Pathogen competition and coexistence and the evolution of virulence

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Summary. Competition between different strains of a micro-parasite which provide complete cross-protection and cross-immunity against each other selects for maximal basic replacement ratio if, in the absence of the disease, the host population is exclusively limited in its growth by a nonlinear population birth rate. For mass action incidence, the principle of $\mathcal{R}_0$ maximization can be extended to exponentially growing populations, if the exponential growth rate is small enough that the disease can limit population growth. For standard incidence, though not in full extent, it can be extended to populations which, without the disease, either grow exponentially or are growth-limited by a nonlinear population death rate, provided that disease prevalence is low and there is no immunity to the disease. If disease prevalence is high, strain competition rather selects for low disease fatality. A strain which would go extinct on its own can coexist with a more virulent strain by protecting from it, if it has strong vertical transmission.

1.1 Introduction

With their rapid turn-over, parasitic populations are ideal objects to study the pattern and processes of evolution (evolution of virulence, co-evolution of hosts and parasites) [3, 25, 58, 60, 59, 61, 13]. In turn, it is important to understand these principles in order to control infectious diseases without creating resistant parasites or drive them towards increased virulence (virulence management) [63, 37, 82, 33]. Mathematical modeling and model analysis are very much needed for deeper understanding and as a theoretical laboratory to devise control and management strategies. Evolution in host-pathogen systems in general and evolution of virulence in particular have been extensively researched in the last 20 or 25 years. An excellent compilation has appeared not too long ago [33], with 50 pages of references and an index of 17 pages. Many theoretical studies on the evolution of virulence start from the assumption that, in the absence of multiple infections and the presence of complete

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cross-immunity, only the parasite strain persists that has the maximal basic replacement ratio ([4, Sec. 23.3] [3, 33, 29, 30] and the references therein). (In this paper I prefer *replacement ratio* over *reproduction number* because we reserve the second for the host population which has its own dynamics with births and deaths). This assumption (also called $\mathcal{R}_0$ maximization) has been found to be valid under quite a few restrictions: the density-dependent regulation of the host occurs through the birth rate, and the infection is horizontally transmitted and does not lower the fertility [11, 23, 21]. The general validity of such a principle has recently been challenged on theoretical grounds [32, 72], because the basic replacement ratio only describes the performance of a strain in an almost infection-free host population but not its capacity of invading a host population already infected with other strains. Indeed, in spite of complete cross-protection and complete cross-immunity, coexistence of several strains in one host population has been found in the following scenarios:

- ◇ The infection occurs both vertically and horizontally [69]. Simulations show that strains with lower virulence can outcompete strains with higher basic replacement ratio.
- ◇ The density-dependent regulation of the host occurs through the death rate rather than the birth rate [6, 1, 2].
- ◇ There is no density-dependent regulation of the host at all such that the host would grow exponentially in the absence of the disease, and the incidence is of standard type [67].

Coexistence of different strains does not only violate the principle of $\mathcal{R}_0$ maximization (typically the coexisting strains will have different basic replacement ratios), but also the principle of competitive exclusion which would allow only one consumer (the parasite) to live on a single resource (the host) [56, 62, 71]. Coexistence of different strains is less surprising if the host population is structured in one way or another effectively creating several resources for the parasite as in the following scenarios:

- ◇ The disease is heterosexually transmitted with differential female susceptibility [22].
- ◇ The disease is homosexually transmitted between and within two host groups with different responses to the disease [65].

The picture becomes more complicated under super-infection and co-infection [64, 20, 43, 18, 33, 57, 77, 36, 83, 31, and references therein], under incomplete cross-immunity [5, 7, 47, 66, 74, 27], or under (frequent) mutation, recombination, or within-host evolution of the parasite [33, 70, 79, 83, 31, and references therein]. The competition between several strains is also influenced by host population structure in the form of partnerships, kinships, or other social structures [33, and references therein], by spatial structure in the form of nearest neighborhood infection or patchiness [51, 24], community structure [8], or, in macro-parasitic diseases, by the mode of parasite reproduction [76].

In this paper, we will extend the conditions under which strain competition will select the maximal basic replacement ratio, we will determine under which conditions something else (actually what?) may be maximized (in both cases with competitive exclusion of sub-optimal strains), and under which conditions different strains may coexist. For mathematical managability, we make the assumption that infection with one strain infers complete cross-protection against infection with other strains during the infection period and complete immunity and cross-immunity during the recovery period (if there is any).

1.2 Host populations with nonlinear birth rates and arbitrary incidence

We consider a host population the size of which, N , develops according to the differential equation $N' = B(N) - \mu N$ in the absence of the infectious disease. Here $B(N)$ is the population birth rate and μ the (constant) per capita mortality rate. This means that the population growth is only regulated by the nonlinear birth rate.

Enters the parasite which, through mutation, can occur in several, n , strains. Mutation is assumed so rare, that it is not included in the mathematical model which describes the competition of the strains in the host population without further mutations. The selection process is assumed to be essentially terminated (i.e. the model dynamics have settled at their large time behavior) when new mutations occur creating a new ensemble of competing strains to which the mathematical model again applies.

VARIABLES AND PARAMETERS

Independent variables

n	total number of strains
j, k	strain indices
$t \geq 0$	time

Dependent variables

N	total population size
I_j	number of infectives with strain j
v_j	proportion of infectives with strain j

Demographic parameters

$\beta > 0$	per capita birth rate of susceptibles
$B(N)$	population birth rate at population size N
$\mu > 0$	per capita mortality rate of susceptibles

Epidemic parameters

$p_j \in [0, 1]$	fraction of horizontal transmission of strain j
$q_j \in [0, 1]$	ratio of fertility in strain j infectives versus susceptibles
$\eta_j > 0$	per capita/capita infection probability (or rate) for strain j
$\gamma_j \geq 0$	per capita recovery rate of strain j infectives
$\alpha_j \geq 0$	disease death rates of strain j infectives

For $j = 1, \dots, n$, I_j denotes the number of infective hosts which are infected by strain j . The host equation must be modified to take account of disease fatalities, α_j is the extra per capita mortality rate of infectives due to strain j . Infection with one strain is assumed to protect completely against the infection with other strains,

$$\left. \begin{aligned} N' &\leq B(N) - \mu N - \sum_{j=1}^n \alpha_j I_j, \\ I_j' &= \tilde{C}(t) \eta_j I_j - (\mu + \alpha_j + \gamma_j) I_j, \quad j = 1, \dots, n, \\ I_j(t) &\geq 0, \quad j = 1, \dots, n; \quad \sum_{j=1}^n I_j(t) \leq N. \end{aligned} \right\} \quad (1.1)$$

The host equation is formulated as an inequality because there may be a class of recovered individuals which is not explicitly modeled. The inequality allows for the recovered individuals to have an increased mortality as well, and for

infective and/or recovered individuals to have a reduced birth rate. From a mathematical point of view, the inequality prohibits the model from being closed such that a discussion of existence and uniqueness of solutions is not meaningful, but the model is complete enough for our purposes. The function $\tilde{C}$ gives the per capita rate of contacts with susceptible individuals. It certainly depends on the number of susceptible individuals, but may also depend on the total population size or the sizes of other epidemiologic classes [23] and may arbitrarily depend on time. In this context, η_j is the average probability at which the contact between a susceptible and infective individual leads to an infection. γ_j is the per capita rate of recovering from an infection with strain j . The recovery may lead to permanent or temporary immunity or directly back into the susceptible class; there is complete cross-immunity in the sense that individuals that are permanently or temporarily immune against one strain are also immune against all other strains. The fraction $\frac{1}{\mu + \alpha_j + \gamma_j}$ is the average sojourn time in the infectious stage if one is infected by strain j (including that the sojourn may be cut short by natural or disease death). The fraction $\frac{\alpha_j}{\mu + \alpha_j + \gamma_j}$ is the probability to die from a strain j infection during the infectious period [86, Sec. 2.1, 2.2]. We define the *relative replacement ratio* of strain j as

$$\mathcal{R}_j = \frac{\eta_j}{\mu + \alpha_j + \gamma_j}. \quad (1.2)$$

If $\tilde{C}$ did not depend on time and gave the per capita contact rate with all individuals in the population, $\tilde{C}\mathcal{R}_j$ were the *basic replacement ratio* (basic reproduction number) of strain j , the average number of secondary infections caused by one typical strain j infective in an otherwise completely susceptible population [9, 34, 35] [4, Sec. 2.2] [53, Sec. 2.2] [86, Sec. 21.2]. Notice that the fraction $\frac{\mathcal{R}_j}{\mathcal{R}_k}$ equals the fraction of the basic replacement ratio of strain j over the basic replacement ratio of strain k in case that meaningful basic replacement ratios can be defined. The next result states that a strain dies out if there is another strain with a higher relative replacement ratio.

