

Dynamics of Indirectly Transmitted Infectious Diseases with Immunological Threshold

Richard I. Joh^{a,*}, Hao Wang^b, Howard Weiss^b, Joshua S. Weitz^{a,c}

^a School of Physics, Georgia Institute of Technology, Atlanta, GA, 30332, USA

^b School of Mathematics, Georgia Institute of Technology, Atlanta, GA, 30332, USA

^c School of Biology, Georgia Institute of Technology, Atlanta, GA, 30332, USA

Received: 15 April 2008 / Accepted: 2 December 2008 / Published online: 19 December 2008
© Society for Mathematical Biology 2008

Abstract There are numerous examples of human pathogens which persist in environmental reservoirs while infectious outbreaks remain rare. In this manuscript, we consider the dynamics of infectious diseases for which the primary mode of transmission is indirect and mediated by contact with a contaminated reservoir. We evaluate the realistic scenario in which the number of ingested pathogens must be above a critical threshold to cause infection in susceptible individuals. This minimal infectious dose is a consequence of the clearance effect of the innate immune system. Infected individuals shed pathogens back into the aquatic reservoir, indirectly increasing the transmissibility of the pathogen to the susceptible. Building upon prior works in the study of cholera dynamics, we introduce and analyze a family of reservoir mediated SIR models with a threshold pathogen density for infection. Analyzing this family of models, we show that an outbreak can result from noninfinitesimal introductions of either infected individuals or additional pathogens in the reservoir. We devise two new measures of how likely it is that an environmentally persistent pathogen will cause an outbreak: (i) the minimum fraction of infected individuals; and (ii) the minimum fluctuation size of in-reservoir pathogens. We find an additional control parameter involving the shedding rate of infected individuals, which we term the pathogen enhancement ratio, which determines whether outbreaks lead to epidemics or endemic disease states. Thus, the ultimate outcome of disease is controlled by the strength of fluctuations and the global stability of a nonlinear dynamical system, as opposed to conventional analysis in which disease reflects the linear destabilization of a disease free equilibrium. Our model predicts that in the case of waterborne diseases, suppressing the pathogen density in aquatic reservoirs may be more effective than minimizing the number of infected individuals.

Keywords Epidemic · Endemic · Cholera · SIR · Minimum infectious dose

*Corresponding author.

E-mail address: ijoh3@gatech.edu (Richard I. Joh).

1. Introduction

Infectious diseases can be classified based on whether the life cycle of the pathogenic agent is exclusively or partially within human hosts (Wolfe et al., 2007). When humans are the exclusive hosts for the causative agent of an infectious disease, then disease transmission depends on direct human-to-human contact. However, many pathogens utilize a combination of alternative zoonotic hosts and free-living stages in order to persist and we represent those states as reservoirs of pathogens which include nonliving environmental reservoirs and nonhuman animal hosts. Transmission between humans and reservoirs of pathogens implies that disease transmission includes an indirect route other than human-to-human contact. Indirect transmission occurs when a susceptible individual comes into contact with a contaminated reservoir. Depending on the disease, infected individuals may also shed pathogens back into the reservoir, completing the indirect transmission cycle. Infection of humans by pathogens increases the pathogen levels in the reservoir which then increases transmissibility to other susceptible individuals.

Alternative hosts are central to the origins and emergence of major human infectious diseases (Wolfe et al., 2007). Pathogens utilizing an indirect transmission route can be bacterial, viral, or parasitic. Examples of bacterial diseases whose primary mode of infection is indirect include cholera, which is caused when individuals ingest fecal contaminated water containing the bacteria *Vibrio cholerae* (Kaper et al., 1995). The transmission cycle of rotavirus disease also strongly implicates an indirect mode of transmission (Estes et al., 1983). Parasitic diseases for which indirect transmission is important include giardiasis (Wolfe, 1992), schistosomiasis (Chitsulo et al., 2000), and cryptosporidiosis (Rose, 1997).

It is widely recognized that human pathogens are prevalent in environmental sources, including drinking water (Jensen et al., 2002; Bove et al., 1995), even if environmental acquisition of disease varies from rare to frequent. The likelihood of getting sick upon contact with a contaminated reservoir depends on the pathogen density and interactions of the pathogen with the immune system. In general, the number of pathogens ingested must be high enough to cause infection to susceptible individuals, otherwise innate immune responses will eliminate the pathogen. For instance, humans need to ingest a large number of *Vibrio cholerae* to become infected: estimates range from 10^3 – 10^6 though there is no universal agreement on the minimal infectious dose (Levine et al., 1981; Colwell et al., 1996).

