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**Research Article**

# Antibiotic Treatment, Duration of Infectiousness, and Disease Transmission

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## Abstract

By curing infectious individuals, antibiotic therapy must sometimes limit the spread of contagious disease among hosts. But suppose that a diseased host stops transmitting infection due either to antibiotic cure or to non-therapeutic removal (e.g., isolation or mortality). An antibiotic`s suppression of within-host pathogen growth increases the likelihood of curing a single infection and may also reduce the probability of non-therapeutic removal. If antibiotic treatment relaxes the total rate of infection removal sufficiently to extend the average duration of infectiousness, between-host transmission can increase. That is, under some conditions, curing individuals with antibiotics can impact public health negatively (more new infections). To explore this counter-intuitive, but plausible effect, this paper assumes that a deterministic within-host dynamics drives the infectious host's time-dependent probability of pathogen transmission, as well as the probabilistic duration of the infectious period.

At the within-host scale, the model varies (1) inoculum size, (2) bacterial self-regulation, (3) the time between infection and initiation of therapy, and (4) antibiotic efficacy. At the between-host scale the model varies (5) the size of groups randomly encountered in the infectious host's environment.

Results identify conditions where an antibiotic can increase duration of a host`s infectiousness, and consequently increase the expected number of new infections. At lower antibiotic efficacy, therapy might convert a rare, serious bacterial disease into a common, but treatable infection.

**Keywords:** Group size; Infectious contacts; Inoculum; Isolation; Pathogen extinction; Within-host dynamics

## 1. Introduction

Antibiotics are administered routinely to humans, agricultural/pet animals, and certain plants [1-3]. Most commonly, antibiotic treatment is intended to control an individual`s bacterial infection [4]. Beyond concerns about the evolution of resistance [5, 6], use of antibiotics to treat infection presents challenging questions, including optimizing trade-offs between antibacterial efficacy and toxicity to the treated host [7]. This study asks if antibiotic treatment of an infection can have untoward consequences at the population scale; the paper models an antibiotic's direct impact on within-host pathogen dynamics and resulting, indirect effects on between-host transmission [8, 9].

The model assumes that the antibiotic`s suppression of within-host bacterial density extends the average waiting time for the host`s removal from infectiousness via other processes (e.g., physical isolation or disease mortality). The paper`s focal question asks how varying the age of infection when antibiotic treatment begins impacts both the duration of disease and the intensity of transmission during the host`s infectious period. When removal equates with disease mortality, the results identify conditions under which an antibiotic may simultaneously increase both survival of an infected individual and the expected number of secondary infections.

### 1.1 The infectious period

Efficacious antibiotics, by definition, reduce within-host pathogen density [10]; for some infections, antibiotics increase host survival. Therapeutic recovery of a treated individual may imply a public-health benefit. If antibiotics shorten the infectious period, the count of infections *per* infection could decline [4]. This interpretation follows from SIR compartment models, where neither the host-removal rate nor the antibiotically-induced recovery rate depends explicitly on within-host pathogen density. That is, antibiotics are assumed to reduce duration of the infectious period and to exert no effect on per-individual transmission intensity. By extension, antibiotics may then reduce pathogen transmission.

However, antibiotic therapy might, in other cases, increase the expected length of the infectious period. Transitions in host status must often depend on a within-host dynamics [8, 11]. As infection progresses, the pathogen density's trajectory should drive change in the rate of host removal while ill (*e.g*., isolation), the rate of recovery from disease, as well as the rate at which infection is transmitted [12, 13]. For many human bacterial infections, an individual can still transmit the pathogen after beginning antibiotic therapy [14]. Common infections remain transmissible for a few days to two weeks [15]. Although not addressed here, sexually transmitted disease may persist within a host for months after antibiotic therapy has begun [16]. Therapeutic reduction in pathogen density might eventually cure the host, while allowing the host to avoid isolation, *etc*. during treatment [17]. The result might be a longer period of infectious contacts and, consequently, increased secondary infections.

This paper assumes that with or without antibiotic treatment, a diseased host`s infectious period may be ended by a removal process that depends on within-

host pathogen density. As a convenience, removal includes any event terminating infectious contacts with susceptible hosts, prior to the antibiotic curing the disease. Social/physical isolation [18] and host mortality are dynamically equivalent removals in that they end the infectious period. The model assumes that an antibiotic, by deterring within-host pathogen growth, increases the expected waiting time for removal, but an increase in antibiotic efficacy reduces the time elapsing until the host is cured. This interaction affects the count of secondary infections; disease reproduction numbers (before and after therapy begins) identify conditions where an antibiotic increases the spread of disease.

### 1.2 Random encounters: susceptible groups

When infection is rare, random variation in the number of contacts between diseased and susceptible hosts influences whether the pathogen does or does not spread at the population scale [19, 20]. Therefore, this paper treats reproduction numbers, *i.e*., infections per infection, as random variables [21]. The environment governs social group size, which can affect contacts between infectious and susceptible hosts, and so impact infection transmission [22-24]. The model asks how the number of hosts per encounter with an infectious individual (with the product of encounter rate and group size fixed) impacts the variance in the count of secondary infections; specifically, the paper asks how group size impacts the probability that a rare infection fails to invade a host population [25, 26].

### 1.3 Organization

The model treats within-host pathogen dynamics deterministically [2]. Removal from the infectious state and between-host transmission are modeled probabilistically [27-29]. At the within-host scale, the model considers both density-independent and self-regulated pathogen growth. The host`s removal rate and the infection-transmission intensity will depend directly on the time-dependent bacterial density. Pathogen density increases monotonically from time of infection until antibiotic treatment begins, given persistence of the host`s infectious state. The antibiotic then reduces pathogen density until the host is cured or removed prior to completing therapy (whichever occurs first).

Counts of secondary infections will require the temporal distribution of infectious contacts, since the transmission probability depends on the time-dependent pathogen density [13, 30]. The results explore effects of antibiotics and inoculum size [31] on length of the infectious period, disease reproduction numbers, and pathogen extinction. The last two results connect logically; the first addresses mean infections per infection, and the second concerns the variance in the count of new infections.

## 2. Within-Host Dynamics: Timing of Antibiotic Treatment

For many bacterial infections of vertebrates, little is known about within-host pathogen growth [32]. In the laboratory, *Pseudomonas aeruginosa* readily infects *Drosophila melanogaster* [33]; the pathogen increases exponentially until the host dies or antibacterial treatment begins [29, 34, 35]. In more complex host-pathogen systems, resource limitation or physical crowding must often decelerate pathogen growth within the host, implying self-regulation [36-39]. Numerical results below compare ways in which the strength of self-regulation interacts with an antibiotic

to influence duration of infectiousness, and intensity of pathogen transmission.