Theorem 1. *Let $\limsup_{N \rightarrow \infty} \frac{B(N)}{N} < \mu$. If $\mathcal{R}_n < \mathcal{R}_j$ for some $j < n$, then $I_n(t) \rightarrow 0$ as $t \rightarrow \infty$.*

Since we can renumber the strains as needed, we obtain that the strain with maximal relative replacement ratio drives all other strains into extinction.

Corollary 1. *Let $\limsup_{N \rightarrow \infty} \frac{B(N)}{N} < \mu$. If $\mathcal{R}_j < \mathcal{R}_1$ for all $j = 2, \dots, n$, then $I_j(t) \rightarrow 0$ for $t \rightarrow \infty$, $j = 2, \dots, n$.*

The theorem can be proved as in [80], [11], or [23]. Here we use the method proposed by Ackleh and Allen [1, 2] which is more flexible.

A Lyapunov type selection functional

We fix j and set

$$y = I_n^{\xi_n} I_j^{-\xi_j},$$

with $\xi_j > 0$ to be determined later. Then

$$\frac{y'}{y} = \xi_n \frac{I_n'}{I_n} - \xi_j \frac{I_j'}{I_j}.$$

We substitute the differential equations for I_j in (1.1),

$$\frac{y'}{y} = \xi_n \left(\tilde{C}(t) \eta_n - (\mu_n + \alpha_n + \gamma_n) \right) - \xi_j \left(\tilde{C}(t) \eta_j - (\mu_j + \alpha_j + \gamma_j) \right).$$

Proof. To prove Theorem 1, we choose $\xi_j = \frac{1}{\eta_j}$. By (1.2),

$$\frac{y'}{y} = \frac{1}{\mathcal{R}_j} - \frac{1}{\mathcal{R}_n} < 0.$$

This implies that $y(t) \rightarrow 0$ as $t \rightarrow \infty$. From the definition of y ,

$$I_n(t)^{\xi_n} \leq y(t) I_j(t)^{\xi_j} \leq y(t) N(t)^{\xi_j}.$$

The assumption for $B(N)$ and the differential inequality for N in (1.1) imply that N is bounded and so $I_n(t) \rightarrow 0$ as $t \rightarrow \infty$.

Corollary 1 only states that all strains but the one with maximal relative replacement ratio go extinct; if the model is closed in an appropriate way, one can show that the strain with maximal relative replacement ratio persists provided that its basic replacement ratio exceeds 1 [11].

1.2.1 Propagule producing parasites

The model (1.1) is quite general as far as the disease incidence is concerned, but restrictive as we assume that the growth of the host population is bounded by a nonlinear population birth rate while the population death rate is linear. It is further restrictive, as the mathematical technique does not work if several infectious stages or a latent period are incorporated into the model or other features are added. As an illustration, we revisit a model [39] for an infectious disease, which is spread both by direct (horizontal) transmission and by waterborne (or otherwise free-living) propagules released by infective hosts. As additional dependent variables, we add the amount of waterborne propagules, W_j , released by infectives with strain j . Recast in the notation used above, the model in [39] takes the form

$$\left. \begin{aligned} N' &= B(N) - \mu N - \sum_{j=1}^n \alpha_j I_j, \\ I_j' &= \tilde{C}(t) (\hat{\eta}_j I_j + \tilde{\eta}_j W_j) - (\mu + \alpha_j + \gamma_j) I_j, \\ W_j' &= \sigma_j I_j - \nu_j W_j, \end{aligned} \right\} \quad j = 1, \dots, n, \quad (1.3)$$

where $B(N) = B$ is constant and $\tilde{C} = S = N - \sum_{j=1}^n I_j$ is the number of susceptible individuals. The parameters σ_j are the per capita release rates of waterborne propagules and ν_j are their per unit destruction rates, for strain j . $\hat{\eta}_j$ is the direct horizontal per capita/capita infection rate, while $\tilde{\eta}$ is the infection rate per capita host and per unit propagule. So far, all attempts have failed to modify the proof of Theorem 1 such that the addition of waterborne pathogens is included. In view of the counterexamples of $\mathcal{R}$ maximization cited in the Introduction and presented below, the mathematical underpinning of the interesting results in [39] still needs to be provided. However, if the parameters σ_j and ν_j are large compared with the other parameters, in other words, if the dynamics of waterborne pathogens are fast compared with the dynamics of the remaining system, a quasi-steady state approximation may be justified for the waterborne pathogens,

$$W_j \approx \frac{\sigma_j}{\nu_j} I_j.$$

If we substitute this relation as an equality into the equations for I_j in (1.3), we obtain (1.1) with

$$\eta_j = \hat{\eta}_j + \tilde{\eta}_j \frac{\sigma_j}{\nu_j},$$

and Corollary 1 applies. This means that the parasite evolves in such a way that $\mathcal{R}$ is increased.

1.2.2 An example of virulence management

Much of the theoretical consideration as to whether parasite evolution leads to low, intermediate, or high virulence is based on the idea that the mutations a parasite may undergo are subject to certain constraints. If a mutation leads to a higher replication rate of the parasite, the greater exploitation of host resources will presumably increase the harm done to the host resulting in decreased mobility and/or fecundity and increased disease mortality. The relationship of these trade offs, which crucially depends on the specifics of the disease, has been considered in many studies [33, 3, 4, 28, 30, 44, 26, 12, and references therein]. If one takes a parasite-centered rather than a host-centered point of view, one can make the case that the impact of waterborne pathogens is possibly even more dramatic than presented in [39, 29]. Let ζ be the replication rate of parasites in an infectious host. Then $\hat{\eta} = \zeta f(\zeta)$ where the decreasing function f takes account of the degree by which the infective individual loses its mobility. If the disease has a diarrhetic component, insufficient hygiene leads to waterborne transmission. We assume that $\tilde{\eta} \frac{\sigma}{\nu} = \kappa_1 \zeta$. We assume that the disease mortality rate responds in a monotone increasing way to an increase in the replication rate, though we assume that this response is weak on the one hand, but stronger than linear on the other hand,

$$\alpha = \kappa_2 \zeta^b,$$

with $b > 1$, and κ_2 being small compared with the other parameters. It is difficult to assess how the replication rate influences the recovery rate γ . Ewald and De Leo [39] assume a decreasing relationship (as has been found for myxomatosis [4, 23.12]), but one can also imagine that a high replication rate triggers a strong immune response such that, while the length of morbidity may increase, the duration of the actual infectious period may decrease. We assume for simplicity that γ does not depend on ζ . So

$$\mathcal{R} = \frac{\zeta f(\zeta) + \kappa_1 \zeta}{\mu + \gamma + \kappa_2 \zeta^b}.$$

We choose $f(\zeta) = \kappa_3 e^{-\kappa_4 \zeta}$. After some scaling, one can assume that $\kappa_3 = \kappa_4 = 1$ and $\mu + \gamma = 1$, and, without loosing any generality, we can consider

$$\mathcal{R}(\zeta, \kappa) = \frac{\zeta e^{-\zeta} + \kappa \zeta}{1 + \epsilon \zeta^b},$$

with suitable compound parameters $\epsilon, \kappa > 0$. The weak response of the disease death rate to an increase in the replication rate means that $\epsilon > 0$ is small. It is more instructive to write $\mathcal{R}$ as a linear combination $\mathcal{R}(\zeta, \kappa) = h(\zeta) + \kappa g(\zeta)$ with

$$h(\zeta) = \frac{\zeta e^{-\zeta}}{1 + \epsilon \zeta^b}, \quad g(\zeta) = \frac{\zeta}{1 + \epsilon \zeta^b}.$$

The compound parameter $\kappa \geq 0$ is proportional to the replication rate of the parasite, to the release rate of waterborne propagules into the water and to their survival time. In particular, it reflects the quality of hygiene in inverse proportion: $\kappa = 0$ means perfect hygiene. Both h and g are uni-modal functions, i.e. they first increase and then decrease. h takes its maximum at some value $\zeta_h(\epsilon) < 1$ and the maximum is less than e^{-1} . g takes its maximum at $\zeta_g(\epsilon) = (\epsilon(b-1))^{-1/b}$ and the maximum is $b^{-1} \epsilon^{-1/b} (b-1)^{1-(1/b)}$. So both the maximum of g and the argument where g takes its maximum tend to infinity as $\epsilon \rightarrow 0$. Under perfect hygiene, $\kappa = 0$, evolution will lead to a replication rate less than the (scaled) value 1 and a per capita disease death rate less than ϵe^{-b} , while for small ϵ and imperfect hygiene, $\kappa > 0$, it will lead to a replication rate much higher than 1 and also to a substantially larger disease death rate. One can even construct a relative replacement ratio which has two local maxima for appropriate κ .

