Optimal Timing of Disease Transmission in an Age-Structured Population

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Abstract

It is a common medical folk-practice for parents to encourage their children to contract certain infectious diseases while they are young. This folk-practice is controversial, in part because it contradicts the long-term public health goal of minimizing disease incidence. We study an epidemiological model of infectious disease in an age-structured population where virulence is age-dependent and show that, in some cases, the optimal behavior will *increase* disease transmission. This provides a rigorous justification of the concept of "endemic stability", and demonstrates that folk-practices may have been historically justified.

1 Introduction

The transmission rate of a disease is a product of the rate at which susceptible individuals come into contact with infectious individuals and the probability of transmission during a contact. The transmission probability during a contact is primarily determined by the mode of transmission. The contact rate depends on the behaviors of infected, susceptible, and sometimes intermediary individuals. Cases like that of Mary Mallon, "Typhoid Mary", show how an infected individual's behavior can greatly increase a contact rate (Leavitt, 1997). A disease like rabies can cause behavior changes in infected individuals that increase the contact rate (Murray, 1993). The contact rates of sexually transmitted diseases are heavily influenced by the behaviors of susceptible individuals. In hospitals, contact rates for some diseases are strongly influenced by the hand-hygiene practices of doctors (Grundmann *et al.*, 2002). Del Valle *et al.* (2005) have shown that behavioral changes can effectively reduce the severity of a smallpox outbreak.

Given that individuals have some control over their contact rates, should they choose behaviors that increase it or decrease it? At first glance, this appears to be a trivial question. Illness is bad, so people should behave to lower their contact rates and avoid infection. However, in some cases it might be better to accept a mild sickness today to avoid a severe illness in the future. We will show that such trade-offs can arise when disease virulence is age-dependent. If the morbidity or mortality of a disease is positively correlated to age of infection, incremental reductions in transmission can increase the risks and costs associated with infection.

This problem was pointed out by (Coleman *et al.*, 2001) and may be relevant to numerous diseases. To explore in greater detail the relationship between age-dependent virulence and behavior choices that affect transmission, we pose a population game based on a compartmental SIR model that divides the population based on their susceptible, infected or recovered (and immune) status. We then present a model of transmission in a host population with two age classes, and show that both high and low transmission rates can be Nash equilibria of individual utility, depending on the contact

rate's plasticity. One Nash equilibrium minimizing transmission exists in cases where virulence in juveniles is higher than virulence in adults but two Nash equilibria can coexist under conditions of reduced virulence in juveniles. When virulence in juveniles is less than that in adults, one of these equilibria will exist at the maximum allowed transmission rate, at which most individuals are infected as juveniles and avoid infection as adults. The results show that there are situations where the optimal behaviors of individuals facilitate the transmission of a disease.

2 Model

Our goal is to determine optimal behavior for an individual in a population where everybody else is also pursuing optimal behavior. We will pose this problem as a population game. The idea is to simultaneously model the problem at the scales of both the population and the individual. At the population scale, the dynamics of the population's state vector $\mathbf{n}$ are described by a system of differential equations

$$\frac{\mathrm{d}\mathbf{n}}{\mathrm{d}t} = \mathbf{G}\left(\mathbf{n}, \overline{\pi}\right) \tag{1}$$

that depend on the average behavior $\overline{\pi}$ of individuals in the population. At the individual-scale, the stochastic dynamics of the state of an individual are described by a continuous-time Markov process

$$\frac{\mathrm{d}\mathbf{p}}{\mathrm{d}t} = \mathbf{Q}\left(\mathbf{n}, \pi\right)\mathbf{p}, \tag{2}$$

where $\mathbf{p}$ is a probability distribution over possible states and $\mathbf{Q}$ is a transition-rate matrix that depends on the population's state $\mathbf{n}$ and the individual's behavior π. Using Eq. (1), we can determine the equilibrium-state $\mathbf{n}^*(\overline{\pi})$ of the population as a function of the average behavior $\overline{\pi}$. Markov decision process theory (Howard, 1960) then tells us that the expected lifetime utility U of a behavior π to an individual is given by

$$U(\pi; \overline{\pi}) = \mathbf{v}^{\mathrm{T}}\left[\delta\mathbf{I} - \mathbf{Q}(\mathbf{n}^*(\overline{\pi}), \pi)\right]^{-1}\mathbf{p}(0), \tag{3}$$

where $\mathbf{p}(0)$ is the initial probability distribution for an individual's state, $\mathbf{v}$ is the expected utility gain per unit time for each state, and δ is the discounting rate of future returns. Here we take the discount rate to be the population's proliferation rate Reluga *et al.* (2007). Details of the general theory are described in Appendix A.