$B_t$ represents the within-host bacterial density at time $t$; $B_0$ is the inoculum size. Antibiotic treatment begins at time $t_A > 0$. Table 1 defines symbols used in this paper.

If the pathogen grows exponentially prior to treatment, $B_t = B_0\, e^{rt}$ for $\leq t_A$ . The intrinsic growth rate $r > 0$ is the difference between bacterial replication and mortality rates per unit density. The latter rate may reflect a nonspecific host immune response [40]; the model does not include explicit immune dynamics, to focus on effects of antibiotic timing and efficacy. Under logistic self-regulation, the per-unit growth rate becomes $(r - cB_t)$ where $c$ represents intra-specific competition. For this case, the within-host density prior to treatment becomes:

$$B_t = r/\left[c + \left(\frac{r}{B_0} - c\right) e^{-rt}\right];\ t \leq t_A$$

| Symbols | Definitions |
|---|---|
| Within-host scale | |
| $t$ | Time since infection; infection age |
| $B_t$ | Bacterial density at time $t$ |
| $B_0$ | Inoculum density |
| $r$ | Pathogen's intrinsic rate of increase |
| $c$ | Pathogen intraspecific competition |
| $\gamma_A^*$ | Bacterial mortality due to antibiotic |
| $t_A$ | Age of infection when antibiotic initiated |
| $\theta$ | Prefactor, pathogen density at time of cure |
| $t_C$ | Age of infection when host cured |
| Individual host scale | |
| $h_t$ | Removal rate of infectious host at time $t$ |
| $\phi$ | Removal rate prefactor |
| $\eta$ | Infection severity parameter |
| $L_t$ | Pr[Host infectious at time $t \leq t_C$] |
| Between-host scale | |
| $\lambda/G$ | Stochastic contact rate, group size $G$ |
| $\nu_t$ | Probability of infection, given contact |
| $\xi$ | Infection susceptibility parameter |
| $p_t$ | Probability new infection occurs at time $t$ |
| $\mathcal{P}$ | Time averaged infection probability |
| $R_1$ | Expected new infections before $t_A$ |
| $R_2$ | Expected new infections on $(t_A, t_C)$ |
| $R_0$ | $R_1 + R_2$ |

**Table 1**: Definitions of model symbols, organized by scale.

where $B_0 < r/c$; the inoculum should be smaller than the ``carrying capacity." For the same $(B_0, r)$, the self-regulated density, of course, never exceeds the exponentially growing density between time of infection and initiation of antibiotic therapy. For both growth assumptions, $B_{t_A}$ represents the within-host density at initiation of therapy.

Most antibiotics increase bacterial mortality [10, 41], though some impede replication [37]. When a bacterial population is treated with an efficacious antibiotic, bacterial density (at least initially) declines exponentially [42-44]. Hence, I assume that a bactericidal antibiotic induces exponential decay of $B_t$.

### 2.1 Host states

The host becomes infectious at time $t = 0$, and remains infectious until either removed or cured by the antibiotic (see Section 2.3). No secondary infections occur after removal or therapeutic cure, whichever occurs first. Hence, transmission can occur during antibiotic therapy, prior to cure. If the host remains infectious at time *t*, both the probability of disease transmission (given encounter with a susceptible) and the removal rate depend explicitly on within-host density $B_t$.

### 2.2 Antibiotic concentration and efficacy

Assumptions concerning antibiotic efficacy follow Austin et al. [37]. Given that the host remains infectious at $t > t_A$, the total loss rate per unit bacterial density is $\mu + \gamma(A_t)$, where $A_t$ is plasma concentration of antibiotic, and $\gamma$ maps $A_t$ to bacterial mortality *per* unit density.

Assume that the antibiotic is `dripped' at rate $D_A$. Plasma antibiotic concentration decays through both metabolism and excretion; let $k_A$ represent the total decay rate. Then, $dA_d/dt = D_A - kA_t$, so that $A_t = (D_A/k)\,(1 - e^{-kt})$, for $t > t_A$. Antibiotic concentration generally approaches equilibrium faster than the dynamics of bacterial growth or decline [37]. Then a quasi-steady state assumption implies the equilibrium plasma concentration of the antibiotic is $A^* = D_A/k$.

Bacterial mortality increases in a decelerating manner as antibiotic concentration increases [41, 45]. Using a standard formulation [7]:

$$\gamma(A_t) = \gamma_{max}\, A_t/(a_{1/2} + A_t);\ t > t_A \quad (1)$$

where $\gamma(A_t) = \gamma_{max}/2$ when $A_t = a_{1/2}$. Applying the quasi-steady state assumption, let $\gamma_A^* = \gamma(A^*)$. Since the antibiotic is efficacious, $\gamma_{A^*} > r$.

### 2.3 Antibiotic treatment duration

Antibiotic therapy begins at time $t_A$. During treatment, within-host pathogen density declines as $dB_t/dt = -(\gamma_{A^*} - r)\,B_t$. Then:

$$B_t = B_{t_A}\, exp[-(\gamma_A^* - r)\,(t - t_A)];\ t > t_A;\ \gamma_A^* > r \quad (2)$$

where only $B_{t_A}$ depends on the presence/absence of self-regulation. For the exponential case $B_t = B_0\, exp[rt - \gamma_A^*\,(t - t_A)]$ after treatment begins. For self-regulated pathogen growth:

$$B_t = \left[\frac{r\, e^{\gamma_A^* t_A}}{ce^{rt_A} + \left(\frac{r}{B_0} - c\right)}\right] e^{-(\gamma_A^* - r)t} \quad (3)$$

Given that the host is not otherwise removed, antibiotic treatment continues until the host is cured at time $t_C > t_A$. A `cure' means that the within-host pathogen density has declined sufficiently that the host no longer can transmit the pathogen; a cure need not imply complete clearance of infection. No host remains infectiousness beyond $t_C$. In terms of pathogen density, $B(t_c) = B_0/\theta$, where $\theta \geq 1$. Hence infectiousness terminated by therapy always

occurs at a within-host density less than (no greater than) the density where the host may first transmit the pathogen. For exponential pathogen growth, we have:

$$B_0/\theta = B_0\, exp[rt_C - \gamma_A^*(t_C - t_A)] \Rightarrow t_C = \frac{\gamma_A^* t_A + ln\theta}{\gamma_A^* - r} > t_A \quad (4)$$

If the cure requires only that $B_t$ return to the inoculum size, then $\theta = 1$, and $t_C = \gamma_A^* t_A/(\gamma_A^* - r)$. Instead of defining cure *via* therapy as a density proportional to $B_0$, suppose that the host is cured if the within-host density declines to $B(t > t_A) = \tilde{B} \leq B_0$ . Let $\tilde{\theta} = \tilde{B}/B_0$. The associated maximal age of infection is $\tilde{t} = (\gamma_A^* t_A - ln\,\theta)/(\gamma_A^* - r)$ . $\tilde{t}$ depends on $\gamma_A^*$, $t_A$, and $r$ as $t_C$ does, and numerical differences will be small unless $B_0$ and $\tilde{B}$ differ greatly.