1.3 Host populations with linear birth rates

We turn to host populations which, like the human population, are assumed to grow exponentially in the time frame of epidemiologic relevance. For mathematical manageability, we restrict our consideration to diseases which only involve susceptible and infective individuals. Since the per capita birth rates

are constant, it is not too complicated to incorporate vertical disease transmission and fertility reduction of infectious individuals. The per capita birth rate of a susceptible individual is denoted by β , the per capita birth rate of a strain j infective by $q_j\beta$ with $q_j \in [0, 1]$, and the proportion of the offspring of a strain j infective which is also infective (with the same strain) by p_j . $1 - q_j$ is the fraction by which the fertility of a strain j infective is reduced compared with a susceptible individual and is one of the measures of the strain's virulence. At this point, we formulate a model with a general incidence which we will specify later. Let $C(N)$ be the rate at which a single individual makes contacts in a population of size N . In this context, let η_j be the probability that a contact between a susceptible individual and an infective individual of strain j leads to an infection. Since I_j/N is the probability that an average contact actually occurs with an infective individual with strain j , the incidence of strain j infectives is given by $\frac{C(N)}{N}S\eta_j I_j$, where $S = N - \sum_{k=1}^n I_k$ is the number of susceptible individuals. The population birth rate is $\beta S + \sum_{k=1}^n q_k\beta I_k = \beta N - \sum_{k=1}^n \beta(1 - q_k)I_k$. Though we will first consider a natural per capita mortality rate μ which does not depend on the population size N , we allow for a size-dependent per capita mortality rate $\mu(N)$ for later purposes. Including disease fatalities, the population mortality rate is $\mu(N)N + \sum_{k=1}^n \alpha_k I_k$. The model equations are these,

$$\left. \begin{aligned} N' &= (\beta - \mu(N))N - \sum_{k=1}^n (\alpha_k + \beta(1 - q_k))I_k, \\ I'_j &= \beta q_j p_j I_j + \frac{C(N)}{N} \left(N - \sum_{k=1}^n I_k \right) \eta_j I_j - (\mu(N) + \alpha_j + \gamma_j) I_j, \\ j &= 1, \dots, n. \end{aligned} \right\} \quad (1.4)$$

It is also informative to derive the equations for the proportions of strain j infectives, v_j , and the proportion of all infectives, v ,

$$v_j = \frac{I_j}{N}, \quad v = \sum_{k=1}^n v_k.$$

By the quotient rule,

$$v'_j = \frac{I'_j}{N} - v_j \frac{N'}{N}.$$

By (1.4),

$$\left. \begin{aligned} N' &= N \left(\beta - \mu(N) - \sum_{k=1}^n b_k v_k \right), \\ v'_j &= v_j \left(C(N)(1 - v)\eta_j - a_j + \sum_{k=1}^n b_k v_k \right). \end{aligned} \right\} \quad (1.5)$$

Here

$$a_j = \alpha_j + \gamma_j + \beta(1 - q_j p_j), \quad b_j = \alpha_j + \beta(1 - q_j). \quad (1.6)$$

Notice that $a_j \geq b_j \geq 0$. We add the equations for v_j in (1.5),

$$v' = C(N)(1-v) \sum_{k=1}^{\infty} \eta_k v_k - \sum_{k=1}^n a_k v_k + v \sum_{k=1}^n b_k v_k. \quad (1.7)$$

Since $a_j \geq b_j$,

$$v' \leq (1-v) \sum_{k=1}^{\infty} (C(N)\eta_k - a_k) v_k, \quad (1.8)$$

with the inequality being strict for $v > 0$. In accordance with the interpretation of v_j we have the following result from this inequality.

Proposition 1. *If $v_j(t) \geq 0$ and $v(t) \leq 1$ holds for $t = 0$, then it holds for all $t > 0$.*

1.4 Exponential growth and mass action incidence

Different strains can coexist, if the host population growth exponentially and the contact rate in a population of size N , $C(N)$, is independent of N (*standard incidence*) [67]. We will derive a condition for competitive exclusion between different strains under the *mass action incidence law* which assumes that $C(N)$ is proportional to N . We absorb the proportionality factor into the parameter η_j such that $C(N) = N$. η_j must now be interpreted as a per capita/capita infection rate, i.e., $\frac{1}{\eta_j}$ is the average time it takes for a typical infective and a typical susceptible individual to contact each other and to transmit the disease. We assume that the population mortality rate is linear (the per capita mortality rate does not depend on population size) and system (1.4) specializes to

$$\left. \begin{aligned} N' &= \beta N - \mu N - \sum_{k=1}^n (\alpha_k + \beta(1 - q_k)) I_k, \\ I_j' &= \eta_j I_j \left(N - \sum_{k=1}^n I_k - \mathcal{R}_j^{-1} \right), \quad j = 1, \dots, n, \end{aligned} \right\} \quad (1.9)$$

with

$$\mathcal{R}_j^{-1} := \frac{\mu + \alpha_j + \gamma_j - \beta q_j p_j}{\eta_j}. \quad (1.10)$$

This system is the multi-strain version of a model in [14] (see also [15, Sec. 2.3]). The notation $\mathcal{R}_j^{-1}$ is motivated by the fact that it is the reciprocal of the relative replacement ratio in (1.2) if there is no vertical transmission, $p_j = 0$. If the proportion of vertical transmission is so small that $\mathcal{R}_j^{-1} > 0$ for $j = 1, \dots, n$,

$$\mathcal{R}_j = \frac{\eta_j}{\mu + \alpha_j + \gamma_j - \beta q_j p_j} \quad (1.11)$$

can be understood as a relative replacement ratio that is amplified by vertical transmission. Recall that

$$D_j = \frac{1}{\mu + \alpha_j + \gamma_j}$$

is the expected sojourn in the strain j infective stage. Then

$$\tilde{D}_j = \frac{1}{\mu + \alpha_j + \gamma_j - \beta q_j p_j} = D_j \frac{1}{1 - D_j \beta q_j p_j} = D_j \sum_{m=0}^{\infty} (D_j \beta q_j p_j)^m$$

is the *expected cumulative sojourn in the infective stage* of a strain j infective individual and all its vertically produced generations. Therefore we call $\mathcal{R}_j$ in (1.11) the *(vertically) cumulative relative replacement ratio* of strain j provided that $\mathcal{R}_j^{-1} > 0$. However, in order to include the case in which some or all $\mathcal{R}_j^{-1}$ are negative or zero, we will formulate the forthcoming results in terms of $\mathcal{R}_j^{-1}$ rather than $\mathcal{R}_j$.

In terms of the proportions of infectives with strain j , (1.5) specializes to

$$\left. \begin{aligned} N' &= N \left(\beta - \mu - \sum_{k=1}^n b_k v_k \right), \\ v'_j &= v_j \left(N(1-v)\eta_j - a_j + \sum_{k=1}^n b_k v_k \right), \end{aligned} \right\} \quad (1.12)$$

and (1.7) to

$$v' = N(1-v) \sum_{k=1}^{\infty} \eta_k v_k - \sum_{k=1}^n a_k v_k + v \sum_{k=1}^n b_k v_k. \quad (1.13)$$

Recall the definitions of a_j and b_j in (1.6). *Throughout this section, we assume without further mentioning that, for each j , $a_j - b_j = \gamma_j + \beta q_j(1-p_j) > 0$.* This means that each strain j has a positive recovery rate or both imperfect vertical transmission and imperfect sterilization by infection. We further assume that $\beta > \mu$ such that the population increases exponentially in the absence of the disease.

Proposition 2. *The parasite population is uniformly weakly persistent in the sense that there exists some $\epsilon > 0$ such that $\limsup_{t \rightarrow \infty} \sum_{j=1}^n \frac{I_j(t)}{N(t)} \geq \epsilon$ for all solutions of (1.9) with $N(0) > 0$, $\sum_{j=1}^n I_j(0) > 0$.*

The host population is strongly uniformly persistent in the sense that there exists some $\epsilon > 0$ such that $\liminf_{t \rightarrow \infty} N(t) \geq \epsilon$ for all solutions of (1.9) with $N(0) > 0$.

Proof. For $v = \sum_{j=1}^n \frac{I_j}{N}$,

$$\begin{aligned}\frac{N'}{N} &\geq \beta - \mu - \left(\max_{k=1}^n b_k\right)v, \\ \frac{v'}{v} &\geq N(1-v) \min_{k=1}^n \eta_k - \max_{k=1}^n a_k.\end{aligned}$$

Choose $\epsilon \in (0, 1)$ such that $\beta - \mu - \epsilon \max_{k=1}^n b_k > 0$. Assume $\limsup_{t \rightarrow \infty} v(t) < \epsilon$. Then $N(t) \rightarrow \infty$ as $t \rightarrow \infty$ by the first equation and $v(t) \rightarrow 1$ as $t \rightarrow \infty$ by the second equation, a contradiction. Hence there exists an $\epsilon > 0$ such that $\limsup_{t \rightarrow \infty} v(t) \geq \epsilon$ for all solutions with $N(0) > 0$ and $v(0) > 0$.

