Parent-to-offspring infection and the struggle for transmission

Minus van Baalen [a] *

[a]Institute of Biodiversity and Ecosystem Dynamics, Section Population Biology, University of Amsterdam, Kruislaan 320, 1098 SM Amsterdam, The Netherlands,
& Institut d'Écologie – UMR 7625, Université Pierre et Marie Curie, Bât. A, 7ème Étage CC237, 7 quai St.-Bernard, 75252 Paris Cedex 05, France

1. INTRODUCTION

Current ideas about the evolution of vertical transmission are that it will evolve if susceptible hosts are rare (Lipsitch et al. 1995b, Turner et al. 1998), and that when it evolves it will favour parasites of lower virulence (Bull et al. 1991, Herre 1993). These insights are based on the assumption that vertical transmission is a secure way into future generations. In reality, however, competition for the host's offspring is likely to occur (Koella and Doebeli 1999). If vertical transmission is common, the payoff for mutant parasites that opt for horizontal transmission might be enhanced. After all, a parasite that is able to 'steal' the offspring of other hosts will then have many opportunities for infection.

One way for a parasite to utilize hosts already vertically infected is through co-infection or super-infection (Nowak and May 1994, van Baalen and Sabelis 1995, Gandon 1998, Mosquera and Adler 1998). Unfortunately, models incorporating multiple infection are more difficult to analyse than models allowing only single infections. However, another mode of competition among the parasites is *for* a host's offspring. If vertical transmission is not immediate, but occurs when the mother is weaning its offspring (termed pseudo-vertical transmission by Wilkinson (1999)), an offspring may acquire infections by other hosts in the population before the parent's parasites succeed to claim it. Thus, host offspring may be infected either horizontally or vertically. This framework has the unrealistic feature that parasites are not challenged by other parasites once they have infected a host, but they have to compete to infect it, even in the case of vertical transmission. The advantage is that it is much more easy to analyse.

If the (external) risk of infection is low (as would be the case when parasites are virulent and rare) then vertical transmission would indeed be a guaranteed mode of reproduction for the parasites. However, if the parasites become less virulent and more common, the risk of external infection rises. As a consequence, the potential benefit of vertical transmission decreases. The shift back to horizontal transmission will affect the force of infection again. The evolutionary equilibrium will thus be determined by this feedback, and consequently changes in the hosts' environment (affecting for example maximum birth rate or background mortality rate) will provoke an evolutionary response in the parasite population. Thus, the model will lead to hypotheses as how parasites will respond to changes in environmental conditions.

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The insights obtained here will apply with little modification to cases with 'real' vertical transmission. Though the simplest host-microparasite models ignore multiple infection, it is an important determinant of the evolution of virulence (Nowak and May 1994, van Baalen and Sabelis 1995, Frank 1996, Gandon 1998). First of all, there will be competition among the strains infecting a host for who will be able to 'claim' the offspring. The more strains, the more intense this competition, and hence the lower the benefit of vertical transmission. But moreover, a parasite that transmitted to an offspring may have a headstart, but it cannot prevent its host from receiving additional infections. If the force of infection is high, the mutant strain would be quickly diluted with resident, horizontally transmitted strains. Effectively, it loses its host to the resident in a very similar fashion to the 'pseudo'-infection model that I analysed here. Also with real vertical transmission there will therefore be competition for the host's offspring.

In evolutionary epidemiology, it is customary to express the fitness of parasites in terms of their basic reproduction R_0. However, some confusion reigns with respect to this quantity, and care must be taken to define it carefully. In classical epidemiology, R_0 measures the expected number of secondary infections produced by a single infected individual in a wholly susceptible population (Kermack and McKendrick 1927, Anderson and May 1991, Heesterbeek 1992). Evolution, however, is about strains of parasites replacing one another. The relevant fitness measure is therefore the reproduction ratio of a mutant parasite in host population where a resident parasite is already present (van Baalen and Sabelis 1995, Mylius and Diekmann 1995). In particular where there is within-host competition or, as is the case in this chapter, where there is competition for vertical transmission between parasite strains, the two R_0 concepts differ. In particular, the 'epidemical' definition does not include the effects of competition for vertical infection. If this aspect is important, using the classical R_0-concept will therefore yield erroneous predictions.

I will analyse a model for pseudo-vertical transmission that includes competition for transmission among parasite strains. I will use this model to explore how the evolutionary feedback depends on characteristics of the host-parasite interactions. When dealing with parasites that can transmit vertically, the expression of parasite virulence becomes important. To a host it is irrelevant (evolutionarily speaking) whether it is castrated or killed by the parasite, but to the parasite it may make a big difference. I will assume that parasite virulence has two components, corresponding to two independent means to produce infectivity, the classical one where the host itself is exploited (leading to a disease-induced mortality rate) and a second where the host's allocation to reproduction is 'siphoned off' (with no ill health effects).

By analysing such a model, hypotheses can be formulated about which conditions favour vertical transmission of parasites. These hypotheses could be tested with examples from the real world (bacteria and their phages, plants and fungi, mammals and their intestinal parasites). The results can also be used to make sense of the outcome of spatial host-parasite interactions involving a kind of 'indirect' vertical transmission (Lipsitch et al. 1995a, van Baalen 2000).

Since the model is simple and has some unrealistic features, it makes no sense to compare the results with data from a specific system. Yet it serves to outline the conceptual issues, and I will briefly discuss the kind of data that are needed to assess the significance of the struggle for vertical transmission. In the Appendix I will outline how a more general model can be formulated and analysed.Such models could be tailored to represent some specific instance, or

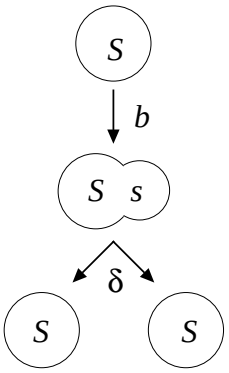

Figure 1. Schematic representation of the formation (through birth, with rate b) of parent-offspring complexes and their subsequent dissociation (with rate δ).

could be used to address more precise questions, such as how juvenile mortality is expected to affect the results or what the consequence of reverse (offspring-to-parent) vertical transmission will be.

2. THE MODEL

The basic idea for the present framework is that whenever a host (denoted S) reproduces, a temporary parent-offspring complex is formed (denoted Ss, throughout I will use the convention that the capital symbol refers to the adult while lowercase symbol refers to the offspring). Parent and offspring will separate only after some time ($1/\delta$) on average (Figure 1). The twist of the model is that if the parent is infected, the infection can be passed on within the complex with a high efficiency, though the offspring is also exposed to external sources of infection. Here I will derive the model equations, by consecutively adding more components. First the disease-free system, then the resident parasite strain will be added and lastly the mutant strain.