If pathogen growth self-regulates and $B(t_C) = B_0/\theta$, the host is cured at:

$$t_C = \frac{\gamma_A^* t_A + ln\theta}{\gamma_A^* - r} - ln\left[1 + \frac{B_0}{r/c}(e^{rt_A} - 1)\right](\gamma_A^* - r)^{-1} \quad (5)$$

$B(t_A)$ is smaller under self-regulated growth than under density independent growth; the antibiotic cures the host faster under self-regulation. Numerical results below let $\theta = 1$, implying a symmetry between the within-host state at initial infectiousness $(B_0 > 0;\ \dot{B} > 0)$ and the state at $t_C$ $(B_{t_C} = B_0;\ \dot{B} < 0)$.

## 3. Duration of Infectious State

Removal includes any event, other than antibiotic cure, that ends the host's infectious period. Removal occurs probabilistically and the rate of removal depends on pathogen density. Noting that removal by mortality becomes more likely with the severity of ``pathogen burden" [46], the model assumes that the removal rate at any time $t$ strictly increases with pathogen density $B_t$.

The model takes removal as the first event of a nonhomogeneous Poisson process; $h_t$ is the instantaneous rate of removal at time $t$ [47]. $L_t$ is the probability that the host, infected at time 0, remains infectious at time $t \leq t_C$. Prior to initiation of therapy:

$$L_t \equiv exp\left[-\int_0^t h_\tau\, d\tau\right];\ t \leq t_A \quad (6)$$

and $(1 - L_t)$ is the probability the host has been removed before time $t$. $h_t$ is the stochastic removal rate at time $t$; assume $h_t = \phi B_t^\eta;\ \phi, \eta > 0$. The parameter $\phi$ scales bacterial density to the timescale of removal. Removal is more/less likely as bacterial density increases/decreases. For $t \leq t_A$, $h_t$ has the form of the Gompertz model for age-dependent mortality among adult humans [48]. $h_t$ saturates $(\eta < 1)$, increases linearly $(\eta = 1)$, or accelerates $(\eta > 1)$ with increasing pathogen density, depending on the host-pathogen combination.

Suppose the pathogen grows exponentially before time $t_A$. Then the host remains infectious prior to antibiotic treatment with probability:

$$L_t = exp\left[-\phi B_0^\eta \int_0^t e^{\eta r\tau}\, d\tau\right] = exp\left[\frac{\phi B_0^\eta}{\eta r}\right] \Big/ exp\left[\frac{\phi B_t^\eta}{\eta r}\right];\ t \leq t_A \quad (7)$$

Simplifying:

$$L_t = exp\left[-\frac{\phi}{\eta r}\left(B_t^\eta - B_0^\eta\right)\right];\ t \leq t_A \quad (8)$$

$L(t=0)=1$, and persistence of infection declines as $t$ increases. For logistic pathogen growth prior to treatment, we have:

$$L_t = exp\left[-\phi r^{\eta}\int_0^t \frac{d\tau}{\left[c+\left(\frac{r}{B_0}-c\right)e^{r\tau}\right]^{\eta}}\right] \quad (9)$$

For given $(B_0, r)$ the self-regulated density at $t \in (0, t_A)$ must be lower than the unregulated density. Consequently, $L_t$ under exponential growth cannot exceed the corresponding probability when pathogen growth self-regulates; pathogen self-regulation increases the chance that the host survives until antibiotic treatment begins.

### 3.1 Antibiotic therapy: removal *vs* cure

During antibiotic treatment, a host has instantaneous removal rate:

$$h_t = \phi B_{t_A}^{\eta}\, e^{-\eta(\gamma_A^*-r)(t-t_A)};\ t > t_A \quad (10)$$

where, again, only $B_{t_A}$ depends on the presence/absence of self-regulation. The probability that the host remains infectious at time $t$, where $t_A < t < t_C$, is the probability of entering treatment in the infectious state, $L_{t_A}$, times the probability of avoiding removal from $t_A$ to $t$ (given the state at $t_A$). Using Eq (10), the probability that the host remains infectious during treatment is:

$$L_t = L_{t_A}\, exp\left[-\phi B_{t_A}^{\eta}\int_{t_A}^{t} e^{-\eta(\gamma_A^*-r)(\tau-t_A)}\, d\tau\right];\ t > t_a \quad (11)$$

where $B_{t_A}$ and, consequently, $L_{t_a}$ depend on presence/absence of self-regulation.

Using Eq (2), we have the probability that infectiousness persists to time $t$ during therapy, for either presence or absence of self-regulation prior to therapy:

$$L_t = L_{t_A}\, exp\left[\frac{\phi B_t^{\eta}}{\eta(\gamma_A^*-r)}\right] \Big/ exp\left[\frac{\phi B_{t_A}^{\eta}}{\eta(\gamma_A^*-r)}\right]$$
$$= L_{t_A}\, exp\left[-\frac{\phi}{\eta(\gamma_A^*-r)}\left(B_{t_A}^{\eta}-B_t^{\eta}\right)\right];\ t > t_A \quad (12)$$

where $B_{t_A} > B_t$ , and $L_{t_A}$ is given by either Eq (8) or Eq (9), as appropriate.

The infectiousness-survival probabilities $L_t$ collect consequences of model assumptions. Delaying initiation of therapy (*i.e.*, increasing $t_A$) increases $B_{t_A}$ and hence decreases $L_{t_A}$, the probability that infectiousness persists until treatment begins. Rephrased, delaying the antibiotic increases the chance that the host is removed (and so stops transmitting infection) before therapy begins. Since $B_{t_A}$ increases with $t_A$, the time required for the antibiotic to cure the host $(t_C - t_A)$ must increase with $t_A$.

Furthermore, since increasing $t_A$ decreases $L_{t_A}$ and increases $(t_C - t_A)$, then $\partial L_{t_C}/\partial t_A < 0$; the probability that the remains infectious until cured decreases with delayed initiation of treatment. These effects always hold for exponential growth; they hold for logistic growth when $B_{t_A} < r/c$, the carrying capacity.

