the vaccination-coverage threshold leading to the higher-virulence equilibrium, p_b, depends upon the amount of phenotypic difference between the mutant and the resident strategy (larger differences decrease p_b). In the black area the parasite population goes to extinction, and this can be used to derive the critical vaccination coverage, p_c, for different levels of parasite virulence (see equation (2.3)). The grey and the white circles indicate the critical vaccination coverage with and without vaccine-driven evolution, respectively. Note that the evolution of parasite virulence allows the parasite to escape eradication for a wider range of vaccination coverage. The following transmission function has been used to compute these examples: $\beta[\alpha] = (1 - e^{-50\alpha})^{100}/1000$. Other parameter values are as given in figure 1.

to avoid extinction by becoming better adapted to a new environment (the vaccinated host population).

When there is an evolutionary bistability, dramatic consequences follow. There is a critical window of vaccination coverage (i.e. $p_b < p < p_c$) where virulence evolution may have negative consequences for the host population. This result contrasts with classical epidemiological models, which identify a vaccination-coverage threshold above which the parasite is driven to extinction. Here, higher vaccination coverage may have very negative consequences for the host population. The switch from the lower to the higher equilibrium that may occur within this window of vaccination coverage carries a twofold cost. First, it increases the intrinsic parasite virulence and, second, it may remove the eradication potential of the vaccine (figure 3).

Anti-growth vaccines can thus render a disease much more difficult to eradicate if virulence evolves. This problem is partly alleviated if there is also an anti-infection component in the vaccine, which effectively reduces the importance of vaccinated hosts and hence the selection for higher virulence (figure 3). Geometrically, this can be seen from figure 2 since a higher value of r_1 increases the slope of the tangent to the fitness set (see equation (2.5)),

always leading to a lower value of the ES virulence. Note that this effect is different from the one caused by reduced risks of superinfections. Here, the anti-infection component selects for lower virulence even when only a single infection occurs, provided that the vaccine has some anti-growth component (i.e. $r_2 > 0$). Thus, anti-infection effects can interact with the anti-growth effects on virulence evolution, while not directly selecting for virulence themselves.

3. DISCUSSION

We studied both the epidemiological and the evolutionary consequences of the use of different types of imperfect vaccine. Not surprisingly, imperfect vaccines always increase the critical vaccination threshold that may lead to disease eradication. Blower & McLean (1994, 1995) and McLean (1999) reached similar conclusions with another epidemiological model, which allowed them to analyse the impact of other forms of vaccine failure. Several studies (Lipsitch 1997, 2002; McLean 1999, 2002) focused on the analysis of the invasion dynamics of vaccine-resistant strains (escape mutants) but the potential impact of vaccines on parasite life-history evolution has been largely overlooked. We have shown previously that different types of vaccine may have qualitatively different consequences for the evolution of parasite virulence (Gandon *et al.* 2001*a*). Here, we investigated the link between such evolution and the eradication potential of the different vaccines. In particular, we showed that vaccines with a strong anti-growth component might select for higher virulence and, consequently, increase the critical vaccination threshold.

These results have implications for the optimization of vaccination strategies. Two parameters could be optimized: (i) vaccine *efficacy* (the different components of the vaccines, r_1 and r_2); and (ii) vaccine *coverage* (p).

(a) *Vaccine efficacy*

The present model indicates that, if possible, the parameter r_1 should be maximized. This component has several beneficial effects (figure 3). There is a short-term epidemiological effect yielding a decrease in the prevalence of the disease and in the eradication threshold. However, there is also a long-term evolutionary impact, which may lead to a decrease in parasite virulence. Two main processes are involved. First, when superinfection occurs ($\sigma > 0$), this form of resistance reduces the within-host competition between different parasite strains and consequently favours less virulent strategies (Gandon *et al.* 2001*a*,*b*). Second, the anti-infection component of the vaccine decreases the probability of infection of vaccinated hosts and this may interact with the effect of the anti-growth component of the vaccine on the evolution of virulence. This anti-infection effect reduces the strength of selection induced by the anti-growth component of the vaccine and selects for lower virulence. Note that this second process does not require superinfections to occur.

By contrast, the parameter r_2 should be chosen to be either very low or very high. Very low values carry a long-term benefit because of the reduced selective pressure for increased virulence. Very high values carry a strong short-term benefit (vaccinated individuals suffer much less from the infection) but they may also reduce the risk of virulence evolution. Selection for higher virulence may be very high in vaccinated hosts but, since the reproductive value in these hosts is very low (because of reduced transmission), virulence is not selected for at the scale of the whole parasite population. The ES virulence is maximized at intermediate values of r_2 (see fig. 2 in Gandon *et al.* 2001*a*).