In deriving the model, I will use a technique derived from theoretical physics. This approach has been successfully applied to model the effects of spatial or social structure on host-parasite dynamics and evolution (van Baalen and Rand 1998, Rand 1998). Instead of giving all the differential equations that do the bookkeeping, I will be focusing on the 'events' that give rise

Table 1
Events governing the dynamics of the disease-free system.

Event	Per-capita rate	Description
$S \to Ss$	b	birth[a]
$S \to \dagger$	μ	death
$Ss \to \dagger$	μ	death[b]
$Ss \to S+S$	δ	dissociation

[a] Birth rate is assumed to be density-dependent, see text.

[b] No juvenile mortality occurs in parent-offspring complexes.

to these equations. The relevant events are birth (giving rise to parent offspring complexes), dissociation (of parent and offspring), death, and infection. The advantage on focusing on these events is that the assumptions underlying them have to be made explicit right from the outset, and do not have to be inferred from the equations. The full set of equations is given in the appendix, but to illustrate the approach I will discuss in some detail how the equations for the disease-free populations linked to the demographic events.

2.1. Host dynamics

The basic events that govern the dynamics of the host in absence of the disease are birth (creation of parent-offspring complexes), dissociation and mortality (see Table 1 and Figure 1). The disease-free host population is therefore characterized by two densities, adult hosts $[S]$ and parent-offspring complexes $[Ss]$ (square brackets indicate densities). A bookkeeping based on these events results in the differential equations

$$\begin{aligned} \frac{d[S]}{dt} &= -(b+\mu)[S] + 2\delta[Ss] \\ \frac{d[Ss]}{dt} &= b[S] - (\mu+\delta)[Ss]. \end{aligned} \tag{1}$$

to describe the dynamics of the disease-free host population. In this framework a host individual is effectively 'born' when it separates from its parent. For simplicity, juvenile mortality (independent of that of its parent) is not assumed to occur (it can be included by assigning a certain rate to the event $Ss \rightarrow S$).

If complex dynamics is sufficiently fast, we can assume that parent-offspring complexes are in pseudo-equilibrium: that is, even if $[S]$ changes, $[Ss]/dt$ will be close to zero, or

$$\widetilde{[Ss]} = \frac{b}{\mu+\delta}[S] \tag{2}$$

Substituting this value in the differential equation for $d[S]/dt$ then yields

$$\frac{d[S]}{dt} = (\tilde{b}-\mu)[S] \tag{3}$$

where $\tilde{b} = b\delta/(\mu+\delta)$ is the effective birth rate. This is, of course, the most fundamental equation for population growth. Note that if none of the vital rates is density dependent, the disease-free population would either go extinct or grow to infinity. To prevent this, I will assume that the birth rate b is linearly density dependent

$$b = b_m(1-\kappa N) \tag{4}$$

where N is the density of hosts competing for resources. Here a number of arbitrary assumptions can be made. One could, for example, assume that all hosts in the population compete for resources, in which case one would take $N = [S] + 2[Ss]$. For simplicity, I will assume, however, that juveniles still associated to their parent do not compete for resources, that is $N = [S] + [Ss]$. From Equations (2–4) we can easily calculate the carrying capacity of the host in absence of parasites.

Table 2
Events governing the dynamics of parasite strain X, where X is either I or J (respectively i or j). Dissociation events are not listed, but are defined in the same way as in Table 1.

Event[a]	Per-capita rate	Description
$X \to Xs$	$(1-\varepsilon_X)b$	birth
$X \to \dagger$	$\mu+\alpha_X$	death
$X\bullet \to \dagger$	$\mu+\alpha_X$	"
$S \to X$	h_X	horizontal transmission to free host
$S\bullet \to X\bullet$	h_X	horizontal transmission to parent
$\bullet s \to \bullet x$	σh_X	horizontal infection to offspring
$Xs \to Xx$	ν_X	vertical transmission

[a] Bullets ($\bullet$) denote a host in any state (S, I or J respectively. s, i, j).

2.2. The resident strain of parasites

Essentially all the assumptions pertaining to the biology of the parasites are summarized in Table 2. The differential equations are nothing more than a bookkeeping of the changes in densities of the different classes of hosts caused by these events. The resident system results when one works out the bookkeeping only for strain I, evolutionary analysis requires two parasite strains to be modeled, the resident I and a mutant J. I will discuss the resident system first.

If the force of infection is h_I, free hosts become infected with probability per unit time h_I. However, also the juveniles in a complex can be infected (with probability per unit time σh_I, where $\sigma < 1$ represents the fact that such hosts may be more difficult to infect). In addition an infected parent in a parent-offspring complex can pass on the infection to its offspring with probability per unit time ν_I (vertical transmission). Infected hosts may reproduce, with a rate $1-\varepsilon_I$ relative to healthy hosts; ε_I thus measures disease-induced sterility.

I will assume that infected offspring do not contribute to the force of infection,

$$h_I = \beta_I([I]+[Is]+[Ii]). \tag{5}$$

This is an assumption merely to simplify the model; in the version that is derived in the Appendix any infected host (be it parent or offspring) can infect any susceptible with specific transmission efficiencies. Note that in the present model, vertical transmission does not go "the wrong way", *i.e.*, an offspring infected by an external source cannot infect its parent. In the more general formulation this sequence of events would occur.

2.3. Introducing a mutant strain of parasites

To understand evolution of the parasites, we need to know under what conditions a mutant strain of parasites can invade a resident host-parasite system. Therefore we need to introduce a second strain in the model. Such a mutant is governed by the same set of events (Table 2), the extra now being that also mixed-infection (Ji and Ij) parent-offspring complexes may be produced (see Figure 2).

The mutant may be different in the following ways: it may reduce its host's reproduction to a different degree ($\varepsilon_J \neq \varepsilon_I$), it may have different transmission parameters ($\beta_J \neq \beta_I$ and/or $\nu_J \neq \nu_I$) and it may induce a different mortality rate ($\alpha_J \neq \alpha_I$). Later on I will consider possible trade-offs among these parameters.