We first construct a population-scale model of an infectious disease with age-dependent virulence. Consider a population subdivided into juvenile (denoted by subscript j) and adult (subscript a) age classes. Within each age class, individuals may be susceptible (S_{j} and S_{a}), infected (I_{j} and I_{a}), or immune (R_{j} and R_{a}). Individuals transition among these six states through the processes of aging, death, birth, infection, and recovery (see Figure 1). Individuals age from juvenile to adult at rate f, while adults die at rate d_{a}, juveniles die at rate d_{j}, and susceptible juveniles are produced by healthy adults at rate r. To maintain as simple a model as possible, we have chosen a formulation of transmission with proportional mixing and standard incidence where

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contact rates are independent of age class. At the population scale, the transmission rate β depends on the resident population's behavior $\bar{\pi}$. The duration of infection is exponentially distributed with expectation $1/\gamma$. A fraction k_j of infected juveniles die and a fraction k_a of infected adults die; the remaining fractions, $1 - k_j$ and $1 - k_a$ survive infection and have life-long immunity against reinfection. Mathematically,

$$\dot{S}_j = (-f - d_j) S_j + r (S_a + R_a) - \lambda S_j, \tag{4a}$$

$$\dot{I}_j = (-f - d_j) I_j + \lambda S_j - \gamma I_j, \tag{4b}$$

$$\dot{R}_j = (-f - d_j) R_j + (1 - k_j) \gamma I_j, \tag{4c}$$

$$\dot{S}_a = f S_j - d_a S_a - \lambda S_a, \tag{4d}$$

$$\dot{I}_a = f I_j - d_a I_a + \lambda S_a - \gamma I_a, \tag{4e}$$

$$\dot{R}_a = f R_j - d_a R_a + (1 - k_a) \gamma I_a, \tag{4f}$$

where the force of infection

$$\lambda = \beta(\bar{\pi}) \frac{I_j + I_a}{N}, \tag{4g}$$

and

$$N = S_j + I_j + R_j + S_a + I_a + R_a \tag{4h}$$

is the population size.

The system of ordinary differential equations in Eq. (4) is homogeneous; the rate of change in the state variables is proportional to the population size. In homogeneous systems, solutions may grow without bound or decay toward zero depending on initial conditions and parameter values (Hadeler *et al.*, 1988; Hadeler, 1992). Homogeneous models are a reasonable approximation to the dynamics of human populations that exhibit sustained growth.

For System (4), there are two densities

$$\mathbf{n}^* = \left[S_j^*, I_j^*, R_j^*, S_a^*, I_a^*, R_a^* \right] \tag{5}$$

with

$$S_j^* + I_j^* + R_j^* + S_a^* + I_a^* + R_a^* = 1 \tag{6}$$

describing homogeneous solutions of the form $\mathbf{n}^* N(0) e^{\delta t}$: a disease-free density $\mathbf{n}_{\text{DF}}^*$ in which there are no infected or resistant individuals, and an endemic density $\mathbf{n}_{\text{E}}^*$ in which there are both infected and resistant individuals (Busenberg and van den Driessche, 1990). For humans, the disease-free density corresponds to a growing population, but is only stable against the introduction of infection when the basic reproduction number of disease