As for the host population, we have that $N(t) = N(0)e^{(\beta - \mu)t} \rightarrow \infty$ as $t \rightarrow \infty$, if $v = \sum_{j=1}^n \frac{I_j}{N}$ is zero at $t = 0$, because then $v(t) = 0$ for all $t \geq 0$. Let us assume that $v(0) > 0$ and that $\limsup_{t \rightarrow \infty} N(t) < \epsilon$ for some $\epsilon > 0$. Set $\gamma_\diamond = \min_k (\gamma_k + \beta q_k (1 - p_k)) > 0$, $\eta^\diamond = \max_k \eta_k$. Since $v \leq 1$ by Proposition 1, it follows from (1.13) that

$$\frac{v'}{v} \leq N\eta^\diamond - \gamma_\diamond.$$

By our assumption, if we choose $\epsilon > 0$ small enough,

$$\limsup_{t \rightarrow \infty} \frac{v'}{v} \leq \epsilon \eta^\diamond - \gamma_\diamond < 0.$$

This implies that $v(t) \rightarrow 0$ as $t \rightarrow \infty$, contradicting our earlier result that the parasite persists uniformly strongly. So we have shown that there exists some $\epsilon > 0$ such that $\limsup_{t \rightarrow \infty} N(t) \geq \epsilon$ for every solution with $N(0) > 0$.

In order to replace $\limsup$ by $\liminf$ in the last statement, we apply [86, Thm. A.32]. We identify the state space of (1.12),

$$X = \left\{ (N, v_1, \dots, v_n); N > 0, v_j \geq 0, \sum_{j=1}^n v_j \leq 1 \right\},$$

which we endow with the metric induced by the sum-norm. We choose the functional ρ on X as $\rho(x) = N$ for $x = (N, v_1, \dots, v_n)$. In the language of [86, Chap. A.5], we have just shown that the semiflow Φ generated on X by the solutions of (1.12) is uniformly weakly ρ -persistent. Notice that the compactness condition (C) in [86, Thm. A.32] holds as the set $\{\epsilon_1 \leq N \leq \epsilon_0\}$, $0 < \epsilon_1 < \epsilon_0$, is compact in X . It follows that the semiflow Φ is uniformly strongly ρ -persistent which translates into the host population being uniformly strongly persistent.

We consider the same type of selection functional as in Section 1.2 [1, 2],

$$y_j = I_j^{\xi_j} I_1^{-\xi_1},$$

with ξ_j to be determined later. Then

$$\frac{y'_j}{y_j} = \xi_j \frac{I'_j}{I_j} - \xi_1 \frac{I'_1}{I_1}.$$

We substitute the appropriate differential equations from (1.9),

$$\frac{y_j'}{y_j} = \xi_j \eta_j \left(N - \sum_{k=1}^n I_k - \mathcal{R}_j^{-1} \right) - \xi_1 \eta_1 \left(N - \sum_{k=1}^n I_k - \mathcal{R}_1^{-1} \right).$$

We choose $\xi_j = \eta_j^{-1}$. Then

$$\frac{y_j'}{y_j} = \mathcal{R}_1^{-1} - \mathcal{R}_j^{-1}.$$

We integrate this equation,

$$y_j(t) = y_j(0) e^{-\delta_j t}, \quad \delta_j = \mathcal{R}_j^{-1} - \mathcal{R}_1^{-1} > 0, \quad j \neq 1.$$

We recall the definition of y_j ,

$$I_j(t) = [y_j(0)]^{\eta_j} [I_1(t)]^{\eta_j/\eta_1} e^{-\eta_j \delta_j t}. \quad (1.14)$$

The next result states that the strain with maximal replacement ratio does not go extinct.

Proposition 3. *Let $\mathcal{R}_1^{-1} < \mathcal{R}_j^{-1}$ for all $j = 2, \dots, n$. Then the first strain uniformly strongly persists, i.e., there exists some $\epsilon > 0$ such that $\liminf_{t \rightarrow \infty} I_1(t) \geq \epsilon$ for all solutions with $I_1(0) > 0$.*

The proof has been banished into the appendix because of its length.

Theorem 2. *Let $\mathcal{R}_1^{-1} < \mathcal{R}_k^{-1}$ for all $k = 2, \dots, n$. Let $j \in \{2, \dots, n\}$ and $\eta_j \leq \eta_1$. Then $\frac{I_j(t)}{I_1(t)} \rightarrow 0$ as $t \rightarrow \infty$. In particular, $\frac{I_j(t)}{N(t)} \rightarrow 0$ as $t \rightarrow \infty$.*

Proof. By (1.14),

$$\frac{I_j(t)}{I_1(t)} = [y_j(0)]^{\eta_j} [I_1(t)]^{\frac{\eta_j}{\eta_1} - 1} e^{-\eta_j \delta_j t}.$$

By Proposition 3, there exists some $\epsilon > 0$ such that $\liminf_{t \rightarrow \infty} I_1(t) \geq \epsilon$. Since $\frac{\eta_j}{\eta_1} \leq 1$,

$$\limsup_{t \rightarrow \infty} \frac{I_j(t)}{I_1(t)} \leq [y_j(0)]^{\eta_j} \epsilon^{\frac{\eta_j}{\eta_1} - 1} \limsup_{t \rightarrow \infty} e^{-\delta_j \eta_j t} = 0.$$

The following result gives a condition under which the strain with maximal replacement ratio drives the suboptimal strains into extinction.

Theorem 3. *Let $\mu + \alpha_1 > q_1 \beta$ and $\mathcal{R}_1^{-1} < \mathcal{R}_j^{-1}$ for all $j = 2, \dots, n$. For $j = 2, \dots, n$, let $\mu + \alpha_j > q_j \beta$ or $\eta_j \leq \eta_1$. Then, for all solutions of (1.4) with $I_1(0) > 0$, the following hold: $I_j(t) \rightarrow 0$ ($t \rightarrow \infty$) for $j = 2, \dots, n$, $\liminf_{t \rightarrow \infty} I_1(t) \geq \epsilon$ and $\limsup_{t \rightarrow \infty} N(t) \leq c$ with $c \geq \epsilon > 0$ not depending on the initial data.*

Proof. Let J be the set of those $j \in \{1, \dots, n\}$ such that $\mu + \alpha_j > q_j \beta$. By assumption, $1 \in J$. Consider a solution with $I_1(0) > 0$. Suppose that there exists some $c > 1$, which can be chosen arbitrarily large, and some $t_c > 0$ such that $N(t) > c \geq 1$ for all $t \geq t_c$. Let $j \notin J$. By assumption, $\eta_j \leq \eta_1$. By (1.14), for $t \geq t_c$,

$$I_j(t) \leq [y_j(0)]^{\eta_j} [N(t)]^{\eta_j/\eta_1} e^{-\eta_j \delta_j t} \leq [y_j(0)]^{\eta_j} N(t) e^{-\eta_j \delta_j t}.$$

This implies

$$v_j(t) \leq [y_j(0)]^{\eta_j} e^{-\eta_j \delta_j t}, \quad j \notin J, t \geq t_c.$$

Let $v_J(t) = \sum_{j \in J} v_j(t)$. Let $\eta_J = \min_{j \in J} \eta_j$ and $\nu = \max_{j \in J} a_j$. Then, for $t \geq t_c$, by (1.12),

$$v'_J \geq c \eta_J \left(1 - \sum_{j \notin J} [y_j(0)]^{\eta_j} e^{-\eta_j \delta_j t} - v_J \right) v_J - \nu v_J.$$

Let $\epsilon > 0$ which will be chosen sufficiently small later. By choosing $c > 1$ large enough, we can achieve that there exists some $t_\epsilon \geq t_c$ such that $v_J(t) \geq 1 - \epsilon$ for all $t \geq t_\epsilon$. By (1.12),

$$\frac{N'}{N} \leq \beta - \mu - \sum_{k \in J} b_k v_k \leq \beta - \mu - \left(\inf_{k \in J} b_k \right) v_J.$$

For $t \geq t_\epsilon$, recalling the definition of b_k in (1.6),

$$\begin{aligned} \frac{N'}{N} &\leq \beta - \mu - \inf_{k \in J} (\alpha_k + \beta(1 - q_k))(1 - \epsilon) \\ &= \max_{k \in J} [\beta(\epsilon + q_k(1 - \epsilon)) - \alpha_k(1 - \epsilon) - \mu]. \end{aligned}$$

By assumption, the right hand side becomes negative, when $\epsilon > 0$ is chosen small enough, and $\frac{N'}{N} < 0$ for $t \geq t_\epsilon$. It follows that $N(t) \rightarrow 0$ as $t \rightarrow \infty$. This contradiction shows that there exists some $c > 0$ such that $\liminf_{t \rightarrow \infty} N(t) \leq c$ for all solution with $I_1(0) > 0$. In order to have this result with $\limsup$ rather than $\liminf$, we are going to apply [86, Thm. A.32]. To this end, we set

$$X = \left\{ (N, I_1, \dots, I_n) \in \mathbb{R}_+^{n+1}; I_1 > 0, \sum_{j=1}^n I_j \leq N \right\}$$

and $\rho(x) = (1 + N)^{-1}$. In the language of [86, Sec. A.5], we have shown that the semiflow induced by the solutions of (1.4) is uniformly weakly ρ -persistent. By Proposition 3, there exists some $\epsilon > 0$ such that $\liminf_{t \rightarrow \infty} I_1(t) \geq \epsilon$ for all solutions with $I_1(0) > 0$. Set $B = \{x \in X; I_1 \geq \epsilon/2\}$. Then condition (C) in [86, Sec. A.5] is satisfied. By [86, Thm. A.32], the semiflow is uniformly strongly ρ -persistent, i.e., there exists some $c > 0$ such that $\limsup_{t \rightarrow \infty} N(t) \leq c$ for all solutions with $I_1(0) > 0$. In particular, $I_1 \leq N$ is bounded and the statement follows from (1.14).