Increasing bacterial self-regulation moderates, but does not reverse, these effects of $t_A$. For $r/c$ large enough, pathogen density $B_{t_A}$ declines as $c$ increases. Then $L_{t_A}$ must increase, and time needed for

therapeutic cure $(t_C - t_A)$ must decrease. Hence $\partial L_{t_C}/\partial c \geq 0$; increasing the strength of self-regulation in pathogen growth never decreases the probability that the host is cured therapeutically.

The model's simple within-host dynamics allows the rate of removal and (its complement) persistence of the infectious state to depend clearly and explicitly on within-host pathogen density. The dynamics of infection transmission, and so any public-health implications, will also depend on within-host pathogen density [49].

## 4. Transmission

The focal infective contacts susceptible hosts as groups. Each group has the same size *G*; often *G* = 1. Contacts occur as a Poisson process, with constant probabilistic rate $\lambda/G$, so that the expected number of individuals contacted in any period does not depend on susceptible-host group size. Contact rate is also independent of time and pathogen state $B_t$.

A contact implies *G* independent Bernoulli trials, and the number of new infections, *per* contact, follows a binomial probability function with parameters *G* and $p_t$. $p_t$ is the conditional probability that any susceptible host *j* acquires the infection, given contact at time *t*. The model writes $p_t$ as a product: $p_t = L_t\, v_t$. $L_t$ weighs ``births" of new infections upon contact [49, 50]. $v_t$ is the conditional probability that any susceptible host *j* is infected at time *t* given that the focal host remains infectious, and contact occurs. Both $L_t$ and $v_t$ depend on within-host density $B_t$.

Given an encounter, the transmission probability $v_t$ assumes a dose-response relationship [30, 51]. Following a preferred model [52], $v_t = 1 - exp[-\xi B_t]$, where $\xi$ is the susceptibility parameter. Then $p_t = L_t\left(1 - e^{-\xi B_t}\right)$. $v_t$ decelerates with $B_t$ since infection of a single host saturates with propagule number [20, 53, 54]. Note that $\partial v_t/\partial B_t > 0$ and $\partial h_t/\partial B_t > 0$. An increase in transmission probability, due to greater within-host pathogen density, is countered by a greater removal rate.

### 4.1 New-infection probabilities: before and during treatment

New infections occur randomly, both before and after treatment begins. To clarify effects of varying the timing of therapy, let $R_1$ represent the expected number of new infections on $(0, t_A]$; let $R_2$ be the expected number of new infections on $(t_A, t_C]$. For simplicity, refer to these respective time intervals as the first and second period. $R_0$ is the expected total number of new infections *per* infection; $R_0 = R_1 + R_2$.

Suppose that *N* such encounters with the infectious host occur on some time interval $(t_x, t_y)$. By the Poisson's memoryless property, the times of the encounters (as unordered random variables) are distributed uniformly and independently over $(t_x, t_y)$ [55]. Uniformity identifies the time averaging for the conditional infection probability $p_t$. For the first period, the unconditional probability of infection at contact is $\mathcal{P}_1$:

$$\mathcal{P}_1 = \frac{1}{t_A}\int_0^{t_A} L_\tau\left(1 - e^{-\xi B_\tau}\right) d\tau \quad (13)$$

Eq (13) applies to both exponential and self-regulated growth. For the former case, we have:

$$\mathcal{P}_1 = \left(exp\left[\frac{\phi B_0}{\eta r}\right]/t_A\right) \times \left(\int_0^{t_A} exp\left[-\frac{\phi B_\tau^\eta}{\eta r}\right] d\tau - \int_0^{t_A} exp\left[-\frac{\phi B_\tau^\eta}{\eta r} - \xi B_\tau\right] d\tau\right) \quad (14)$$

For the second period, averaging uniformly yields $\mathcal{P}_2$, the infection probability after treatment begins. $\mathcal{P}_2$ has the form as Eq (13), with averaging over $(t_C - t_A)$. For both exponential and logistic within-host growth, we obtain:

$$\mathcal{P}_2 = \left(\frac{L_{t_A}}{t_C - t_A}\Big/ exp\left[\frac{\phi B_{t_A}^\eta}{\eta(\gamma_A^* - r)}\right]\right) \times \left(\int_{t_A}^{t_C} exp\left[\frac{\phi B_\tau^\eta}{\eta(\gamma_A^* - r)}\right] d\tau - \int_{t_A}^{t_C} exp\left[\frac{\phi B_\tau^\eta}{\eta(\gamma_A^* - r)} - \xi B_\tau\right] d\tau\right) \quad (15)$$

where $L_{t_A}$ is given above (and depends on the presence/absence of self-regulation), and $B_\tau$ is given by Eq (2). $\mathcal{P}_1$ and $\mathcal{P}_2$ collect effects of within-host density, modulated by antibiotic treatment, on between-host transmission of infection. Since the within-host dynamics affects both persistence of the infectious state and the probability of transmitting infection upon contact, the strength of self-regulation should impact the number of secondary infections *per* infection.

### 4.2 $R_0$

For each of the two periods, the number of infections sums a random number of random variables. Each element of the sum is a binomial variable with expectation $G\mathcal{P}_z$ and variance $G\mathcal{P}_z(1 - \mathcal{P}_z)$; $z = 1, 2$. The number of encounters with susceptible hosts is a Poisson variable with expectation during the first period $(\lambda/G)\, t_A$, and expectation during the second period $(\lambda/G)\, (t_C - t_A)$.

Let $X_1$ be the random count of new infections during the first period, and $X_2$ be the second-period count. From the time of infection until antibiotic treatment begins, $R_1 = E[X_1] = \lambda\mathcal{P}_1 t_A$ and $V[X_1] = R_1[1 + \mathcal{P}_1(G - 1)]$. For the second period, $R_2 = E[X_2] = \lambda\mathcal{P}_2(t_C - t_A)$, and the variance of $X_2$ is $R_2[1 + \mathcal{P}_2(G - 1)]$.

By construction, the expected number of infections both before and after antibiotic treatment begins does not depend on group size *G*. But each variance of the number of new infections increases with group size. Finally, the total number of new infections *per* infection has expectation $R_0 = E[X_1 + X_2] = \lambda[\mathcal{P}_1 t_A + \mathcal{P}_2(t_C - t_A)]$. The variance of the total number of new infections is $V[X_1 + X_2] = R_0 + (G - 1)[\mathcal{P}_1 R_1 + \mathcal{P}_2 R_2]$.