$$\mathcal{R}_0 = \frac{\beta(\bar{\pi}) \left[(\gamma + f) \left(S_j^* + S_a^* \right) + d_j S_a^* + d_a S_j^* \right]}{(\gamma + f + d_j)(\gamma + d_a)} < 1. \tag{7}$$
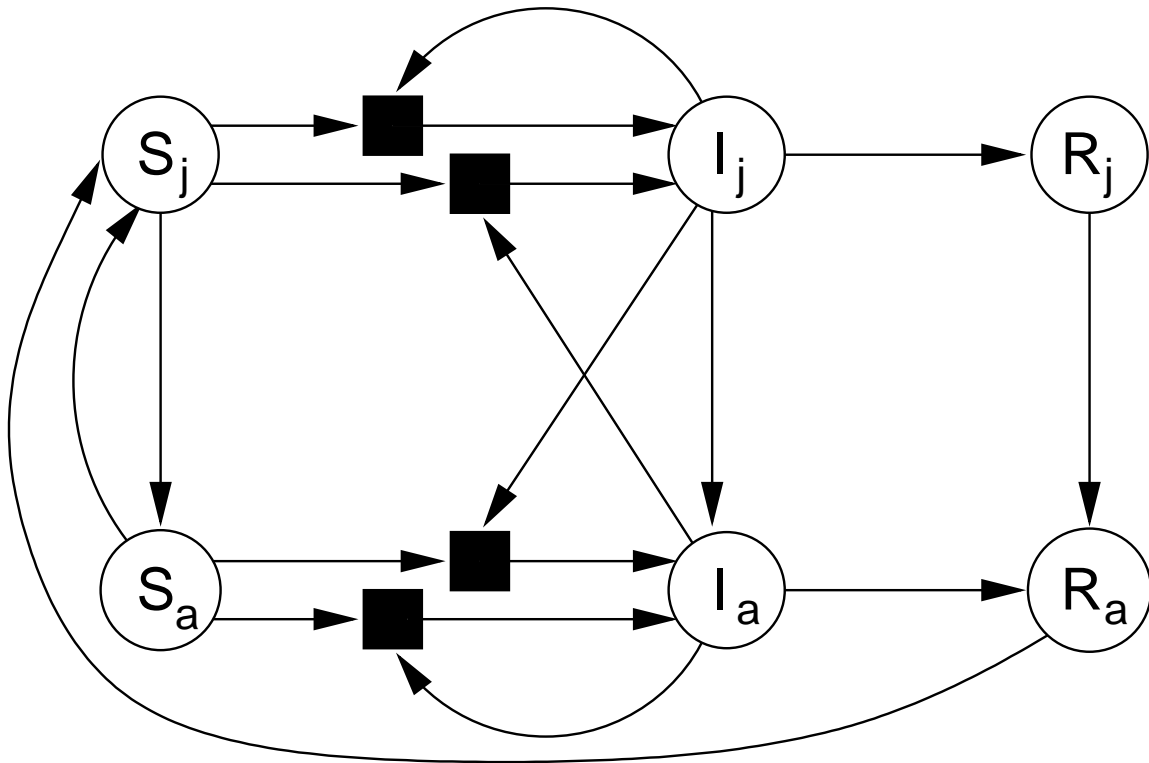
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Figure 1: A hypergraph representation of the reactions that compose Eq. (4). All transition steps are linear except for the transmission process, which requires the interaction of susceptible and infected individuals.

$\mathcal{R}_0$ is the expected number of new infections generated per infection in a naive population (Anderson and May, 1991). When $\mathcal{R}_0 > 1$, the disease-free density is unstable and the endemic density appears to be stable in numerical simulations. The value for $\mathcal{R}_0$ was calculated using the methods described by van den Driessche and Watmough (2002), but the approximation $\mathcal{R}_0 \approx \beta(\overline{\pi})/\gamma$ is a good approximation when the time scales of aging and death are much longer than the time scales of infection. The endemic density has a population proliferation rate δ_E that is slower than that of the disease-free proliferation rate δ_DF due to disease-induced death and transient infertility. In cases of high transmissibility and low survival rates, population size may decline.

Along with the population-scale model in System (4), there is an individual-scale Markov model for the state-dynamics of an individual where the transition rates depend on the individual's behavior. All individuals enter the population in the susceptible juvenile state, so their initial state is given by

$$\mathbf{p}(0) = [1, 0, 0, 0, 0, 0]^\mathrm{T}, \tag{8}$$

and the transition rates between life-history states are static, given by

$$\mathbf{Q}(\mathbf{n}^*, \pi) = \begin{bmatrix} -f - d_\mathrm{j} - \lambda^* & 0 & 0 & 0 & 0 & 0 \\ \lambda^* & -f - d_\mathrm{j} - \gamma & 0 & 0 & 0 & 0 \\ 0 & (1 - k_\mathrm{j})\gamma & -f - d_\mathrm{j} & 0 & 0 & 0 \\ f & 0 & 0 & -d_\mathrm{a} - \lambda^* & 0 & 0 \\ 0 & f & 0 & \lambda^* & -d_\mathrm{a} - \gamma & 0 \\ 0 & 0 & f & 0 & (1 - k_\mathrm{a})\gamma & -d_\mathrm{a} \end{bmatrix}, \tag{9a}$$

where

$$\lambda^* = \beta(\pi)\left(I_\mathrm{j}^* + I_\mathrm{a}^*\right) \tag{9b}$$

and π is the individual's behavior. The life-history dynamics of an individual with an invading behavior are similar to the life-history dynamics of an individual with the resident behavior, except that the invading behavior π alters that individual's risk of contracting disease. The term $\beta(\pi)$ can be interpreted as both the transmission rate and the acquisition rate of disease, since transmission by one individual corresponds to acquisition by another.

Finally, we specify the instantaneous utility gains of each state. The healthy adult states S_a and R_a have equal utility gains. Neither juvenile nor infected states have any instantaneous utility gain. To normalize utility, we measure it in terms of reproductive rate, so the vector of state-dependent utility gains is

$$\mathbf{v}^\mathrm{T} = [0, 0, 0, r, 0, r]. \tag{10}$$

This model supplies the information needed to calculate utility using Eq. (3).