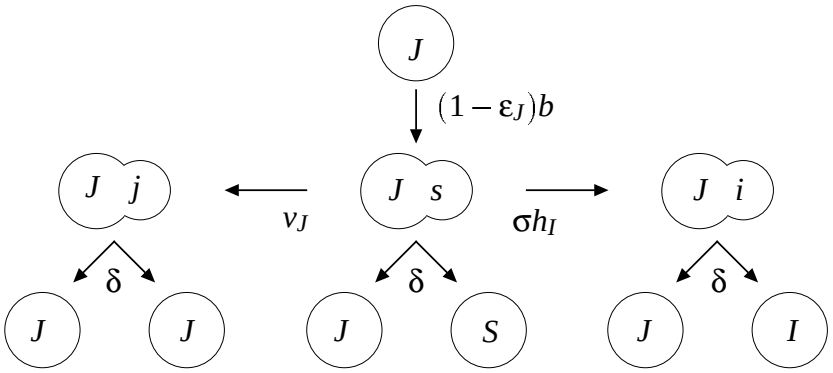

Figure 2. The events affecting vertical transmission of a mutant parasite J in the presence of resident strain I. There is birth (with rate $(1-\varepsilon_J)b$), vertical infection (ν_J), horizontal transmission (h_I, σh_J) and dissociation (δ). I represents the resident strain of parasites. Notice that if J is rare (h_J is vanishingly small) Jj complexes only arise through vertical transmission.

These new states and their transitions mean that the original equations acquire new terms, and that four more differential equations are necessary to keep track of the mutant parasite. I will not give the full model, however, as I am primarily interested in the invasion conditions for a rare mutant strain.

Even though the assumptions that underlie the model are fairly simple, the resulting dynamical model (presented in the Appendix) is rather complex. The resident host-parasite system is given by six differential equations (for $[S]$, $[Ss]$, $[I]$, $[Is]$, $[Ii]$, and $[Si]$) while analysis of the mutants dynamics requires to consider six others in addition. To discuss the evolutionary aspects, I will consider a more simple version of the model that allows the parasites R_0 to be calculated easily.

2.4. Simplified model

Much insight can be gained if one makes the not unreasonable assumption that the rates of vertical infection and of dissociation are so large that we can ignore mortality in parent-offspring complexes. Then, all parent-offspring complexes can be considered to be in pseudo-equilibrium, and the dynamical variables reduce to those for S, I and J-type hosts. To avoid cluttering the expressions with symbols, I will drop the awkward notation based on the subscripts I and J. In the rest of the chapter, an asterisk will refer to the resident (I) whereas a plain symbol refers to the mutant's (J) traits.

For the given additional assumption, the resident system simplifies to

$$\begin{aligned}\frac{d[S]}{dt} &= \frac{\delta}{\delta+\sigma h^*}b[S] + \frac{\delta}{\delta+\nu^*+\sigma h^*}(1-\varepsilon^*)b[I] - (\mu+h^*)[S]\\ \frac{d[I]}{dt} &= h^*[S] + \frac{\sigma h^*}{\delta+\sigma h^*}b[S] + \frac{\nu^*+\sigma h^*}{\delta+\nu^*+\sigma h^*}(1-\varepsilon^*)b[I] - (\mu+\alpha)[I],\end{aligned} \tag{6}$$

where $h^* = \beta^*[I]$. Under the simplifying set of assumptions, offspring are released immediately. However, only a fraction $\delta/(\delta+\sigma h^*)$ of susceptible host's offspring remain uninfected, the remainder is infected (horizontally) before dissociating. For infected hosts, the fraction infected

offspring is $(v^* + \sigma h^*)/(\delta + v^* + \sigma h^*)$. Note this contains both the contributions of vertical and horizontal transmission. For the resident parasite, we cannot distinguish between vertical and horizontal transmission.

For a rare mutant strain we can assess the importance of vertical transmission. Since being rare, its force of infection is negligible. If its host produces offspring infected with the mutant, then we can be virtually sure that it is the result of vertical transmission. Would this host produce offspring infected with the resident, we can be sure that it is a consequence of horizontal infection. The differential equation for the mutant's dynamics, which contains these terms, can be derived in a similar way. Here, however, I will pass directly to a derivation of the mutant's R_0.

3. THE MUTANT PARASITE'S REPRODUCTION RATIO

Evolution proceeds through the creation (through mutation of existing strains) and disappearance of strains of parasites. We therefore need to know what allows strains to invade a given system, and which strains will be ousted. In principle, this can be assessed from the system of differential equations (given in the Appendix) that describes a mutant's dynamics. However, this is mathematically rather cumbersome, as it requires manipulation of 6×6 matrices even in the simplest case. Here, I will limit the analysis to the simplified model.

In principle, one can derive the invasion condition for a mutant strain of parasites from the dynamical equations for the simplified model, but it is more insightful to derive a mutant parasite's invasion conditions from consideration of what happens to a host infected with a rare mutant J in a system dominated by a strategy I. The reproduction ratio of the mutant is then the number of secondary cases it will produce. If this number is larger than one, the mutant will have a net positive growth rate and barring special conditions that govern branching points (see Geritz et al. 1997), it will replace the resident population. This process of invasion and establishment will continue until an evolutionary endpoint is reached, where no mutant has a reproduction ratio larger than one.

An adult host infected with a rare mutant parasite J lives on average $(\mu + \alpha)^{-1}$ time units. During this time it can infect four types of hosts: its own offspring (vertical transmission) and three types of hosts through horizontal infection: susceptible adults, the offspring of susceptibles, and the offspring of hosts infected with the resident parasite.

Consider the possibilities for vertical transmission first. The mutant's host will produce offspring with rate $(1-\varepsilon)b$. To these offspring, three things can happen: they can dissociate before being infected (with rate δ), they can become infected vertically with the mutant (with rate v) and they can become infected with the resident (with rate $\sigma\overline{h^*}$). Therefore the host produces offspring infected with the mutant with a rate

$$\frac{v(1-\varepsilon)b}{\delta + v + \sigma\overline{h^*}}.$$

At the same time, the host may infect other hosts horizontally. First of all, it may infect susceptible adult hosts. This occurs with rate $\beta[S]$. However, it may also infect the offspring that these uninfected hosts produce. Such offspring are produced with rate $\beta[S]b$ and every one is 'available' for infection (with relative efficiency σ) by the mutant for a period of $1/(\delta + \sigma\overline{h^*})$. The terms representing infection of susceptible hosts can be taken together, as