Since group size affects only the variance of the reproduction numbers, any increase *G* can increase $Pr[X_1 + X_2 = 0]$, the probability of no new infections, even though $R_0 > 1$. No new infections requires that each $X_z = 0; z = 1, 2$. The probability of no pathogen transmission at a single encounter is $(1 - \mathcal{P}_z)^G$, since outcomes for each susceptible are mutually independent. Given *N* encounters in period *z*, the conditional probability of no new infections during that period is $Pr\{X_z = 0|N\} = [(1 - \mathcal{P}_z)^G]^N$. Unconditionally:

$$Pr[X_z = 0] = \sum_{N=0}^{\infty} [(1 - \mathcal{P}_z)^G]^N \, Pr[N] \quad (16)$$

Since $(1 - \mathcal{P}_z)^G < 1$, $Pr[X_z = 0]$ is given by the probability generating function for *N*, evaluated at $(1 - \mathcal{P}_z)^G$. From above, *N* is Poisson with parameter $(\lambda/G)\, t_A$ during the first period, and:

$Pr[X_1 = 0] = exp[(\lambda/G)\, t_A\, ([1 - \mathcal{P}_1]^G - 1)]$ (17)

For the second period, $Pr[X_2 = 0] = exp[(\lambda/G)(t_C - t_A)\, ([1 - \mathcal{P}_2]^G - 1)]$. Each probability of no infection increases as $G$ increases. The chance of no new infections is, of course, the product of the independent probabilities.

## 5. Numerical Results

Figures (1) and (2) show results motivating this paper. Consider first how $R_0$ varies with $t_A$, at different levels of self-regulation. If antibiotic therapy begins immediately after the host becomes infectious ($t_A < 2$ in Figure 1c) then $R_0 < 1$ in both the presence and absence of self-regulation; the disease will likely fail to invade a susceptible population. But antibiotics are seldom administered at the onset of infectiousness [3, 39]. A relatively small delay in $t_A$ allows the infection to spread. That is, reasonably rapid initiation of antibiotic treatment allows $R_0 > 1$, for both self-regulated and unregulated growth before $t_A$. As $t_A$ continues to increase, only strong self-regulation produces further, though quickly decelerating, increase in $R_0$. More interestingly, for both exponential growth and weak self-regulation, delaying therapy sufficiently leaves $R_0 < 1$ again, inhibiting the spread of infection. For the exponential example, results for larger $t_A$ equate essentially to no antibiotic therapy: ($L_{t_A} \to 0;\ R_2 = 0$).

In this case relatively early initiation of antibiotic therapy increases the probability the host will be cured (Figure. 1f) but allows the disease to advance among hosts ($R_0 > 1$). But no antibiotic therapy (or $t_A$ delayed sufficiently) prevents initial spread of infection ($R_0 < 1$).Why does increasing the time elapsing between infection and initial treatment (or no treatment) sometimes reduce the chance that disease will spread? Why does relaxed pathogen self-regulation increase this effect? A small $t_A$ implies a low $B_{t_A}$; early treatment maintains a reduced within-host density and a consequently reduced removal rate for ($t > t_A$).

The host's chance of being cured, rather than first being removed, increases when treatment begins relatively soon after infection. That is, therapy begun at low $t_A$ more likely cures the host, but (on average) leaves the host infectious longer. The latter effect maximizes $R_0$ at a lower $t_A$ in both the exponential and weakly self-regulated examples.

Earlier initiation of treatment must reduce $R_1$. For exponential and weakly self-regulated pathogen growth, the spread of infection among hosts, for low $t_A$, is due more to transmission during antibiotic treatment; $R_0$ and $R_2$ reach their respective maxima at nearly the same $t_A$ value. For any $t$, $t_A < t < t_C$, the reduction in the infection probability $\nu_t$ due to the antibiotic's regulation of within-host pathogen density is more than compensated by the increase in $L_t$, the probability that the host remains infectious. The focal point is that $R_0 < 1$ with no antibiotic therapy, though $R_0$ can exceed 1 with therapy

. When removal and therapeutic cure without removal depend differently on the within-host dynamics, this non-obvious effect of $t_A$ can occur.

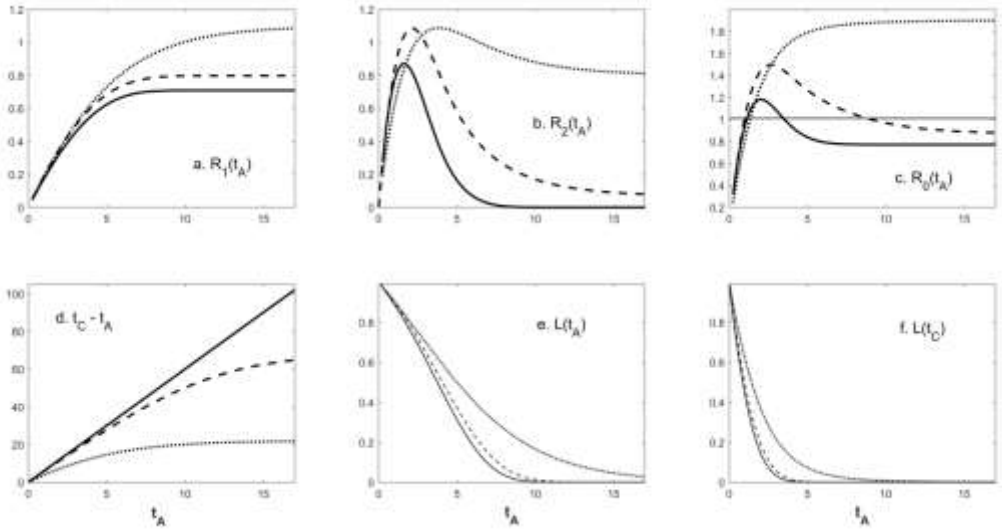


**Figure 1**: Antibiotic therapy can sometimes promote infection transmission. Each plot: solid line is exponential, dashed line is weak self-regulation ($c = 10^{-6}$), dotted line is stronger self-regulation ($c = 10^{-5}$). (a) $R_1$ expected infections before $t_A$. (b) $R_2$ expected infections after antibiotic started. (c) $R_0$ total expected infections *per* infection. (d) Time required for treatment curing the host. (e) Probability host begins antibiotic therapy. (f) Probability host is cured before removal. $B_0 = 10^4$, $r = 0.3$, $\phi = 10^{-5}$, $\gamma_A^* = 0.35$, $\eta = \theta = 1.0$, $\lambda = 0.2$, $\xi = 1.0$.

Stronger self-regulation reduces $B_{t_A}$ and so lowers the removal rate for $t > t_A$.The host is then more likely to remain infectious until cured. The example with strong self-regulation reduces the time-dependent removal rate enough that $R_0$ increases monotonically with increasing $t_A$.