Unless otherwise specified, we use the following parameter values, scaled to adult death rate, for simulations and figures: $r = 2$, $f = 4$, $d_\mathrm{j} = 0$, $d_\mathrm{a} = 1$, $\gamma = 1000$, $k_\mathrm{j} = 0.01$, and $k_\mathrm{a} = 0.8$. The value of γ is relatively large because the duration of infection is usually very short compared to the expected lifetime of an individual.
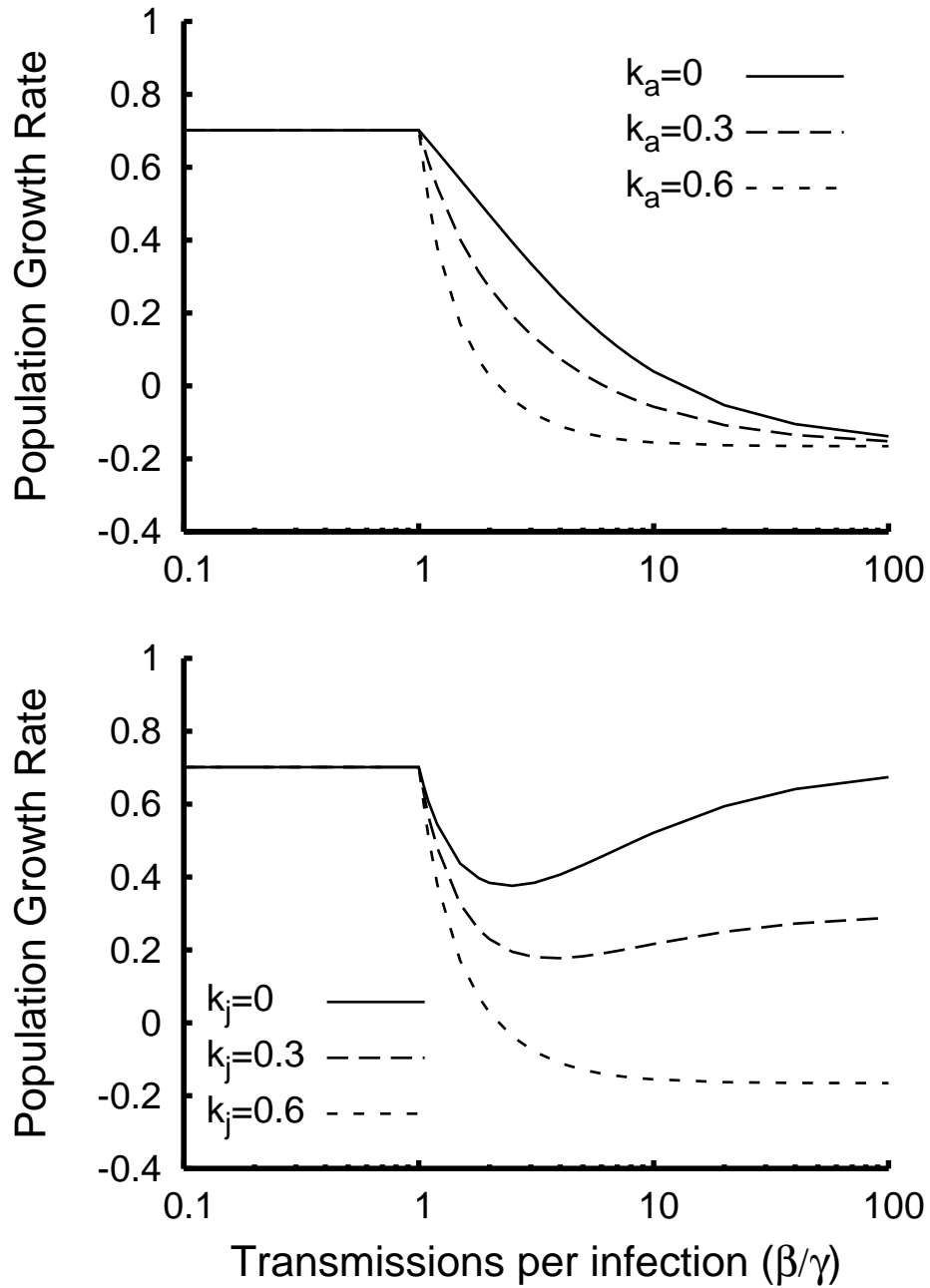
Figure 2: Proliferation rate $\delta(\overline{\pi})$ of the population, depending on the transmission rate and virulence of disease. In cases where infection has higher virulence in juveniles than adults (top), behaviors that increase transmission will always slow population proliferation. But in cases where infection has higher virulence in adults (bottom), intermediate transmission rates slow proliferation the most. $k_{\mathrm{j}} = 0.6 \geq k_{\mathrm{a}}$ (top) and $k_{\mathrm{a}} = 0.6 \geq k_{\mathrm{j}}$ (bottom).