$$\beta[S]\left(1 + \sigma\frac{b}{\delta + \sigma\overline{h^*}}\right).$$

And finally, the mutant may infect the offspring of hosts infected with the resident parasite, before resident succeeds in achieving vertical transmission. The density of such hosts is $\overline{[I]}$, they produce offspring with a rate of $(1-\varepsilon^*)b$ that are available for infection by the mutant (with efficiency σ) for a period of on average $1/(\delta+\nu^*+\sigma\overline{h^*})$. The rate of infection through this route is therefore

$$\sigma\frac{\beta[I](1-\varepsilon^*)b}{\delta+\nu^*+\sigma\overline{h^*}}.$$

These elements can be taken together to calculate the total number of adult hosts infected by the parasite, either directly, or through the infection of offspring. The basic reproduction ratio of mutant parasite J in a population dominated by resident parasite J is

$$R_0(J|I)=\frac{\beta[S]\left(1+\sigma\frac{b}{\delta+\sigma\overline{h^*}}\right)+\frac{\nu(1-\varepsilon)b}{\delta+\nu+\sigma h^*}+\sigma\frac{\beta[I](1-\varepsilon^*)b}{\delta+\nu^*+\sigma h^*}}{\mu+\alpha} \tag{7}$$

In this expression, the first term in the numerator is equivalent to the 'standard' terms of infection of susceptibles that is found in any expression of R_0. The other terms reflect the competition for vertical transmission. The second represents successful vertical transmission of the mutant in the face of competition with the resident. Note that this depends negatively on the resident's force of infection. The third term represent the successful infection by the mutant of the resident's offspring.

These latter two terms are the crux of the phenomenon. If the resident parasite I is rare, then only the vertical transmission term remains,

$$\lim_{h^*\to 0}R_0(J|I)=\frac{\beta[S]\left(1+\sigma\frac{b}{\delta}\right)+\frac{\nu}{\delta+\nu}(1-\varepsilon)b}{\mu+\alpha}. \tag{8}$$

Note that this is the setting for the 'classical' R_0 concept: invasion of parasites in a parasite-free host population. As becomes clear by comparing the classical R_0 with the full expression (Equation (7)), all aspects of competition among parasite strains have disappeared. In particular, the contribution of vertical transmission is maximal. Would this expression be used for an evolutionary analysis, erroneous predictions may result, as the benefits of vertical transmission are overestimated.

In contrast, if the resident is abundant, the option for vertical transmission of the mutant becomes insignificant as the resident will have infected its host's offspring before the mutant had a chance, and

$$\lim_{h^*\to\infty}R_0(J|I)=\frac{\beta[S]+\frac{\beta}{\beta^*}(1-\varepsilon^*)b}{\mu+\alpha} \tag{9}$$

Note that in this case, the term representing horizontal infection of its competitor's offspring does not disappear. The offspring of every host infected with the resident will become infected very quickly (with a rate proportional to $h^*=\beta^*[I]$), but at the same time, there will be very many of them ($[I]$, in fact) and these effects cancel out when $[I]$ becomes large. This means

that when there are many resident parasites, the potential for horizontal transmission is actually enhanced: it becomes profitable to try to infect the offspring of hosts infected with the resident type.

Thus, optimal transmission strategies not only depend on the relative availability of susceptible hosts, but also on the intensity of competition between the parasites. Vertical transmission will be selected against in parasite-ridden host populations, whereas it may be favoured in disease-free populations.

4. CONSTRAINTS

From the expression for mutant's reproduction ratio it is obvious that it will invade if, for example, its transmission efficiency β is large enough. It stands to reason, however, that increasing transmissivity will be associated with an increase in the negative consequences experienced by the host. Usually it is assumed that an increase in infectivity will be associated with an increase in the disease-induced mortality rate. However, this is but one of the possible relationships. Normally the disease-induced mortality rate α is equated to the parasite's 'virulence' but one should be aware that parasites can depress host fitness also in other ways (Hochberg 1998). To a host, there is not really a difference between a parasite that kills and a parasite that castrates; both reduce the host's fitness to zero, both are equally 'virulent' from the host's perspective.

Suppose that the parent-to-offspring transmission rate (v) is fixed, and that parasite virulence is characterized by two traits. Both affect (horizontal) infectivity but one is associated with the host's survival, and the other with the host's reproduction. The specific assumption I will make is that a strain's infectivity β, its disease-induced mortality rate α and disease-induced sterility (ε) are linked in the following way

$$\beta(\alpha,\varepsilon) = \frac{A\alpha}{B+\alpha} + \gamma\varepsilon b \tag{10}$$

(where $a \geq 0$, $0 \leq \varepsilon \leq 1$). Thus, infectivity is assumed to be the sum of two components, one that increases the host's mortality, and another that converts the host's reproductive output into parasite infective stages (with conversion parameter γ). The first component can always be increased, but at a fast increasing cost in terms of disease-induced mortality (van Baalen and Sabelis 1995). The second component obviously cannot increase when the host is completely castrated.

Insight into the balance between horizontal and vertical is gained if the expression for R_0 is rearranged such that the effects of the two transmission routes are grouped together,

$$R_0(J|I) = \frac{\beta(\alpha,\varepsilon)\overline{[H]} + \dfrac{v}{\delta+v+\sigma\overline{h^*}}(1-\varepsilon)b}{\mu+\alpha} \tag{11}$$

where

$$\overline{[H]} = \overline{[S]}\left(1+\sigma\frac{\bar{b}}{\delta+\sigma\overline{h^*}}\right) + \overline{[I]}\frac{\sigma(1-\varepsilon^*)\bar{b}}{\delta+v^*+\sigma\overline{h^*}} \tag{12}$$

is the effective density of hosts susceptible to horizontal infection, which is determined in various ways by the resident (*i.e.*, by its virulence, level of horizontal infection and disease-induced

sterility) but cannot be changed by the mutant. Similarly, to the mutant the net efficiency of vertical transmission is a given constant. It does depend on the resident's force of infection, but the mutant cannot affect this. (It is, of course, possible to envisage scenarios where the parasite *can* affect parameters such as v but for the moment I'll assume that this efficiency is independent of horizontal transmission efficiency).