While it is not very likely that the assumption $\eta_j \leq \eta_1$ is satisfied for all $j \geq 2$ or the assumption $\mu + \alpha_j > q_j \beta$ is satisfied for all j , the following example shows that the assumption in Theorem 3, $\mu + \alpha_j > q_j \beta$ or $\eta_j \leq \eta_1$ for all $j \geq 2$, can easily be satisfied.

Example 1. We consider a disease with direct transmission only (without the waterborne propagules we have considered in Section 1.2.2) and without vertical transmission, $p_j = 0$. Let ζ again be the parasite replication rate. It is suggestive that the disease death rate α is an increasing functions of ζ and q , the fertility ratio of an infective to a susceptible individual, is a decreasing function of ζ . If γ does not depend on ζ or only weakly so, then the cumulative expected sojourn in the infectious stage $\frac{1}{\mu + \gamma + \alpha}$ will be either a decreasing function of ζ or a uni-modal function of ζ which increases on some interval $[0, \zeta_1]$ and decreases on $[\zeta_1, \infty)$ (see [4, Fig. 23.13] for myxomatosis; notice that, in this figure, $\mathcal{R}_0$ is proportional to the average sojourn time in the infectious stage). Since we only consider direct transmission, it is reasonable to assume that the transmission rate η is an increasing function of ζ or an uni-modal function of ζ which increases on an interval $[0, \zeta_2]$ and decreases on $[\zeta_2, \infty)$. Either way, it makes sense to assume that η grows more slowly than $\mu + \gamma + \alpha$ for high replication rates ζ such that $\mathcal{R} = \frac{\eta}{\mu + \gamma + \alpha}$ takes its maximum at some finite positive argument ζ^* . Since the demographic dynamics are typically much slower than the epidemic dynamics, β is close to μ such that $\mu + \alpha - \beta q > 0$ should be satisfied at $\zeta = \zeta^*$. For many diseases (obviously so for myxomatosis), it makes sense to assume that $0 \leq \zeta_1 \leq \zeta_2 \leq \infty$, i.e., the per capita transmission rate η takes its maximum at a higher replication rate than the cumulative expected sojourn in the infectious stage. This means that $\mathcal{R}$ is an increasing function on $[0, \zeta_1]$ and a decreasing function on $[\zeta_2, \infty)$ and so $\zeta_1 \leq \zeta^* \leq \zeta_2$. This implies that η increases on $[0, \zeta^*]$ and $\frac{1}{\mu + \gamma + \alpha}$ decreases on $[\zeta^*, \infty)$. Let now the first strain have the replication rate $\zeta_1 = \zeta^*$ such that $\mathcal{R}_1$ is the maximum of the relative replacement ratio as a function of ζ . As we argued above, $\mu + \alpha_1 - \beta q_1 > 0$. Any other strain $j > 1$ has a replication rate $\zeta_j \neq \zeta^* = \zeta_1$. If $\zeta_j < \zeta_1$, then $\eta_j < \eta_1$ because η increases on $[0, \zeta_1]$. If $\zeta_j > \zeta_1$, $\mu + \alpha_j - \beta q_j > \mu + \alpha_1 - \beta q_1 > 0$. This shows that the assumption of Theorem 3 are satisfied and its assertion holds.

1.5 Density-dependent per capita mortality and mass-action incidence

There are several ways in which Verhulst's celebrated logistic equation for the growth of a disease-free population,

$$N' = (\beta - \mu - \nu N)N,$$

can be adapted to a host-parasite system. Here νN is the density-dependent part of the per capita mortality $\mu(N) = \mu + \nu N$. If the disease did not interfere

with the host dynamics except possibly adding disease related mortality, this would lead to a system

$$\begin{aligned} N' &= (\beta - \mu - \nu N)N - \sum_{k=1}^n \alpha_k I_k, \\ I_j' &= S\eta_j I_j - (\mu + \nu N + \alpha_j + \gamma_j)I_j, \\ &\quad j = 1, \dots, n, \end{aligned}$$

where $S = N - \sum_{k=1}^n I_k$ is the size of the susceptible part of the population. For such a model, coexistence of two different parasite strains is possible [1, 6]. As pointed out to me by Hans Metz, competitive exclusion still holds if infective individuals are too sick to reproduce and to take part in the competition for the resources the lack of which leads to the density-dependent part of the disease-independent mortality. Under this assumption the model takes the following form,

$$\begin{aligned} S' &= (\beta - \mu - \nu S)S - S \sum_{k=1}^n \eta_k I_k, \\ I_j' &= S\eta_j I_j - (\mu + \nu S + \alpha_j + \gamma_j)I_j, \\ &\quad j = 1, \dots, n. \end{aligned} \tag{1.15}$$

It is not difficult to see that the solutions of this system are bounded. The same analysis as in Section 1.2 shows that all strains go extinct except those for which

$$\mathcal{S}_j = \frac{\eta_j - \nu}{\mu + \alpha_j + \gamma_j}$$

is maximal and positive.

Theorem 4. *If $\mathcal{S}_j < \mathcal{S}_1$ for $j = 2, \dots, n$, then $I_j(t) \rightarrow 0$ as $t \rightarrow \infty$ for $t \rightarrow \infty$, $j = 2, \dots, n$.*

While a maximization principle holds in this case, it is not a basic replacement ratio that is being maximized. If the number of susceptibles S is constant, the average duration of the infectious period (including death) is $\frac{1}{\mu + \nu S + \alpha_j + \gamma_j}$ and the respective replacement ratio is $\mathcal{R}_j(S) = \frac{\eta_j S}{\mu + \nu S + \alpha_j + \gamma_j}$. The basic replacement ratio is obtained by evaluating this expression at the carrying capacity $S = K = \frac{\beta - \mu}{\nu}$ to which the population size converges in the absence of the disease, $\mathcal{R}_j(K) = \frac{\eta_j K}{\beta + \alpha_j + \gamma_j}$. It is not difficult to find examples where $\mathcal{R}_j(K)$ and $\mathcal{S}_j$ are maximized for different j . It should be mentioned that logistic growth is a rather particular case as the Verhulst equation is the special case of the Bernoulli equation $N' = (\beta - \mu - \nu N^\theta)N$, $\theta > 0$, for $\theta = 1$. If $\theta \neq 1$, a clear-cut maximization principle seems to hold no longer for the analog of the model discussed above.

1.6 Linear birth rates and standard incidence

Under standard incidence, depending on the situation, different strains can either coexist or exclude each other in a host population which would grow exponentially in the absence of the disease [67]. I will show that low disease prevalence favors strains with higher net replacement ratio, while high disease prevalence favors strains with lower disease death rate. This also holds, when population growth would be limited by a nonlinear population death rate in absence of the disease. Standard incidence results when the per capita contact rate $C(N)$ in a population of size N does not depend on N . We absorb the constant contact rate into the parameters η_j such that $C(N) = 1$. Now η_j is to be interpreted as per capita infection rate. System (1.4) specializes to

$$\left. \begin{aligned} N' &= (\beta - \mu(N))N - \sum_{k=1}^n (\alpha_k + \beta(1 - q_k))I_k, \\ I'_j &= \beta q_j p_j I_j + \left(1 - \sum_{k=1}^n \frac{I_k}{N}\right) \eta_j I_j - (\mu(N) + \alpha_j + \gamma_j) I_j, \\ j &= 1, \dots, n. \end{aligned} \right\} \quad (1.16)$$