3 Results

As seen in Figure 2, the asymptotic proliferation rate $\delta(\overline{\pi})$ of the population depends on both the transmission rate and the virulence of disease. If virulence in juveniles is greater than virulence in adults, then populations grow fastest when the basic reproduction number of disease $\mathcal{R}_0 \approx \beta/\gamma < 1$. Increased transmission erodes population proliferation. If virulence in juveniles is less than virulence in adults, then the fastest growing populations are still those for which $\mathcal{R}_0 < 1$ but behaviors that increase transmission may increase the population proliferation rate, depending on the resident population's behavior prior to the initial introduction of the disease.

However, the asymptotic proliferation rate is a measure of population success, not individual success. Local maxima in the proliferation rate may be unstable to invasion by individuals with alternative behaviors. Exploration of the stability of behaviors against invasion leads to the concept of a Nash equilibrium. Consider a large (effectively infinite) population into which we introduce a small number of individuals with a strategy[1] that differs from the general population's resident strategy. The new strategy can "invade" the population if it has greater utility than the resident strategy (Maynard Smith, 1982). A resident strategy is a Nash equilibrium if no alternative strategy has greater utility than the resident strategy (Hofbauer and Sigmund, 1998). Mathematically, the population is at Nash equilibrium against alternative strategies π if

$$U(\overline{\pi}; \overline{\pi}) \geq U(\pi; \overline{\pi}). \tag{11}$$

The resident strategy $\overline{\pi}$ is a strict Nash equilibrium if condition (11) is a strict inequality for all strategies $\pi \neq \overline{\pi}$ (McNamara *et al.*, 2001). This last requirement is stricter than the standard conditions of an evolutionarily stable strategy (ESS) (Maynard Smith, 1982), but will be sufficient for our exploration since a strict Nash equilibrium is always an ESS (Hofbauer and Sigmund, 1998).

To find the stable optimal behaviors in the population, we consider the case where an invader's transmission rate, $\beta(\pi)$, deviates from the resident transmission rate, $\beta(\overline{\pi})$, and determine the strict Nash equilibria of Eq. (3). Let us assume that transmission rates can range between $\beta_{\min}$ and $\beta_{\max}$, depending on the behavior. Individuals with the resident behavior always have neutral utility ($U(\overline{\pi}; \overline{\pi}) = 1$). Suppose the virulence in juveniles is less than the virulence in adults. From the invasibility plot in Figure 3A, we see that if $\beta_{\min} < \gamma$, every behavior π^* with $\beta(\pi^*) \in [\beta_{\min}, \gamma]$ is a Nash equilibrium. If $\beta_{\min} > \gamma$ but $\beta_{\min}$ and $\beta_{\max}$ are sufficiently small, then $\beta(\pi^*) = \beta_{\min}$ is the unique pure Nash equilibrium. If $\beta_{\min}$ is sufficiently large, then $\beta(\pi^*) = \beta_{\max}$ is the unique pure Nash equilibrium. For intermediate $\beta_{\min}$, both $\beta = \beta_{\min}$ and $\beta = \beta_{\max}$ are pure-strategy Nash equilibria. When juvenile virulence is higher than adult virulence (see Figure 4), an individual's optimal behavior always minimizes his transmission rate, independent of the resident population's transmission rate $\beta(\overline{\pi})$. Thus, behaviors π^* such that $\beta(\pi^*) = \beta_{\min}$ are always Nash equilibria.

Thus, depending on a population's initial state and potential variations in transmission, there are circumstances where reduced juvenile virulence favors behaviors that increase transmission.