5. NON-KILLING PARASITES

To begin with, let us consider the evolution of a parasite that cannot kill but only castrate. That is, the parasite's ability of infect horizontally depends entirely on its conversion of the host's reproductive output:

$$\beta(\varepsilon) = \gamma\varepsilon b \tag{13}$$

In absence of vertical transmission, such a parasite should of course attempt to convert all of its host's reproductive output into its own horizontal transmission. If, however, the efficiency of infection of offspring is much enhanced, compared to the efficiency of infecting other hosts, it may pay the parasite to reduce its virulence, utilize the vertical transmission route next to horizontal transmission. From the expression for a mutant's R_0 we know that it depends linearly on ε, and a decrease in virulence is favoured if

$$\gamma\overline{[H]} < \frac{v}{\delta + v + \overline{\overline{h^*}}}$$

Thus, in general, it pays to decrease virulence only if the density of susceptibles decreases below a certain threshold. This threshold itself depends on the force of infection of the resident. If the resident is common, this threshold goes up; vertical transmission becomes less profitable.

Both the density of susceptibles and the force of infection of the resident depend on population dynamics, which, in turn, depends on the virulence of the resident strain. As can be seen in Figure 3, these quantities depend quite sensitively on the resident's virulence. If its virulence is close to zero, the resident parasite strain can hardly maintain itself and the force of infection will be low. With increasing virulence the force of infection rises, up to the point where the resident becomes too virulent and it will disappear again (Figure 3A). Note that the force of infection depends on the parasite-induced regulation of the host population; avirulent parasites do not control the host population at low densities, virulent parasites severely reduce the host population (Figure 3B; recall that the total number of hosts available for horizontal infection includes offspring still in association with their parent). From a population point of view, intermediate virulence is thus 'optimal'. At this optimum, the proportion of offspring born to infected parents that is infected is very high. However, as can be seen in Figure 3C, the proportion of 'true' vertical transmission (*i.e.*, infection by its own parent) is then at a minimum. (This can be assessed by evaluating the R_0 of a mutant that is identical to the resident.) For this set of parameters, more than half of the apparent vertical transmission is effectively the result of horizontal transmission. Such competition for the host's offspring reduces the profitability of vertical transmission and hence the advantage of reducing virulence. From this we may already expect the population optimum not to be evolutionarily stable. Indeed, the selection pressure on virulence is positive at the population optimum (Figure 3). The ESS level of virulence is approximately 50% castration for the combination of parameters used to draw these plots.

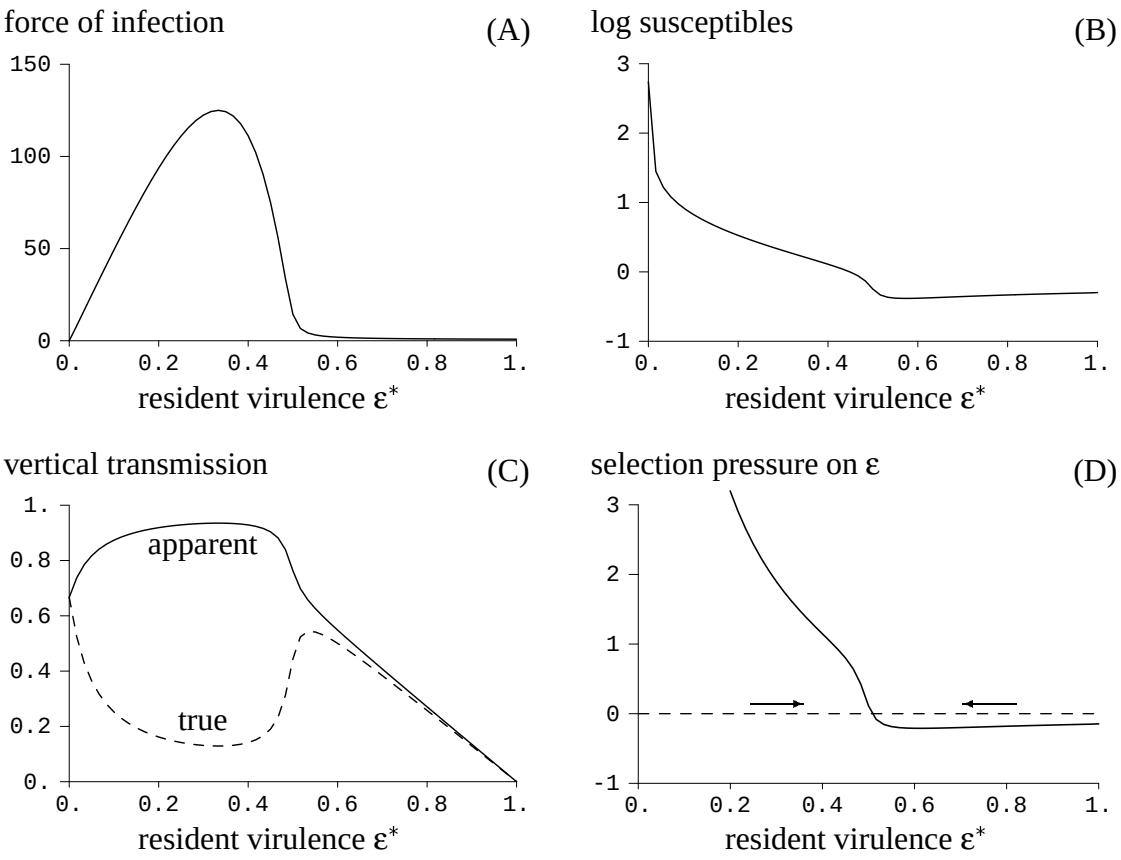

Figure 3. The endemic equilibrium of a non-killing parasite as a function of parasite-induced sterility (virulence). (A) The force of infection of the resident parasite, (B) the logarithm of the total density of hosts susceptible to horizontal infection, (C) the rate of apparent vertical transmission (infected offspring born to infected adults, drawn line) and the proportion of 'true' vertical transmission (dashed), and (D) the intensity of selection pressure on virulence. (Parameters: $b_m = 1.5$, $\mu = 1$, $\kappa = 0.001$, $\delta = 10$, $v^* = 20$, $\sigma = 1$, $\alpha^* = 0$, $\gamma = 1$.)

Intermediate virulence requires that selection pressure on virulence is zero. Condition (5) shows that the evolutionary equilibrium will be characterized by a balance between the payoffs of horizontal and vertical transmission. Changes in parameter values are likely to change both simultaneously, and such that the new ESS be either higher or lower virulence. For example, for low reproduction rates, horizontal transmission is the ESS (the density of susceptible actually goes *up* when birth rate decreases, it is the density of infecteds that drops), beyond a certain mixture of horizontal and vertical transmission, where virulence first decreases and than rises again (Figure 4A). The rise in virulence at high productivity profits the parasites as well and competition for the hosts' offspring becomes more intense (Figure 4B).