(b) *Vaccine coverage*

The optimization of vaccination coverage depends on the efficacy of the vaccine. Even if coverage is below the eradication threshold, a vaccine inducing very high r_1 immunity and either low or very high r_2 immunity will not, at any vaccination coverage, impose much selection for increasing virulence. In this situation, coverage should be maximized.

If the vaccine has an intermediate r_2 component and a low r_1 value (figure 3*g*,*h*), evolutionary bistability may occur and intermediate or high vaccination coverage may lead to the evolution of a dramatically higher virulence through a switch to the higher bistable equilibrium. In these situations, it would be better to adopt either small vaccination coverage (to decrease the selection for increased virulence) or very high vaccination coverage (to lead to eradication). For high vaccination coverage, eradication may actually occur before virulence evolution. The choice between these two opposite strategies could be made after estimating the basic reproductive ratio of the parasite. In particular, for diseases with large R_0^S and p_c (e.g. malaria), where imperfect vaccines are unlikely to lead to eradication, sparing use of vaccines would minimize virulence evolution.

It may not always be possible to minimize the eradication threshold while simultaneously minimizing disease-induced mortality: greater vaccine coverage will decrease the force of infection but it may also select for more virulent pathogens. This would generate some management dilemmas (van Baalen 2002). In electronic Appendices A and B we show that it is possible to use a more integrative measure of public health (which takes into account both the force of infection and virulence), the host life expectancy in a population, $L[p,r_1,r_2]$, which is a function of coverage and the efficacy of the different components of a vaccine. In principle, such functions could be used to optimize the short-term (without pathogen evolution) and medium-term (with pathogen evolution) success of a vaccination programme. We note, however, that precise quantitative predictions about optimal levels of coverage depend critically on the precise form of the virulence–transmission relationship, about which we currently know little for any disease. Such knowledge of the relationships and constraints among parasite life-history traits is required for human infectious diseases for which vaccines are in use or imminent.

More broadly, we emphasize that the above optimization criteria are derived from a very simple epidemiological model and that they may be altered under more complicated assumptions. For example, it is well known that, even in the absence of parasite evolution, intermediate vaccination coverage may yield undesirable outcomes if the risk of serious illness increases with the age of the host (Anderson & May 1983, 1991). Similarly, parasite

evolution can lead to a decrease in its prevalence even towards its extinction. A necessary condition for such evolutionary suicides is the existence of a discontinuous transition to extinction such as the one induced by an Allee effect (Gyllenberg & Parvinen 2001). These Allee effects may be quite common in host–parasite systems because of a strong impact of the inoculum size on the success of an infection (Regoes *et al.* 2002). It would be interesting to study the evolution of virulence in the context of vaccination using models incorporating age-specific susceptibility to the disease and dose-dependent infection rates.

It is also worth noting that our analysis focuses on evolutionary endpoints but says nothing about the transient dynamics. The outcome of vaccination (eradication or not) will depend strongly on the speed at which the parasite can evolve. Eradication could occur before virulence evolution. The speed of virulence evolution will depend both on the amount of genetic variation in the parasite population and on the strength of selection (Gandon *et al.* 2001*a*). The strength of selection will itself depend on several other components of the model, namely, the type of vaccine, the shape of the trade-off relating transmission to virulence and the vaccination coverage. In particular, the strength of selection can be very high beyond the evolutionary threshold (i.e. when $p_b < p < p_c$). It may also depend on complexities that we have not yet explored, such as the presence of vaccine escape and drug-resistant mutants, which may interfere with virulence evolution.

Our model predicts that an anti-growth component of host resistance may select for higher parasite virulence. There may already be examples where this has occurred. For example, there have been large increases in virulence over the past few decades in Marek's disease virus, a lymphoproliferative disease of chickens. While there may be other causes of the emergence of more virulent strains, vaccination is a leading contender (Witter 1997*a*, 1998). More virulent strains perform better in vaccinated chickens (Witter 1997*b*) and there is no evidence that the more virulent strains are antigenically distinct from mild strains. The resistance that selects for higher virulence may be induced by vaccines or drugs but could also emerge naturally in host populations. The virulence of the myxoma virus, as assayed in standard laboratory rabbits, increased in Australia during the 1990s, almost certainly in response to the emergence of resistance in wild rabbit populations (Fenner & Fantini 1999). This is in accord with our model: natural resistance has a strong anti-growth component, higher virulence may be associated with higher transmission rates (Best & Kerr 2000), and host death stops transmission. These cases, and the theoretical arguments above, suggest to us the need for further consideration of the effects of vaccination and, more generally, of host resistance on pathogen life-history evolution.

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