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[1]Population games typically use the term "strategy" which we use interchangeably with "behavior".
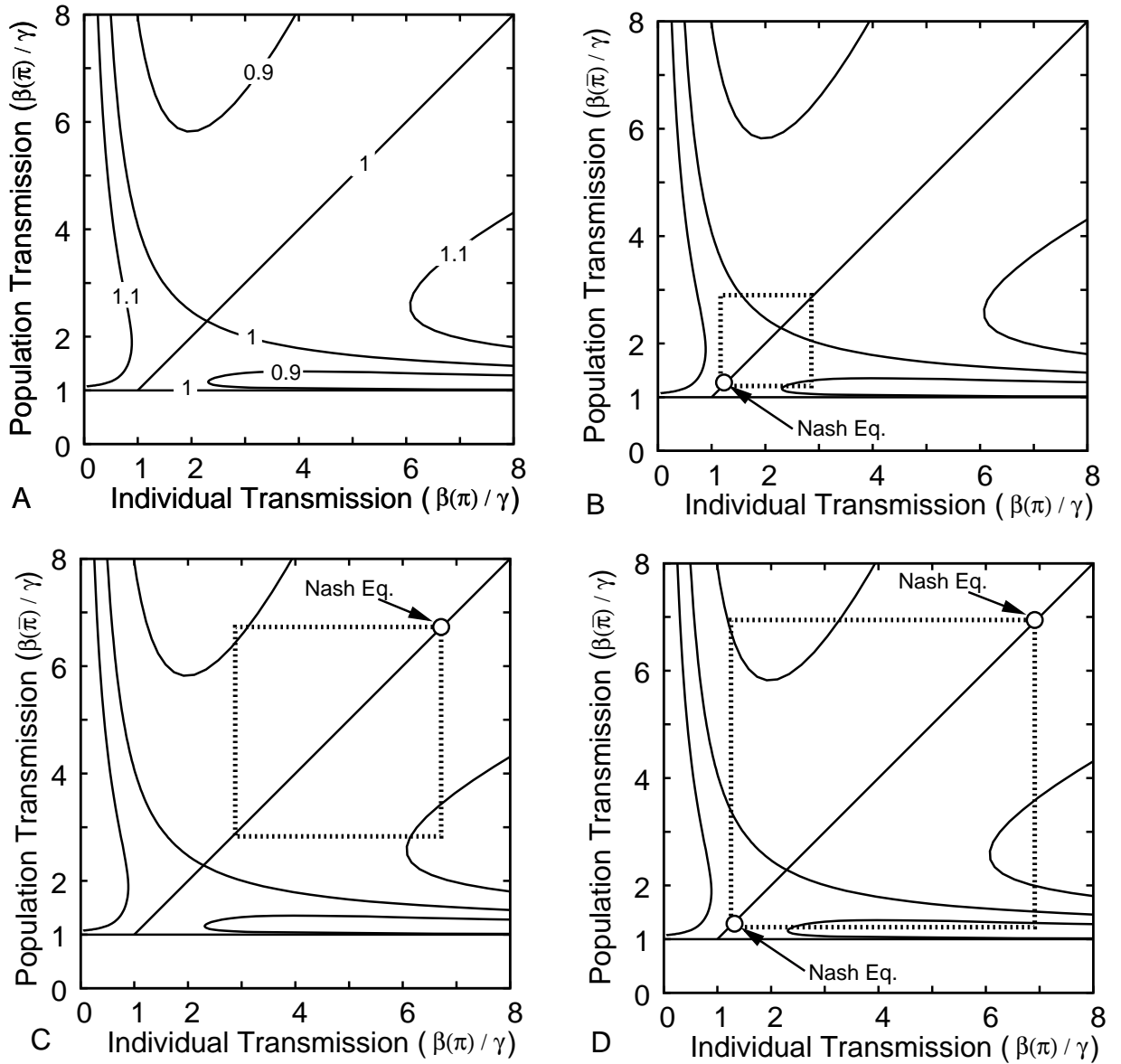
Figure 3: Pairwise invasibility plots of individual utility $U(\pi; \overline{\pi})$ when juvenile virulence is reduced. The contour levels are identical in all four plots. (A) If $\beta(\overline{\pi}) < \gamma$ (approximately), disease is transient and the utility $U = 1$ for all $\beta(\pi)$. If $\beta(\overline{\pi}) > \gamma$, the utility as a function of the individual behavior decreases from a maximum for $\beta(\pi) = 0$ to a minimum and then increases again. The unique isolated singular point is unstable. The dotted boxes in plots B, C, and D represent example boundaries $\beta_{\min}$ and $\beta_{\max}$ for feasible transmission rates. The Nash equilibria are points where the utility is maximized over $\beta(\pi)$ and $\beta(\pi) = \beta(\overline{\pi})$. Depending on the values of $\beta_{\min}$ and $\beta_{\max}$, $\beta(\overline{\pi}) = \beta_{\min}$ may be the only pure Nash equilibrium (B), $\beta(\overline{\pi}) = \beta_{\max}$ may be the only pure Nash equilibrium (C), or both may be pure Nash equilibria (D). Parameter values : $r = 2$, $f = 4$, $d_{\mathrm{j}} = 0$, $d_{\mathrm{a}} = 1$, $\gamma = 1000$, $k_{\mathrm{j}} = 0.01$, $k_{\mathrm{a}} = 0.8$.
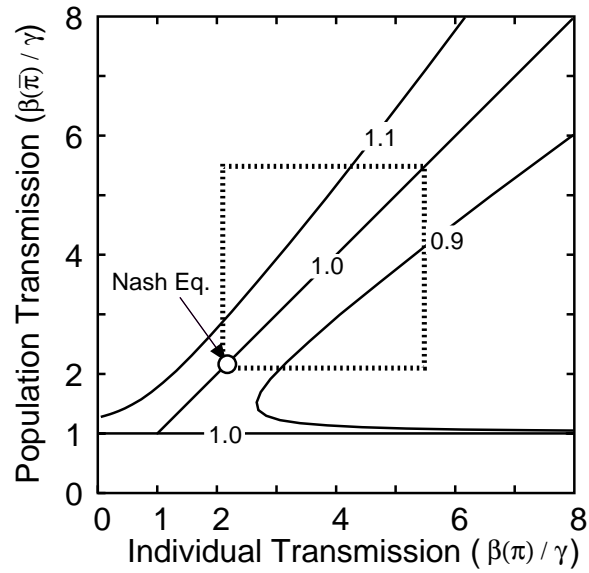
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Figure 4: Pairwise invasibility plots of individual utility $U(\pi; \overline{\pi})$ when juvenile virulence is elevated. If $\beta(\overline{\pi}) > \gamma$, the individual utility decreases monotonely from a maximum for $\beta(\pi) = 0$. If $\beta(\overline{\pi}) < \gamma$ (approximately), $U(\pi; \overline{\pi}) = 1$. The dotted box represents example boundaries $\beta_{\min}$ and $\beta_{\max}$ of feasible transmission rates. There is always a Nash equilibrium corresponding to behaviors that minimize transmission. Parameter values : $r = 2$, $f = 4$, $d_j = 0$, $d_a = 1$, $\gamma = 1000$, $k_j = 0.8$, $k_a = 0.01$.