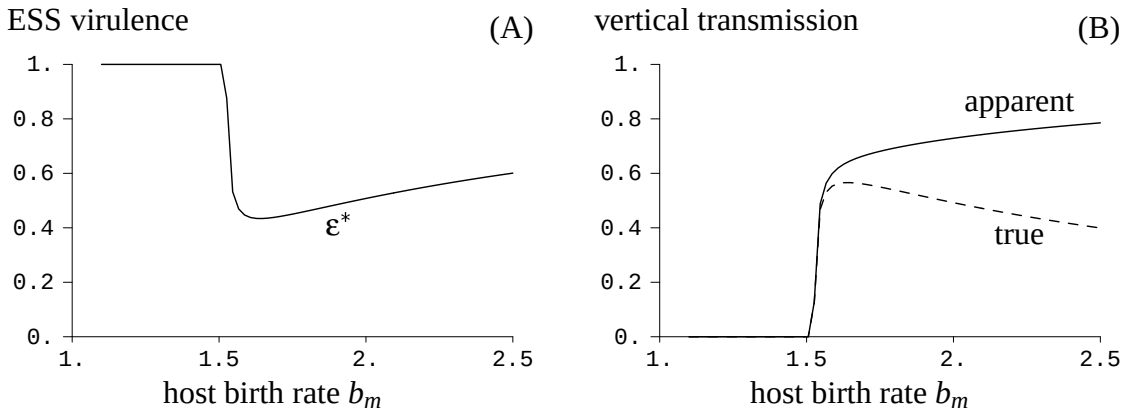

Figure 4. The ESS level of virulence of non-killing parasites as a function of the productivity of the environment measured in maximum rate of reproduction of the host. (A) ESS level of castration, and (B) the proportion of infected offspring born to infected adults (drawn line) and the proportion of 'true' vertical transmission (dashed). (Parameters as in Figure 3.)

6. KILL OR CASTRATE?

As discussed before, parasites may have multiple ways to exploit their hosts, and hence multiple virulence components. The question is how such virulence evolves when it is expressed in different ways. Consider the 'classical' virulence concept of disease-induced mortality. The idea is that if there is vertical transmission, parasites are selected to be more careful with their hosts. Indeed, if we allow α to evolve, the model predicts that if the castration rate ε^* is fixed and set equal to zero (no castration virulence), disease-induced mortality will decrease if the parent-to-offspring transmission rate increases (Figure 5A). However, if castration virulence evolves alongside with disease-induced mortality, there is no longer such an effect (Figure 5B). For low transmission efficiencies, the parasites convert all of their hosts' reproductive output for horizontal transmission. Since vertical transmission does not occur when $\varepsilon^* = 1$, there cannot be an effect of v^* on killing virulence α. However, the surprising result is that when parasites start to exploit the vertical transmission route (at higher transmission efficiencies), disease-induced mortality stays constant. Changes in v^* affect the level of castration virulence only.

The ESS potentially depends on many parameters. For example, the above results are based on the assumption that there is weak density-dependent host population growth (so that the host population is regulated strongly by the parasites). Figure 6A shows that if competition for resources (embodied in the parameter κ) becomes sufficiently intense, the ESS may shift from partial to complete castration. Note that also in this case disease-induced mortality is less affected than is the level of castration. That is, changes in environmental parameters are likely to provoke an evolutionary response castration virulence rather than killing virulence.

In other cases, the effects of environmental parameters may defy easy explanations. For example, if the background mortality rate increases from a very low value to a high value, the overall effect is increased virulence. This is not surprising as high mortality rates counter the parasites' ability to 'manage' their hosts. However, the specific pattern is rather surprising: the parasite ESS is first to kill but not castrate, then to castrate and kill, then to castrate partially

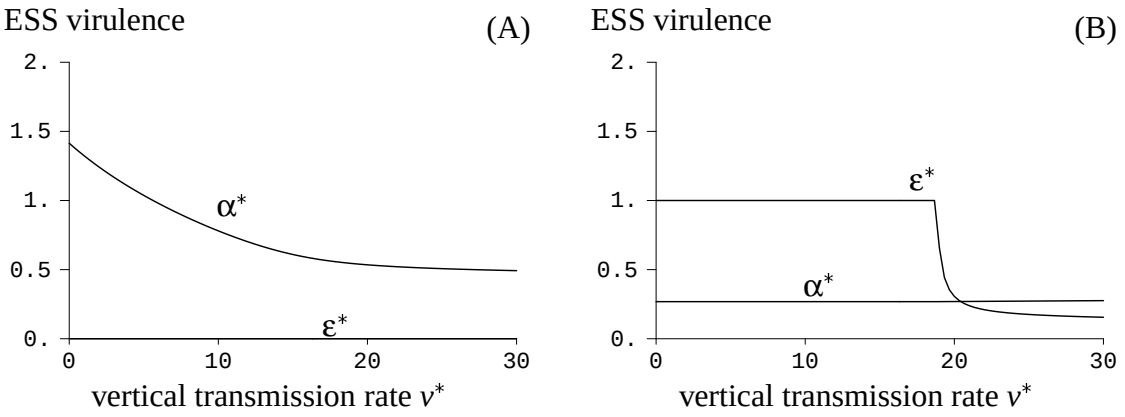

Figure 5. ESS disease-induced mortality rate α^* as a function of the parent-to-offspring transmission rate v^*, (A) when parasites cannot castrate their hosts (ε^* fixed at zero), and (B) when castration virulence ε coevolves with α. (Parameters: $b_m = 1.5, \kappa = 0.001, \mu = 1, \sigma = 1, A = 4, B = 2, \gamma = 1$.)

but not kill, then again to castrate and kill, to, eventually, to fully castrate and kill (Figure 6B). The general pattern is thus an increase in 'virulence' as one might expect. If background host mortality increases it pays less to be benign to the host, be it in terms of its survival or of its reproduction. But just why this increase in overall virulence is expressed such that the dominant aspect varies so much is not easy to state. It depends both on the large-scale process of host population dynamics, as well as on the small scale interaction among parasites (competition for transmission).

7. DISCUSSION

If there is competition among parasites to infect the offspring of their hosts, there will be a feedback loop that may prevent the evolution of 'pure' vertical transmission. Unless parasites can truly monopolize their hosts, there will be a considerable payoff for mutant parasites that invest in horizontal transmission when vertical transmission is common. Whether competition occurs at the pseudo-infection stage, as envisaged in this article, or whether it arises through multiple infection, vertical transmission is not a guaranteed mode of reproduction.