Consider the exponential case and suppose that avoiding removal through the antibiotic treatment implies surviving disease; the host is either removed by mortality or cured by the antibiotic. Then, the infected host obviously benefits from therapy. But there can be a cost at the among-host scale as the infection spreads. A rare ($R_0 < 1$), but virulent infection in the absence of antibiotics can become a common ($R_0 > 1$), through treatable disease when antibiotic therapy begins soon after initial infection.

Figure 2 verifies how increasing susceptible-host group size increases the probability of no secondary infections, despite independence of $R_0$ and group size. Larger groups increase the variance in the total count of infections *per* infection.

As a result, the probability of no new infections (pathogen ``extinction") increases strongly with $G$. Even for the $t_A$ levels maximizing $R_0$ in Figure 1, sufficiently large group size (under both exponential and weakly self-regulated growth) assures that pathogen extinction is more likely than is spread of infection.

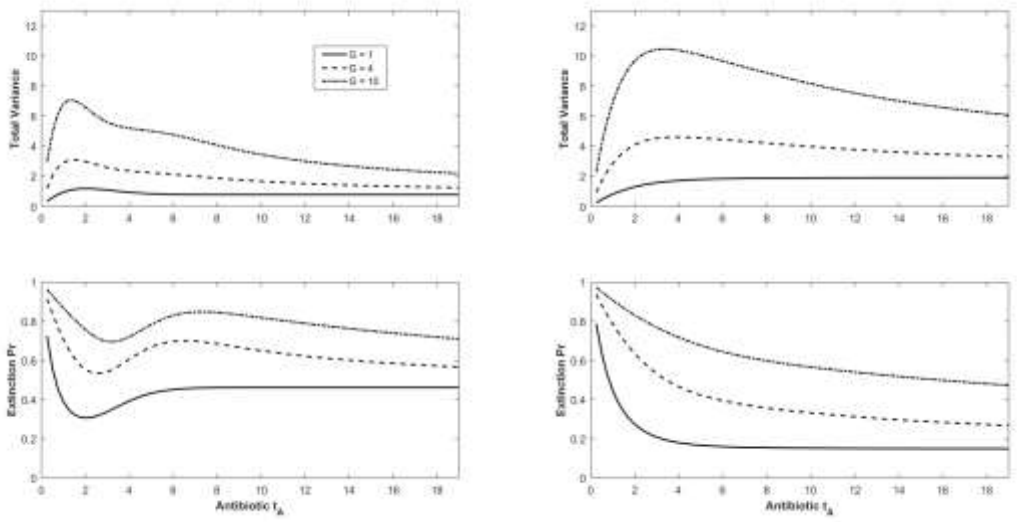


**Figure 2:** Susceptible group size and disease-extinction probability. Each plot: $G = 1$ (solid line), $G = 4$ (dashed line), $G = 10$ (dotted line). Left column: Exponential pathogen growth. Right column: logistic growth ($c = 10^{-5}$). Variance in the count of infections *per* infection increases when groups are larger but encountered less often. Probability of no secondary infections *per* infection (``extinction") increases as group size increases.

### 5.1 Inoculum size, antibiotic efficacy, and $R_0$

The preceding numerical results varied $t_A$, and held both inoculum size $B_0$ and antibiotic efficacy $(\gamma_A^* - r)$ constant.

Variation in inoculum size can impact within-host pathogen growth [56-58] and infectiousness [31, 51, 59]. Of course, increasing $(\gamma_A^* - r)$ should increase the likelihood of curing, rather than removing, the host.

Figure 3 varies the inoculum $B_0$ and antibiotic mortality $\gamma_A^*$. Dependent quantities are $R_0$ and the probability that a host remains infectious until cured $(L_{t_C})$; results were calculated for a smaller and larger $t_A$.

For these parameter values, $R_0$ reaches a maximum at low antibiotic efficacy and small inoculum; the pattern holds for both exponential pathogen growth (subplot a) and stronger self-regulation [subplot (e)]. Subplots (a) and (e) show results for $t_A = 4$; the surfaces have the same shape for both smaller and larger $t_A$ levels.