Disease	Host	Juvenile Age	Juvenile Fatality (k_j)	Adult Fatality (k_a)	Reference
Chickenpox	Humans	< 20 years	1.4×10^{-5}	30.9×10^{-5}	Preblud (1986)
Rabbit haemorrhagic disease	Rabbits	< 8 weeks	0.6	0.9	Morisse *et al.* (1991)
Poliomyelitis	Humans	< 16 years	0.0095	0.083	Weinstein *et al.* (1952)
Rotavirus	Humans	< 5 years	0.0034	≈ 0	Parashar *et al.* (2003)

Table 1: Documented age-dependent differences in virulence, measured in terms of the case-fatality probability, for 4 diseases.

4 Discussion

Our analysis suggests that when virulence decreases with age, the optimal behaviors for individuals will minimize transmission. Conversely, when virulence increases with age, the best behaviors may minimize or maximize transmission depending on the plasticity of the contact rate.

Approximate age-dependent case-fatality probabilities for 4 diseases are shown in Table 1. Some diseases like rotavirus have elevated juvenile virulence, but a number of human and animal diseases have reduced juvenile virulence that can encourage behaviors increasing transmission (Coleman *et al.*, 2001). Classic childhood viral diseases such as mumps and chickenpox exhibit increased morbidity and mortality in older patients (Mandell *et al.*, 2005). Similarly, prior to its control through vaccination, poliomyelitis may have exhibited a higher case fatality rate in older age groups (Weinstein *et al.*, 1952; Paul, 1971), although trends in age-specific incidence are more difficult to interpret (Nathanson and Martin, 1979).

Our arguments also apply to cases where utility is measured in terms of reduced health risks during pregnancy. Rubella, erythema infectiosum, and mumps all increase fetal death rates if initially contracted during pregnancy (Mandell *et al.*, 2005). Increasing transmission beyond a certain level will decrease the probability of acquiring the infection during reproductive years, decreasing risks during pregnancy. Thus, acquisition of these diseases during childhood can be beneficial.

Humans have previously implemented behavioral solutions to problems of increased morbidity with age due to a reduction in transmission. Intentionally gathering infected and susceptible children for "chickenpox parties" reduces adult incidence (Pado, 2005). Similarly, public-health officials have recognized the danger in reducing transmission and thereby increased age of acquiring childhood diseases: in 1993 Greece experienced an epidemic of congenital rubella secondary to many years of partial vaccine coverage (Panagiotopoulos *et al.*, 1999). Consequently, the World Health Organization advises that nations consider vaccination programs that only target women of

childbearing age, or in some cases, completely forego rubella vaccination (World Health Organization, 2000). Indeed, as Anderson and May (1991) point out, contrary to the usual ideal vaccination policy from an individual's perspective, that every one but that individual be vaccinated, for rubella, the ideal policy is that no one is vaccinated except the individual in question.