In terms of the proportions of infectives with strain j , system (1.5) specializes to

$$\left. \begin{aligned} \frac{N'}{N} &= \beta - \mu(N) - \sum_{k=1}^n b_k v_k, \\ \frac{v'_j}{v_j} &= \left(1 - \sum_{k=1}^n v_k\right) \eta_j - a_j + \sum_{k=1}^n b_k v_k, \\ a_j &> b_j, \end{aligned} \right\} \quad (1.17)$$

and (1.7) specializes to

$$v' = (1 - v) \sum_{j=1}^n \eta_j v_j - \sum_{j=1}^n a_j v_j + v \sum_{j=1}^m b_j v_j. \quad (1.18)$$

Recall the definitions of a_j and b_j in (1.6). If the host population grows exponentially in the absence of the disease (μ does not depend on N and is smaller than β), system (1.16) is a *homogeneous* differential equation [49, 50]. Homogeneous differential equations have no stationary solutions (steady states), except for rare combinations of parameters; the role of stationary solutions are taken by exponential solutions [49, 50]. This means, at ‘equilibrium’, in the presence of the disease, the host population continues to show exponential increase (at the same or a lower rate than in the absence of the disease) or is converted to exponential decline [16, 17] [15, Sec. 2.13.2] [54, Sec. 5] [84]. Either way, the proportions v_j of strain j infectives become much more relevant than the absolute numbers I_j . For this epidemiologic reason, we will now study strain competition in terms of proportions. There is also a mathematical

benefit, as the equations for the proportions are decoupled from the equation for the host population and we have reduced our system by one dimension which makes its analysis much easier. Another nice feature is the elimination of the natural per capita mortality rate from the equations for the proportions which makes the following considerations largely independent of as to whether the natural population death rates are linear or nonlinear.

For a moment, let us consider the situation where there is just one strain,

$$\frac{v_1'}{v_1} = (1 - v_1)\eta_1 - a_1 + b_1v_1.$$

Assume $a_1 > b_1$. It is easy to see that the disease dies out in proportion ($v_1(t) \rightarrow 0$ as $t \rightarrow \infty$) if $\frac{\eta_1}{a_1} \leq 1$, and persists in proportion ($\liminf_{t \rightarrow \infty} v_1(t) > 0$, actually $v_1(t)$ converges to a positive limit) if $\frac{\eta_1}{a_1} > 1$. The number

$$\mathcal{R}_1^\circ = \frac{\eta_1}{a_1} = \frac{\eta_1}{\alpha_1 + \gamma_1 + \beta(1 - q_1p_1)}$$

has the form of a basic replacement ratio, except that the per capita mortality rate μ has been replaced by $\beta(1 - q_1p_1)$. The term ‘basic’ is appropriate here because, due to the choice of standard incidence, η_1 is the transmission rate of an average infective individual in an otherwise susceptible population. If $\beta > \mu$ and there is no vertical transmission, $p_1 = 0$, the replacement of μ by β can be interpreted as the proportional effect of infections being discounted by the growth of the population. The discount effect can be weakened or even turned upside down, if there is vertical transmission and no or only weak fertility reduction by the disease. Partially adopting the language of [15, Sec. 2.13.2], we call $\mathcal{R}_1^\circ$ the *net replacement ratio* of strain 1. Analogously, we call

$$\mathcal{R}_j^\circ = \frac{\eta_j}{a_j} = \frac{\eta_j}{\alpha_j + \gamma_j + \beta(1 - q_jp_j)} \quad (1.19)$$

the *net replacement ratio* of strain j .

In order to find out what strain competition selects for, we fix j and again use the functional

$$z = v_n^{\xi_n} v_j^{-\xi_j}, \quad (1.20)$$

with $\xi_j > 0$ to be determined later [1, 2]. Then

$$\frac{z'}{z} = \xi_n \frac{v_n'}{v_n} - \xi_j \frac{v_j'}{v_j}.$$

We substitute the differential equations (1.17),

$$\begin{aligned} \frac{z'}{z} &= \xi_n \left((1 - v)\eta_n - a_n + \sum_{k=1}^n b_k v_k \right) \\ &\quad - \xi_j \left((1 - v)\eta_j - a_j + \sum_{k=1}^n b_k v_k \right). \end{aligned} \quad (1.21)$$

1.6.1 Selection for high net replacement ratio

By analogy, our previous results suggest that competition selects for strains with maximal net replacement ratio. This is the case, indeed, under the proviso that disease prevalence is low. We choose $\xi_j = \frac{1}{\eta_j}$ in (1.20). By (1.21),

$$\frac{z'}{z} = \frac{1}{\mathcal{R}_j^\circ} - \frac{1}{\mathcal{R}_n^\circ} + \left(\frac{1}{\eta_n} - \frac{1}{\eta_j} \right) \sum_{k=1}^n b_k v_k.$$

Proposition 4. *Assume that, for some $j < n$, $\mathcal{R}_n^\circ < \mathcal{R}_j^\circ$ and*

$$\frac{1}{\mathcal{R}_j^\circ} - \frac{1}{\mathcal{R}_n^\circ} + \left(\frac{1}{\eta_n} - \frac{1}{\eta_j} \right) \limsup_{t \rightarrow \infty} \left(\sum_{k=1}^n b_k v_k \right)^\infty < 0.$$

Then $\frac{I_n(t)}{N(t)} \rightarrow 0$ as $t \rightarrow \infty$.

If disease prevalence is low for large times (all v_k are small), differences in net replacement ratio matter much more than differences in η_j for the assumption in this proposition.

Proof. First let $\eta_n \geq \eta_j$. Then $\sup_{t \geq 0} \frac{z'(t)}{z(t)} < 0$. If $\eta_n < \eta_j$,

$$\limsup_{t \rightarrow \infty} \frac{z'(t)}{z(t)} \leq \frac{1}{\mathcal{R}_j^\circ} - \frac{1}{\mathcal{R}_n^\circ} + \left(\frac{1}{\eta_n} - \frac{1}{\eta_j} \right) \limsup_{t \rightarrow \infty} \left(\sum_{k=1}^n b_k v_k \right)^\infty < 0$$

by assumption. In either case, $z(t) \rightarrow 0$ as $t \rightarrow \infty$ and $v_n(t) = \frac{I_n(t)}{N(t)} \rightarrow 0$ by (1.20).

Set $v^\infty = \limsup_{t \rightarrow \infty} v(t)$.

Proposition 5. *Assume that there is no fertility reduction in infectives, $q_j = 1$, and no vertical transmission, $p_j = 0$, for all j . Then $v^\infty \leq \left[1 - \frac{\beta}{\bar{\zeta}} \right]_+$ where $\bar{\zeta} = \max_{j=1}^m (\eta_j - \alpha_j)$.*

Proof. Under these assumptions, by (1.6) and (1.18),

$$v' \leq (1 - v) \sum_{k=1}^n (\eta_k - \alpha_k) v_k - \beta v \leq (1 - v) \bar{\zeta} v - \beta v.$$

If the per capita birth rate is sufficiently large, competition essentially selects for the largest modified basic replacement ratio.

Theorem 5. *Assume that there is no fertility reduction in infectives, $q_j = 1$ and no vertical transmission, $p_j = 0$, for all j . Assume that, for some $j < n$, $\mathcal{R}_n^\circ < \mathcal{R}_j^\circ$ and*

$$\frac{1}{\mathcal{R}_j^\circ} - \frac{1}{\mathcal{R}_n^\circ} + \left(\frac{1}{\eta_n} - \frac{1}{\eta_j} \right) \bar{\alpha} \left[1 - \frac{\beta}{\bar{\zeta}} \right]_+ < 0,$$

where $\bar{\alpha} = \max_{k=1}^n \alpha_k$. Then $\frac{I_n(t)}{N(t)} \rightarrow 0$ as $t \rightarrow \infty$.

1.6.2 Selection for low disease fatality under high disease prevalence

In order to see what competition selects for if disease prevalence is high, we choose $\xi_j = 1 = \xi_n$ in (1.20). High disease prevalence ($> 80\%$) has been observed in the Arizona grass *Festuca arizonica* for the endophytic fungus *Neotyphodium* [81]. By (1.21),

$$\frac{z'}{z} = (1 - v)(\eta_n - \eta_j) + a_j - a_n.$$

We define $v_\infty = \liminf_{t \rightarrow \infty} v(t)$.

Proposition 6. *Let there exist some $j < n$ such that $a_j < a_n$ and $a_j - a_n + (1 - v_\infty)(\eta_n - \eta_j) < 0$. Then $\frac{I_n(t)}{N(t)} \rightarrow 0$ as $t \rightarrow \infty$.*

If disease prevalence is high for large times, i.e., v_∞ is close to 1, differences in a_j matter much more than differences in η_j for the assumption in this proposition.

Proof. First assume that $\eta_n \leq \eta_j$. Then $\frac{z'}{z} \leq a_j - a_n < 0$. Now assume that $\eta_n > \eta_j$. Then

$$\limsup_{t \rightarrow \infty} \frac{z'}{z} \leq a_j - a_n + (1 - v_\infty)(\eta_n - \eta_j) < 0.$$

In either case, $z(t) \rightarrow 0$ as $t \rightarrow \infty$ and so $v_n(t) \leq z(t)^{1/\xi_n} \rightarrow 0$ as $t \rightarrow \infty$.