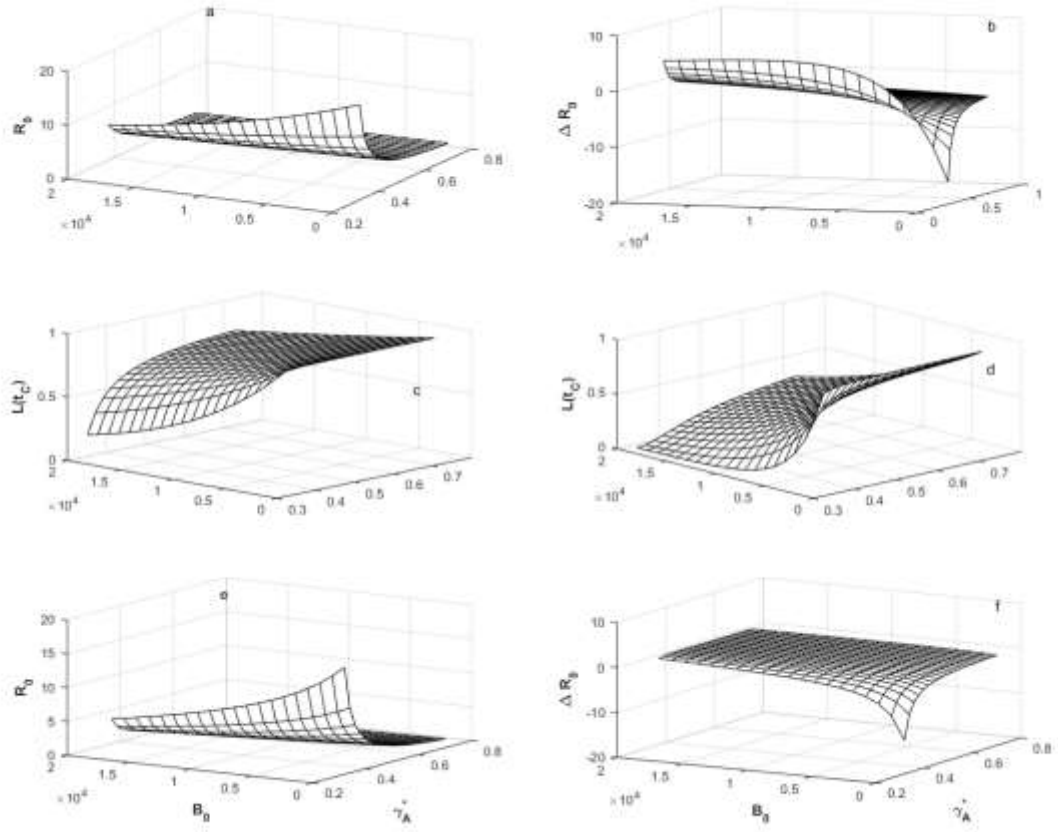


**Figure 3:** Effects of varying $B_0$ and $\gamma_A^*$. (a) $R_0$ for $t_A = 4$ (smaller $t_A$); $B_t$ exponential. $R_0$ declines monotonically as inoculum size $B_0$ increases; $R_0$ also declines as antibiotic efficacy increases. (b) $\Delta R_0$ is $R_0$ for smaller $t_A$ *minus* $R_0$ for $t_A = 8$ (larger $t_A$), exponential growth. For medium and larger $B_0$, combined with lower antibiotic efficacy, earlier treatment generates more secondary infections. (c) Probability treated host is cured, smaller $t_A$. (d) Probability host cured, larger $t_A$. (e) $R_0$ for $t_A = 4$; $B_t$ logistic. (f) $\Delta R_0$ is $R_0$ for smaller *minus* $R_0$ for larger $t_A$; $B_t$ logistic. All plots: $r = 0.3$, $\phi = 10^{-6}$, $\eta = \theta = 1.0$, $\xi = 0.7$, and $\lambda = 0.4$. Plots e and f: $c = 10^{-5}$, stronger self-regulation.

Why does $R_0$ decline as inoculum size increases? Any increase in $B_0$ increases $B_t$ for all $t \leq t_c$. The removal rate $h_t$ increases as a result, and the expected duration of infectiousness must consequently decline. For these parameters, where susceptibility $\xi$ is comparatively large, any increase in the transmission probability $\nu_t$ with $B_t$ does not compensate for the reduction in duration of infectiousness. Hence, by increasing the likelihood of early removal, a larger inoculum can decrease the expected number of secondary infections. Increasing antibiotic efficacy decreases not only $R_0$, but also the sensitivity of $R_0$ to variation in inoculum size.

Subplots (c) and (d) of Figure 3 verify, for exponential growth, that the chance of the host

remaining infectious until cured (*i.e.*, avoiding removal) declines as $B_0$ increases. Note the clear quantitative differences between the two $L_{t_C}$-surfaces. For any $(B_0, \gamma_A^*)$-combination, the host's probability of remaining infectious is greater for low $t_A$ (subplot c) than for high $t_A$ (subplot d). If removal equates with mortality, so that $L_{t_C}$ becomes the host`s survival probability, the host should 'prefer' earlier therapy.

Subplot (b) in Figure 3 shows the difference between $R_0$ values for two $t_A$ levels; $\Delta R_0$ is the difference between $R_0$ values of a lesser and greater $t_A$ level. For greater antibiotic efficacy $(\gamma_A^* \geq 0.5)$, $\Delta R_0 \leq 0$. A stronger antibiotic allows earlier start of therapy to decrease the expected number of secondary infections, despite extending the duration of infection (by reducing the removal rate).

However, for lesser antibiotic efficacy $(\gamma_A^* \leq 0.4)$, $\Delta R_0 \geq 0$ for sufficiently large $B_0$. Earlier treatment still increases duration of the infective state (*i.e.*, $L_{t_C}$ increases), and now also increases $R_0$. When small inoculum size is combined with lower antibiotic efficacy, the infected host benefits most, in terms of the chance of being cured, from earlier therapy (low $t_A$).

But the consequence is accelerated spread of infection at the among-host scale, since $\Delta R_0 > 0$. Sufficiently strong self-regulation of within-host growth can eliminate this effect (subplot f), since host survival until cured is, overall, much less sensitive to variation in $t_A$.

### 5.2 Group size, $R_0$ and pathogen `extinction'

Figure 4 shows, for exponential pathogen growth, how varying $R_0$ and susceptible-group size $G$ affects the probability that the focal host transmits no secondary infections. $R_0$ was varied by varying $B_0$. Given $G$, pathogen-extinction probability never increases, and sometimes declines, as $R_0$ increases. The decline is greatest when susceptible hosts are encountered as solitaries, *i.e.*, when the infection-number variance is minimal. Given $R_0$, the chance of pathogen extinction increases strictly monotonically as $G$ increases. Each plot in Figure 4 includes regions where, for sufficiently large group size, $R_0 > 1$ but pathogen extinction is more likely than not.

## 6. Discussion

This paper assumes that any increase in within-host pathogen density makes removal/mortality due to infection more probable. Antibiotic therapy reduces pathogen density and so lowers the instantaneous removal rate. Removal and therapeutic recovery *via* antibiotics interact through their separate functional relationships with pathogen density, and this interaction governs both duration of infectiousness and disease-transmission probabilities during the infectious period. Model results show that antibiotic therapy may sometimes benefit the individual treated while imposing costs (additional disease) at the public-health scale [60].

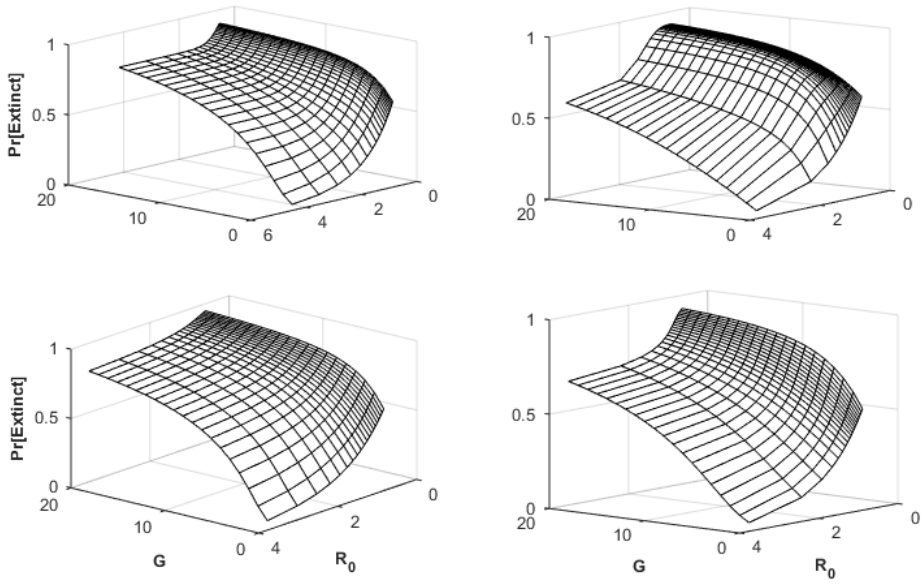


**Figure 4**: Probability of no new infections. Each plot shows the probability of no new infection both before and after antibiotic therapy begins. Chance of extinction shown as function of $R_0$ and group size $G$; note directions of axes. $R_0$ varied by increasing inoculum size $B_0$ form $10^3$ to $2 \times 10^4$. Top row: $\gamma_A^* = 0.35$. Bottom row: $\gamma_A^* = 0.7$. Left column: $t_A = 4$ (lower $t_A$). Right column: $t_A = 8$ (greater). Pathogen extinction less likely as $R_0$ increases; extinction always more likely as group size $G$ increases. Increase in extinction due to larger group size increases at greater $R_0$. Each plot shows a substantial region where $R_0 > 1$, but probability of pathogen extinction exceeds 0.5. All plots: $r = 0.3$, $\phi = 10^{-5.5}$, $\eta = \theta = 1.0$, $\xi = 0.5$, $\lambda = 0.1$.