Parasites that opt for vertical transmission should allow their hosts to reproduce instead of killing and/or castrating it. As a consequence, parasitism will less intensely regulate the host population, and host density would go up. The force of infection would go up even more, as the proportion infected hosts will increase as well. The result of this, however, is that competition among the parasites will become more intense. First of all, because there will be few susceptible hosts in the population, secondly it will favour mutants that have a competitive advantage in multiply infected hosts, parasites that can 'steal' hosts from other parasites. Such intensified competition will therefore favour parasites that shift to horizontal transmission.

Exactly how the parasites achieve horizontal infectivity (whether it be by exploiting their host's reproductive output or by killing it) depends on costs and benefits as well as on global dynamics of the host-parasite system (whether there are density-dependent factors apart from

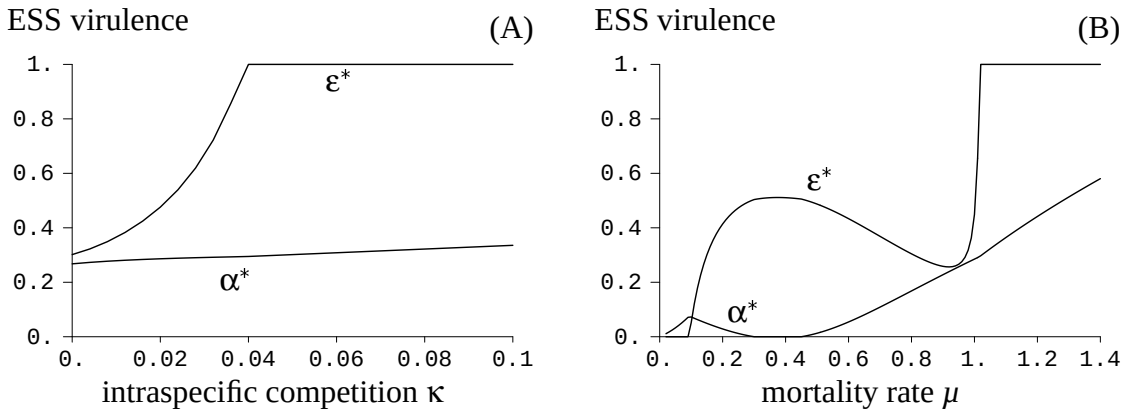

Figure 6. ESS virulence as a function of the intensity of intraspecific competition in the host population (A) and of the background mortality rate of the host (B). Parameters as in Figure 5.

parasitism that regulate the host population and so on). With respect to castration, all outcomes from complete castration to no effect at all are possible. Interestingly, other things may happen too: parasites may stop killing their hosts. Then, they achieve their transmissivity solely by converting part of their host's reproductive effort into parasite propagules (see for example Figure 6B). This shows once more that 'virulence' is not just the same as host mortality.

Parasite evolution may be a mechanism that helps regulate host densities. Under unfavourable conditions, host densities will be low and consequently competition among the parasites will not be very intense. They will still be rather virulent but they do not need invest in competitive ability with other parasites, which benefits their hosts as well. When the hosts' conditions become more favourable, however, the parasites increase as well, and intensified among-strain competition will favour even more virulent strains.

The model predicts that under certain conditions, parasites will reduce their classical virulence to nil. However, as long as there are options for horizontal transmission, they will be selected to make use of it.

7.1. Trade-offs

In the models presented here, I have assumed that the vertical transmission efficiency (v) is a fixed constant. In reality, however, it will depend on the parasite's host-exploitation strategies. Usually it is assumed that there is a negative trade-off between horizontal and vertical transmission (see, *e.g.* Lipsitch et al. 1995b, Turner et al. 1998). If anything, in the present framework, one would expect a *positive* functional relationship between the two: the mother needs to be infective just as for horizontal infection. Numerical analysis of a variant of the model which has a functional link between infectivity and vertical transmission efficiency (v proportional to β), gave results (not shown) essentially similar to the results already presented.

One could envisage, however, that vertical transmission requires special adaptations. In that case, there would be a negative trade-off between the two kinds of infectivity. This case still needs to be analysed in more detail.

7.2. Evidence

Presently, there does not seem to be many data that allow assessment of the importance of competition for vertical transmission. The problem is that it does not suffice just to record what proportion of offspring is infected: in principle, such an infection might be caused by an external source. Some insight into the importance of horizontal component would be gained if it were known how many infected offspring *uninfected* mothers produce. Where this proves substantial, we'll have to assume that the offspring of infected mothers will be subject to a similar external force of infection. Yet this would still not give us insight into all components of competition among the parasites. In particular, we have to assess the frequency of multiple infection as this also leads to within-host competition for transmission. The acid test, therefore, would be to genetically type the parasites and assess the differences in composition of the parasite populations infecting parent and offspring. This would require sufficient (neutral) genetic variation among the parasites. One dataset exists for four number cases of mother-to-child infection of HIV. In three out of four cases only a subset of the strain diversity infecting the mother was found in the child, but no evidence for differences between strains were observed. Of course, four cases is too small a sample to warrant any conclusions with respect to bias (Pasquier et al. 1998).

Perhaps an interesting system to study in this respect is human commensalistic bacteria like *Neisseria* infections (Maiden 1993). These bacteria are carried by virtually everybody, most of which are nonsymptomatic. Not much is known about their transmission but one may suppose that pseudo-vertical transmission is an important component but by no means the only route. The interesting aspect of this system is that there is evidence of genetic recombination in some of these bacteria. This not only indicates that multiple infections do occur, but would also facilitate mother-offspring comparisons.

A more experimental approach could be based on bacteria-phage systems. By manipulating the relative frequeny of vertical transmission relative to horizontal transmission episodes, Messenger et al. (1999) were able to show that vertical transmission favours decreased virulence, as predicted. The phage that they studied (phage f1 infecting *Escherichia coli*) apparently can block superinfection, so that it can draw the full benefit of vertical transmission. It would be interesting to repeat the experiment with another phage that cannot do so, varying the force of (horizontal) infection.