We show that the disease prevalence is high if there is no recovery from the disease and both horizontal and vertical transmission are strong. This has been numerically demonstrated for mass action incidence [68]; in the mathematically easier case of standard incidence, it is possible to provide qualitative estimates.

Proposition 7. *Let $\mathcal{R}_j^\circ > 1$ and $\gamma_j = 0$ for $j = 1, \dots, n$. Then*

$$1 - v_\infty \leq \beta \frac{\psi^*}{\phi_* + \beta \psi^*},$$

where

$$\phi_* = \min_{j=1}^n (\eta_j - \alpha_j - \beta(1 - q_j p_j)) > 0$$

and

$$\psi^* = \max_{j=1}^n q_j(1 - p_j).$$

Proof. By (1.7),

$$v' = (1 - v) \sum_{j=1}^n \eta_j v_j - \sum_{j=1}^n a_j v_j + v \sum_{j=1}^n b_j v_j.$$

By (1.6), since $\gamma_j = 0$,

$$v' = (1 - v) \sum_{j=1}^n (\eta_j - \alpha_j - \beta(1 - q_j p_j)) v_j - v \beta \sum_{j=1}^n q_j (1 - p_j) v_j.$$

Since $\mathcal{R}_j^\circ > 1$ for all j , $\phi_* > 0$ and

$$v' \geq \phi_* (1 - v) v - \beta \psi^* v^2.$$

This implies that $v_\infty \geq \frac{\phi_*}{\phi_* + \beta \psi^*}$ and the assertion follows.

If both horizontal and vertical transmission are high for all strains, competition essentially selects for some combination of the smallest disease fatality, the highest vertical transmission rate and the lowest fertility reduction. The latter two may conflict with each other, as the vertical infection of offspring may go along with a decrease of its vitality.

Proposition 8. *Let $\gamma_j = 0$ and $\mathcal{R}_j^\circ > 1$ for $j = 1, \dots, n$. Assume that there exists some $j \in \{2, \dots, n\}$ such that $\alpha_j < \alpha_n$ and*

$$\alpha_j - \alpha_n + \beta \left(\frac{(\eta_n - \eta_j) \psi^*}{\phi_* + \beta \psi^*} + q_n p_n - q_j p_j \right) < 0,$$

with ϕ_ and ψ^* as in Proposition 7. Then $\frac{I_n(t)}{N(t)} \rightarrow 0$ as $t \rightarrow \infty$.*

We can rewrite the condition in Proposition 8 as

$$\alpha_j + \beta(1 - q_j p_j) - (\alpha_n + \beta(1 - q_n p_n)) + (\eta_n - \eta_j) \frac{\beta \psi^*}{\phi_* + \beta \psi^*} < 0,$$

which shows that, for the formula (1.19) for the net replacement ratio, strain competition selects much more strongly for a small denominator than for a large numerator.

We must caution, though, that this result holds under the assumption that no one recovers from the disease and that all competing strains have a net replacement ratio above 1. If recovery is incorporated into the model, it becomes much harder to estimate the disease prevalence, and typically two types of conditions rather than one need to be made for one strain to outcompete another [2].

1.6.3 Persistence of protective subthreshold strains

A subthreshold strain (whose net replacement ratio is smaller than one) dies out, if it is the only strain circulating in the population. Can it possibly persist if it protects against a more virulent superthreshold strain? This surprising phenomenon has been observed in numerical simulations for mass action incidence [69]; in the mathematically easier case of standard incidence, it is possible to give precise qualitative conditions for its occurrence.

By (1.17), at most two strains can coexist at equilibrium, except for exceptional values which form a set of measure 0. While this does not necessarily imply that all but two strains die out in proportion, we restrict the forthcoming analysis to two strains.

One-strain equilibria

We assume that the first strain, which is a superthreshold strain, is at equilibrium with no other strain being present,

$$\begin{aligned} v_1^\diamond &= \frac{\eta_1 - a_1}{\eta_1 - b_1}, \\ \eta_1 &> a_1 > b_1, \\ v_2^\diamond &= 0. \end{aligned} \tag{1.22}$$

At this equilibrium, the equation for the second strain becomes

$$\frac{v_2'}{v_2} = (1 - v_1^\diamond)\eta_2 - a_2 + b_1 v_1^\diamond > 0.$$

This shows that the second strain (sub- or super-threshold) can invade if and only if

$$\eta_2 - a_2 > v_1^\diamond(\eta_2 - b_1).$$

In general, an invading strain does not necessarily persist [73]; but since we have a planar system and no multiple boundary equilibria, it follows from standard persistence theory as we have used it earlier that the second strain is uniformly strongly persistent. If the second strain dies out when left on its own, then both strains coexist.

Theorem 6. *Let the number of circulating parasite strains be $n = 2$. If $\eta_2 - a_2 > v_1^\diamond(\eta_2 - b_1) > 0$, the second strain is strongly uniformly persistent: there exists some $\epsilon > 0$ such that $\liminf_{t \rightarrow \infty} v_2(t) > 0$ whenever $v_2(0) > 0$, with the eventual lower bound ϵ being independent of the initial data. If $\mathcal{R}_2^\circ < 1 < \mathcal{R}_1^\circ$, then both strains are strongly uniformly persistent in this sense.*

In order to illustrate that the conditions of Theorem 6 are feasible we consider the extreme case that the second strain transmits vertically only, i.e., $\eta_2 = 0 = \mathcal{R}_2^\circ$. The condition above takes the form

$$b_1 v_1^\diamond > a_2,$$

which implies that $a_1 > b_1 > a_2 \geq b_2$ (because $v_1^\circ \in (0, 1)$) and is equivalent to

$$\frac{a_2}{b_1} < \frac{\eta_1 - a_1}{\eta_1 - b_1}.$$

We recall the definitions of a_j and b_j and find the following condition for the uniform strong persistence of both strains,

$$\frac{\alpha_2 + \gamma_2 + \beta(1 - q_2 p_2)}{\alpha_1 + \beta(1 - q_1)} < \frac{\eta_1 - (\alpha_1 + \gamma_1 + \beta(1 - q_1 p_1))}{\eta_1 - (\alpha_1 + \beta(1 - q_1))},$$

with both numerator and denominator of the second fraction being positive. The left hand side of this inequality can be brought close to 0, if there is no recovery from strain 2, $\gamma_2 = 0$, the vertical transmission of the second strain is almost perfect, p_2 close to 1, and the virulence of the second strain is sufficiently less than that of the first strain, in particular $\alpha_2 \ll \alpha_1$ and $q_2 \ll q_1$. The right hand side of the inequality can be brought close to 1, if at least one of the following holds:

- ◇ there is no recovery from the first strain as well, $\gamma_1 = 0$, and the vertical transmission of the first strain is also almost perfect,
- or
- ◇ the per capita transmission rate of strain 1, η_1 , is large enough.

1.7 Discussion

Emerging and re-emerging infectious diseases [45, 38] have led to a renewed interest in host-parasite systems, and their mathematical modeling [9, 10, 19, 20, 34, 33, 53, 78, 86] (see the bibliographic remarks in [86, Chap. 17] for more references). The fact that not only humans and their food sources (domestic animals and agronomic plants), but also natural animal and plant populations are afflicted, has also directed attention to the fascinating role of parasites in ecosystems [48, 55, 75, 52].

In this paper, we revisit the question of competition between several parasite strains for one host and the evolution of virulence. In particular, we investigate the validity of the often made hypothesis that the strain with maximal replacement ratio outcompetes the other strains. This hypothesis has been the starting point for investigating whether evolution would lead to low, intermediate, or high virulence of the parasite. From a host perspective (which we adopt here), virulence is the degree by which the parasite lowers the basic reproduction ratio of the host by increasing the host mortality and morbidity and/or reducing the host fertility.

For mathematical managability, we assume that infection with one strain infers complete protection against other strains during the infection and complete immunity and cross-immunity during the recovery period (if there is one). We first extend the known result that the principle of maximizing the

basic replacement ratio, $\mathcal{R}^\circ$, holds for host populations which, in the absence of the disease, are exclusively regulated by a nonlinear birth rate. In view of the discussion as to whether mass action, standard or some interpolating form of incidence are appropriate (see [53, Sec. 2.1] for a discussion and references) and the big differences that they can make for the dynamics of the disease [46], we emphasize that this result holds for all forms of incidence provided that transmission is only horizontal. Its proof does no longer work when a latent period or the release of long-living propagules [39, 29] is added to the model. For short-living propagules the result can be salvaged by a quasi-steady state approach. The shifts in virulence evolution produced by a change of hygiene in diseases with both direct and propagule transmission may be even more dramatic as previously thought [39, 29].