Our work highlights how greater disease transmissibility may in some cases be beneficial. In the case of childhood diseases, contracting the infection early in life may carry a reduced cost, and a behavior to facilitate transmission can be stable against invasion by behaviors that reduce transmission. But many situations, both applied and theoretical, are unexplored. Further work may include a careful application to specific childhood diseases using contemporary and historical data, as well as incorporation of sociological studies of parental perceptions of disease.

Acknowledgments

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A   Methods

Here, we review one formulation of a population game, generalizing that used by van Baalen (1998). Let the vector $\mathbf{n}(t)$ be the abundances of individuals from the population in each possible life-history state and the vector $\mathbf{p}(t)$ be a probability density over the life-history state space for an individual with the invading strategy at time t. We will refer to $\mathbf{p}(t)$ as the individual-scale state since it represents the life-history state of a single individual, and we will refer to $\mathbf{n}(t)$ as the population's state because it is the total of all individuals' states. The dynamics of the population's state are governed by a system of differential equations

$$\frac{d\mathbf{n}}{dt} = \mathbf{G}\left(\mathbf{n}, \overline{\pi}\right), \tag{12}$$

while the dynamics of the individual-scale state with the invading strategy are governed by a continuous time Markov process

$$\frac{d\mathbf{p}}{dt} = \mathbf{Q}\left(\mathbf{n}, \pi\right)\mathbf{p}. \tag{13}$$

Here, $\mathbf{G}$ is a nonlinear vector-valued function and $\mathbf{Q}$ is the transition-rate matrix of the life-history process. The population-scale dynamics do not depend on the invading strategy π because the strategy is rare. In this formulation, the individual-scale dynamics only depend on the resident strategy $\overline{\pi}$ indirectly through the population's state $\mathbf{n}$, but there may be biological situations where this restriction needs to be relaxed.

Because of the complexity of utility formulation when populations and environments exhibit ongoing oscillations and disturbances (Metz *et al.*, 1992; McNamara, 1997; Brommer *et al.*, 2000), we will restrict our analysis to cases where dynamics are at equilibrium. Let $\mathbf{n}^*(\overline{\pi})$ be an equilibrium density of the population state, such that

$$\mathbf{G}(\mathbf{n}^*, \overline{\pi}) = \delta\mathbf{n}^* \tag{14}$$

where δ is the population's proliferation rate. Note that the proliferation rate δ implicitly depends on the resident strategy $\overline{\pi}$. The individual-scale dynamics will be at equilibrium if Eq. (14) is satisfied and either $\delta = 0$ or the transition matrix $\mathbf{Q}$ is a zeroth-order homogeneous function of $\mathbf{n}$ such that

$$\mathbf{Q}(e^{\delta}\mathbf{n}^*, \pi) = \mathbf{Q}(\mathbf{n}^*, \pi). \tag{15}$$

When the population state is at an equilibrium density, we can calculate the utility in a manner analogous to the optimization criteria used in economics and operations research (Arrow and Kurz, 1970). The utility of an individual with strategy π is given by the discounted reproduction number

$$U(\pi; \overline{\pi}) = \int_0^\infty e^{-\delta t}\mathbf{v}^{\mathrm{T}}\mathbf{p}(t)\,dt, \tag{16}$$

where $\mathbf{v}$ is a vector of state-dependent utility gains per unit time and δ is the population's proliferation rate. The proliferation rate δ acts to discount future reproduction relative to current returns Reluga *et al.* (2007). The individual-scale state equation can then be solved explicitly in terms of the matrix exponential and the initial state $\mathbf{p}(0)$, allowing us to calculate utility of an invading behavior.

$$U(\pi; \overline{\pi}) = \int_0^\infty \mathbf{v}^{\mathrm{T}} e^{t(\mathbf{Q}^* - \delta \mathbf{I})} \mathbf{p}(0) \, \mathrm{d}t = \mathbf{v}^{\mathrm{T}} \left[\delta \mathbf{I} - \mathbf{Q}^* \right]^{-1} \mathbf{p}(0), \tag{17}$$

with

$$\mathbf{Q}^* = \mathbf{Q}\left(\mathbf{n}^*(\overline{\pi}), \pi \right), \tag{18}$$

provided the Perron–Frobenius eigenvalue of $\mathbf{Q}^*$ is less than δ. The resident strategy always has a utility of one because it is neither an inferior or superior competitor compared to itself. Only strategies with a utility $U(\pi; \overline{\pi}) > 1$ are improvements over the resident behaviors and will increase in frequency in the population. If the resident strategy is a strict Nash equilibrium, all alternative strategies must have a utility less than one.