An example of a system where pseudo-vertical transmission might be important is that of anther smut fungus *Microbotryum violaceum* infecting plants of the family Caryophyllaceae (Thrall et al. 1993). This fungus, transmitted by pollinators, first infects the plant systemically and then sporulates in its anthers to obtain transmission. This directly blocks the male function but also usually prevents female function. In most species all flowers are affected, but in some species for some combinations of fungal strains and host plants only a proportion of the plant's flowers show the symptoms of infection. Further, some infected plants have functional stigmas and ovaries, producing some seed. Since there is no evidence of 'true' vertical transmission in these species (Jacqui Shykoff, personal communication) pseudo-vertical transmission could provide the explanation for the observed partial sterilization. Indeed, the plant's seeds do not travel well and pollinators could be efficient in transmitting the fungus from the mother to the nearby offspring. Thus, a focus of infection could spread (at least in part) via the expansion of its host. This mechanism would be favoured if there is little (local) competition for transmission in this system. At present, however, the intensity of competition for transmission is unknown

and difficult to assess. Analysis of such 'viscous systems' (systems characterized by local interactions and limited mobility, see van Baalen and Rand 1998) would nevertheless be an interesting case to study.

An important aspect determining the intensity of competition among parasites is the force of infection, the risk of becoming infected per unit time. The analysis predicts an evolutionary difference between parasites that are common (endemic) and parasites that are rare. For the latter type of parasites, infection of offspring through external sources can be safely ignored and the standard ideas of vertical transmission apply. However, for parasites that are common, we *do* have to take into account competition for vertical transmission, either through competition for infection as envisaged here or through multiple infection. It is precisely the latter type of parasites that is interesting from the point of view of the evolution of mutualistic relationships which I will discuss below.

7.3. Vertical transmission and mutualism

It has long been thought that parasites will inevitably evolve to become less virulent and end up as commensals or even mutualists. However, this 'conventional wisdom' has been shown to be fallacious by Anderson and May (1982). Parasites have their own evolutionary interests, and in general they will evolve towards a definite level of virulence that balances the cost and benefits of virulence. Complete avirulence is therefore not expected, let alone mutualism; parasites remain parasites. Thus, the theory of the evolution of virulence does not support the idea that mutualism evolves out of parasitism. To resolve this conflict, it has been proposed that vertical transmission of parasites (from parent to offspring) is the determining factor. Indeed, it is then not only in the interest of the parasites that their host lives longer but also that it reproduces. Would the parasites transmit themselves *exclusively* vertically and to all of its host's offspring, there would no longer be a conflict of interests — and host-parasite complexes would have become a unit of selection (see, *e.g.*, Yamamura 1993, Yamamura 1996, Law and Dieckmann 1998, Hochberg 2000).

Such transitions would explain the origin of mitochondria and other intracellular organelles (Margulis 1970, Maynard Smith and Szathmáry 1995), and could explain how symbiotic partnerships such as lichens are formed (Law and Dieckmann 1998). The emergence of vertical transmission is thought to be a crucial aspect of such transitions (but see Genkai-Kato and Yamamura 1999). Because parasites cannot monopolize their hosts, an among-parasite conflict of interests may ensue, to the detriment of the host harbouring these parasites. Vertical transmission might actually intensify the among-parasite conflict, as it will in general increase the density of infecteds.

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APPENDIX: THE FULL MODEL

The statistical mechanics framework is essentially a sophisticated way of doing a bookkeeping, based on a set of states that individuals may be in, and the allowed transitions between these states (which are associated with a certain rate, or probability per unit time).

As discussed in the text, in absence of parasites, the hosts can be in two states and hence the model is characterized by two dynamic variables, adult hosts $[S]$ and host parent-offspring complexes $[Ss]$, whose dynamics are governed by equations (1). Introducing the resident parasites adds 4 variables to track, $[I]$, $[Is]$, $[Si]$ and $[Ii]$. Doing the bookkeeping for the events involving the resident parasite (given in Table 2) leads to the following differential equations (the notation '+=' implies that the right hand side should be added to the previous definition of the differential equations)

$$\begin{aligned}
\frac{d[S]}{dt} &+= -[S]h_I + \delta([Si]+[Is]) \\
\frac{d[Ss]}{dt} &+= -(h_I+\sigma h_I)[Ss] \\
\frac{d[I]}{dt} &= -(1-\varepsilon_I)b[I] + [S]h_I + \delta([Si]+[Is]+2[II]) \\
\frac{d[Is]}{dt} &= (1-\varepsilon_I)b[I] + h_I[Ss] - (v_I+\sigma h_I)[Is] - (\mu+\alpha_I+\delta)[Is] \\
\frac{d[Si]}{dt} &= \sigma h_I[Ss] - (\mu+\delta)[Si] \\
\frac{d[Ii]}{dt} &= h_I[Si] + \sigma h_I[Is] - (\mu+\alpha_I+\delta)[Ii].
\end{aligned} \tag{14}$$

As can be seen, the structure of the differential equations is straightforward, but their number rises fast when the number of states a host can be in increases. One could include in this model

uncorrelated deaths in parent offspring complexes (for example, juvenile mortality, represented by the event $Ss \to S$), 'backward vertical infection' ($Si \to Ii$), and so on.

The simplified model results from a time-scale separation, assuming that the rates affecting offspring in parent-offspring complexes are much higher than mortality.

The dynamics of the mutant is governed by the following additional 6 equations, derived in a similar fashion:

$$\begin{aligned}
\frac{d[J]}{dt} &= -(1-\varepsilon_J)b[J] + h_J\overline{[S]} - (\mu+\alpha_J)[J] + \delta([Js] + 2[Jj] + [Ji] + [Ij]) \\
\frac{d[Js]}{dt} &= (1-\varepsilon_J)b[J] + h_J\overline{[Ss]} - (\mu+\alpha_J+\nu_J+\sigma(\overline{h_I}+h_J)-\delta)[Js] \\
\frac{d[Jj]}{dt} &= (\nu_J+\sigma h_J)[Js] - (\mu+\alpha_J+\delta)[Jj] \\
\frac{d[Ji]}{dt} &= h_J\overline{[Si]} + \sigma\overline{h_I}[Js] - (\mu+\alpha_J+\delta)[Ji] \\
\frac{d[Sj]}{dt} &= \sigma h_J\overline{[Ss]} - (\mu+h_I+\delta)[Sj] \\
\frac{d[Ij]}{dt} &= \overline{h_I}[Sj] + \sigma h_J[Is] - (\mu+\alpha_I+\delta)[Ij]
\end{aligned} \tag{15}$$

where $h_J = \beta_J([J]+[Js]+[Jj]+[Ji])$ is the force of infection of the mutant. Under the simplifying assumption of fast offspring dynamics, mutant dynamics collapses into a single differential equation, justifying the derivation of the reproduction ratio as carried out in the text. If, however, mortality rates are of the same order as the other rates, then the invasion analysis becomes more complex. See van Baalen and Rand (1998) for a treatment of an invasion analyses for such cases.