If vertical transmission is added [69] to the model, coexistence of different strains becomes possible, and strains with lower $\mathcal{R}^\circ$ can outcompete strains with higher $\mathcal{R}^\circ$. The simulations which show this result have been performed for mass action incidence [69], but presumably coexistence may occur for standard incidence as well (see below).

The principle of $\mathcal{R}^\circ$ maximization still holds if both the population birth rate and the population death rate are linear, but the exponential growth rate of the host population (without the disease) is low enough that the disease can limit population growth. Further the incidence is assumed to be of mass action type and immunity nonexistent. If the concept of $\mathcal{R}^\circ$ is appropriately extended, vertical transmission can be included.

If host population growth is limited by a nonlinear mortality rate, coexistence of different strains is possible [1, 6] under mass action incidence, but it is not clear whether strains with low $\mathcal{R}^\circ$ can outcompete strains with higher $\mathcal{R}^\circ$. We show that both phenomena are possible if standard incidence is assumed and $\mathcal{R}^\circ$ is interpreted as net replacement ratio: if both horizontal and vertical transmission are high for all circulating strains (in particular if they all have $\mathcal{R}^\circ > 1$) and if there is no disease recovery (resulting in high disease prevalence), competition selects for a combination of low disease fatality, high vertical transmissibility, and low fertility reduction (with the latter two possibly conflicting with each other) rather than for a large net replacement ratio.

If the per capita birth rate, β , is large enough to cause low disease prevalence (the disease can hardly keep pace with a fast population turnover), $\mathcal{R}^\circ$ maximization holds *cum grano salis*, i.e., strains are selected which are close to maximal net replacement ratio. Otherwise, coexistence of different strains can occur, even to the degree that a strain with exclusive but incomplete vertical transmission which would go extinct on its own can persist by protecting against a more virulent strain which also transmits horizontally. More generally, a subthreshold strain with little virulence can coexist with a highly virulent superthreshold strain by providing protection against it. This surprising phenomenon has already been observed in simulations for mass action incidence [69], but in the mathematically easier case of standard incidence it

is possible to give precise conditions under which it occurs. A vertically transmitted parasite with no apparent horizontal transmission is the endophytic fungus *Neotyphodium* in the Arizona grass *Festuca arizonica*. So far, the persistence of this endophyte is a mystery, because its vertical transmission is not perfect and no competitive advantages have been found that it might give to infected plants [41, 40, 42]. Protection against a more virulent strain or a more virulent other parasite would be a possible explanation, but a candidate has been elusive so far. Persistence of subthreshold strains (whose basic replacement ratio is smaller than one) is also possible by a mechanism opposite to protection where the subthreshold strain can infect individuals which have recovered from infection by a superthreshold strain [74].

1.8 Appendix

We prove Proposition 3: *Let $\mathcal{R}_1^{-1} < \mathcal{R}_j^{-1}$ for all $j = 2, \dots, n$. Then the first strain uniformly strongly persists, i.e., there exists some $\epsilon > 0$ such that $\liminf_{t \rightarrow \infty} I_1(t) \geq \epsilon$ for all solutions with $I_1(0) > 0$.*

Proof. By Proposition 2, there exists some $\epsilon_0 > 0$ such that

$$\liminf_{t \rightarrow \infty} N(t) > \epsilon_0$$

for all solutions of (1.9) with $N(0) > 0$. Since $\beta > \mu$ by assumption, we can choose $\epsilon > 0$ small enough that

$$(\beta - \mu)\epsilon_0 - (\alpha_1 + \beta(1 - q_1))\epsilon > 0.$$

Assume that

$$\limsup_{t \rightarrow \infty} I_1(t) < \epsilon.$$

By (1.14), $I_j(t) \rightarrow 0$ as $t \rightarrow \infty$ for $j = 2, \dots, n$. By the first equation in (1.9), $\liminf_{t \rightarrow \infty} N'(t) > 0$. This implies $N(t) \rightarrow \infty$ as $t \rightarrow \infty$. By the equation for I_1 in (1.9), $\frac{I_1'(t)}{I_1(t)} \rightarrow \infty$ as $t \rightarrow \infty$ and so $I_1(t) \rightarrow \infty$ as $t \rightarrow \infty$. This contradiction shows that $\limsup_{t \rightarrow \infty} I_1(t) \geq \epsilon$ for every solution with $I_1(0) > 0$. We apply [85, Thm. 6.2]. We identify the state space

$$X = \left\{ (N, I_1, \dots, I_n) \in \mathbb{R}_+^{n+1}, I_j \geq 0, \sum_{j=1}^n I_j \leq N \right\}$$

and the semiflow Φ induced by the solutions of (1.9) on X . We set $X_1 = \{(N, I_1, \dots, I_n) \in X; I_1 > 0\}$ and $X_2 = \{(N, I_1, \dots, I_n) \in X; I_1 = 0\}$. Then X is the disjoint union of X_1 and X_2 , X_2 is closed in X and X_1 is open in X , and Φ is a continuous semiflow on X_1 . By (1.14), $\frac{I_j(t)}{[I_1(t)]^{n_j/n_1}} \rightarrow 0$ as $t \rightarrow \infty$. To satisfy [85, Ass. 6.1] we choose

$$Y_1 = \{(N, I_1, \dots, I_n) \in X_1; I_j \leq I_1^{\eta_j/\eta_1}, j = 2, \dots, n\}.$$

Then part (A) is satisfied. Parts (C_{6.1}), and (C_{6.2}) are trivially satisfied because every bounded set in $\mathbb{R}^{n+1}$ has compact closure. The following is a stronger version of part (R) of the Assumptions:

($\tilde{\mathbf{R}}$) For any sufficiently $\epsilon > 0$ there are a bounded subset D of X_1 and some $\delta \in (0, \epsilon)$ and time $t > 0$ with the following properties:

- (i) There is no element $x \in Y_1 \setminus D$ such that $d(x, X_2) = \epsilon$ and $d(\Phi_s(x), X_2) < \epsilon$ for all $s \in (0, t]$.
- (ii) If $x \in Y_1 \setminus D$ and $r \in (0, t]$ is such that $d(x, X_2) = \epsilon = d(\Phi_r(x), X_2)$ and $d(\Phi_s(x), X_2) < \epsilon$ for all $0 < s < r$, then $d(\Phi_s(x), X_2) \geq \delta$ for all $0 \leq s \leq r$.
- (iii) $D \cap Y_1$ is bounded.

Notice that $d(x, X_2) = I_1$ for $x = (N, I_1, \dots, I_n)$. Let $\epsilon \in (0, 1]$. Let $t = 1$ and $\delta = \epsilon/2$. We choose $N_\epsilon > 0$ sufficiently large that

$$(\beta - \mu)N_\epsilon - (\alpha_1 + \beta(1 - q_1))\epsilon - \sum_{j=2}^n (\alpha_j + \beta(1 - q_j))\epsilon^{\eta_j/\eta_1} > 0$$

and

$$N_\epsilon - \epsilon - \sum_{j=2}^n \epsilon^{\eta_j/\eta_1} - \sum_{j=1}^n \frac{1}{\mathcal{R}_j^\circ} > 0$$

and $D = \{(N, I_1, \dots, I_n) \in X_1; N \leq N_\epsilon\}$. Then D is bounded and (iii) is satisfied. Suppose that $x \in Y_1 \setminus D$ such that $d(x, X_2) = \epsilon$. Let $(N(s), I_1(s), \dots, I_n(s)) = \Phi_s(x)$. Then $N(0) > N_\epsilon$, $I_1(0) = \epsilon$ and $I_j(0) \leq \epsilon^{\eta_j/\eta_1}$ for $j = 2, \dots, n$. By choice of N_ϵ and the differential equation for I_1 in (1.9), $I_1'(0) > 0$ and $d(\Phi_s(x), X_2) = I_1(s) > I_1(0) = \epsilon$ for some $s \in [0, t]$. So (i) is satisfied.

Assume that $x \in Y_1 \setminus D$ and that $\Phi_s(x) \in Y_1$ for all $s \geq 0$. Again this implies $N(0) > N_\epsilon$. Further let $0 < r$ such that $d(x, X_2) = \epsilon = d(\Phi_r(x), X_2)$ and $d(x, \Phi_s(x)) \leq \epsilon$ for all $s \in [0, r]$. Then $I_1(s) \leq \epsilon$ for all $s \in [0, r]$ and $I_j(s) \leq \epsilon^{\eta_j/\eta_1}$. By (1.9) and our choice of N_ϵ and by $N(0) > N_\epsilon$, $N(s) \geq N_\epsilon$ for all $s \in [0, r]$ and $I_1(s) \geq I_1(0) = \epsilon$. So part (ii) is trivially satisfied. By [85, Thm. 6.2], X_2 is a uniform strong repeller for X_1 . By our choice of X_1 and X_2 , this translates into the strong persistence of the first strain.

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