The model was motivated by two observations. First, adults and children routinely take antibiotics (often accompanied by fever-reducing medicine) for upper respiratory infections, and then return to work or school as soon as symptoms begin to subside. Sometimes these presentees [61] remain infectious after beginning antibiotic treatment, and they transmit the associated pathogen [15]. Removal (remaining home while infectious) would diminish transmission, though at some inconvenience to the focal infective. A survey conducted within the last decade suggests that each week nearly $3 \times 10^6$ employees in the U.S. go to work sick [62], fearing lost wages or loss of employment [17]. Tension between pursuit of income and measures intended to curb the spread of infectious disease has become common during pandemic [63].

The second observation concerns self-medication in chimpanzees (*Pan troglodytes*). Chimpanzees consume a diverse plant diet, and at times select plants with antiparasitic properties [64]. When infested by intestinal nematodes, a chimpanzee will withdraw from its social group, and while isolated will eat plants with chemical and/or physical characteristics that usually reduce its parasite load [18, 65]. As symptoms moderate, the still-parasitized individual can return to the group [66] where its presence may promote transmission of the parasite.

Plausibly, self-medication increases survival of the first chimpanzee, and indirectly increases the parasitism within the group. The next several subsections suggest a few questions about the way antibiotics may impact linkage between within-host pathogen growth and among-host transmission.

### 6.1 Bacteria

Genetic resistance to antibiotics, whether arising *de novo* or acquired *via* plasmids, challenges control of bacterial disease [4, 6, 67, 68]. Phenotypic tolerance presents related, intriguing questions [44]. Some genetically homogeneous bacterial populations consist of two phenotypes; one grows faster and exhibits antibiotic sensitivity, while the other grows more slowly and can persist after exposure to an antibiotic [43]. Phenotypes are not fixed; individual lineages may transition between the two forms [39]. An antibiotic's effect on densities of the two forms might easily extend the duration of infectiousness, but the probability of transmission, given contact, might decline as the frequency of the persistent type increases.

### 6.2 Antibiotic administration

If an antibiotic is delivered periodically as a pulse, rather than dripped, the therapeutically induced mortality of the pathogen can depend on time since the previous administration [44]. Complexity of the impact on the within-host dynamics could then depend on the difference between the antibiotic's decay rate and the pathogen's rate of decline. Some authors refer to an ``inoculum effect," suggesting that antibiotic efficacy can vary inversely with bacterial density. That is, the *per* unit density bacterial mortality effected by a given antibiotic concentration declines as bacterial density increases [10].

This paper asks if variation in the time elapsing between initial infectiousness and the start of antibiotic therapy could affect outcomes at the individual and population scale. Hence, $t_A$ was treated as an independent variable [68]. Extending the model could treat the time therapy begins as a positive random variable. Since $R_0$ depends nonlinearly on $t_A$, randomization of the delay to treatment should produce new qualitative predictions. In some applications $t_A$ might be a symptom-driven function of within-host density [7, 39]. Faster within-host growth, given inoculum size, would presumably induce earlier treatment. In this case, the presence/absence of pathogen self-regulation might prove important at both the within-host and between-host scales [60].

### 6.3 Infected host

This paper neglects immune responses so that the duration of treatment, given cure by the antibiotic, depends explicitly on the antibiotic's efficacy and the age of infection when treatment begins. Incorporating both a constitutive and inducible immune response should be straightforward. The constitutive response imposes a constant, density-independent mortality rate on the pathogen. This response (common to vertebrates and invertebrates) is innately fixed; its effect can be inferred by varying this paper's pathogen growth rate *r*. Induced immune responses impose density-dependent regulation of pathogen growth; pathogen and induced densities are sometimes coupled as a resource-consumer interaction [40].

The timing of antibiotic therapy might be modulated so that the current infection might be eliminated just slowly enough to prompt a lasting immunological memory, a ‘vaccination’ against future exposure to

the same pathogen [69]. Antibiotic dosing might be optimized similarly [68].

### 6.4 Transmission

This paper assumes a constant (probabilistic) rate of infectious contact with susceptible hosts. The number of contacts available may be limited, so that each transmission event depletes the local-susceptible pool. Regular networks capture this effect for spatially detailed transmission [54], and networks with a random number of links per host do the same when social preferences drive transmission [20]. For these cases, contact structure of the susceptible population can affect both $R_0$ and the likelihood of pathogen extinction when rare [28].

Contact avoidance may sometimes be more important than contact depletion [12]. If susceptible hosts recognize correlates of infectiousness, they can avoid individuals or locations where transmission is likely [70]. If antibiotics extend the period of infectiousness and reduce symptom severity, correlates of infectiousness might be more difficult to detect.

## 7. Conclusion

The results indicate several interrelated predictions, summarized here.

- The expected count of secondary infections is often a single-peaked function of the time since infection when therapy begins. But sufficiently strong pathogen self-regulation can imply that $R_0$ increases montonically with time elapsing until therapy begins.
- Less efficacious antibiotics may increase the expected count of secondary infections beyond the level anticipated without antibiotic intervention.
- Strong pathogen self-regulation increases the probability that the host remains infectious until therapeutically cured, and decreases the time elapsing between initiation of treatment and cure.
- Treatment with a less efficacious antibiotic soon after infection can increase the probability of curing the disease, but also can increase the expected count of secondary infections. However, early treatment with a strong antibiotic can both increase the likelihood of curing the disease and reduce the count of secondary infections. Antibiotics may almost always benefit the individual treated, but the consequence for public health may not be so uniform.
- If hosts are moderately to highly susceptible to infection, duration of the infectious state and the expected count of secondary infections decline as inoculum size increases.
- When susceptible hosts are grouped, and larger groups are encountered less frequently, the social structuring increases the variance of the secondary infection count and, consequently, increases the probability of no new infection.

Note that the predictions do not depend on whether removal equates with isolation (usually faster) or host mortality (usually slower).

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