The dynamics of diseases that are directly transmitted between humans have traditionally been studied using modified forms of Susceptible-Infected-Recovered/Removed (SIR) models (Kermack and McKendrick, 1927). A central concept in SIR models is the basic reproductive ratio, R_0 (Dietz, 1993), equal to the number of secondary cases caused by a small number of infected individuals in an otherwise naive population. There is no such central organizing principle in the study of indirectly-transmitted human diseases when disease dynamics and immunological thresholds are necessarily linked.

In this manuscript, we introduce and analyze a family of reservoir mediated SIR models with a threshold pathogen density for infection. We term these iSIR models, where the lower case “i” denotes indirect transmission dynamics. These models are distinct from previous vector-borne models (Ross, 1908; Macdonald, 1952) in that the pathogen can stably persist in reservoirs, leading to distinct mechanisms of disease emergence. An epidemic outbreak or endemic disease state can occur in two ways: first, via the introduction

of a small, but not infinitesimal, number of infected individuals into the population, and alternatively, via small, but not infinitesimal, fluctuations in the pathogen density in a reservoir. Our analysis shows that if the pathogen carrying capacity in the reservoir in the absence of human-mediated pathogen shedding is greater than a rescaled level corresponding to the minimal infectious dose, the disease will almost surely become endemic. The situation is more complex if the pathogen carrying capacity is below the rescaled minimal infectious dose. Then depending on an enviro-epidemiological parameter, which we term the pathogen enhancement ratio, the dynamics will follow one of two scenarios: (i) almost every initial condition leads to the disease dying out; (ii) almost every initial condition will lead to either the disease dying out or an endemic state, depending on initial conditions. In the latter case, the system becomes bistable and there are two coexisting attracting equilibrium points. These equilibrium points correspond to the disease-free equilibrium and an endemic disease equilibrium state. The disease-free stable equilibrium is a consequence of the threshold corresponding to the minimal infectious dose.

In conventional SIR models, the disease free state is either stable or unstable depending on the value of R_0 (Dietz, 1993). In the present analysis of iSIR models, the disease free state is stable subject to small, but not infinitesimal, fluctuations in either pathogen density or infected individuals. To quantify these two possibilities, we define two new measures indicating whether a pathogen is likely to cause an epidemic outbreak or endemic disease state: (i) the minimum ratio of infected individuals within the total population; (ii) the minimum in-reservoir pathogen density fluctuation. These measures provide guidance as to the effectiveness of control methods which reduce infected individuals and/or suppress pathogen density in the reservoir.

2. Model formulation

Modeling the dynamics of indirectly transmitted human diseases depends on explicit consideration of pathogen dynamics within a reservoir. Indirect transmission models differ from vector-based models in that the pathogen can be free-living, or alternatively, the reservoirs are unknown so that explicit accounting of vector dynamics is impossible. The first indirect disease transmission model that we are aware of was developed by Capasso and Paveri-Fontana (1979) to describe the interaction of infected individuals with an aquatic population of pathogenic *V. cholerae*. Codeço (2001) extended Capasso's model to link SIR dynamics with dynamics of bacteria within reservoirs. Codeço assumed that the bacterial density decreases exponentially in the absence of infected individuals. More recently, Hartley et al. (2006) considered a model of cholera transmission that included two types of bacterial states, using the indirect transmission framework. All of these models assumed exponential decay for bacteria in the reservoir, despite the fact that it is not commonly observed for bacteria in aquatic reservoirs that may be free-living or have other zoonotic hosts. In such cases, it is reasonable to assume that the bacterial density fluctuates around a constant level. Recently, Jensen et al. (2006) proposed a model with logistic growth of the pathogen. None of these cholera models includes a minimal infectious dose (MID), i.e., they assume disease transmission is possible even with infinitesimally small densities of aquatic pathogens. However, it is known for cholera that a susceptible individual must ingest approximately 10^3 – 10^6 *Vibrio cholerae* to become infected (Levine et al., 1981;

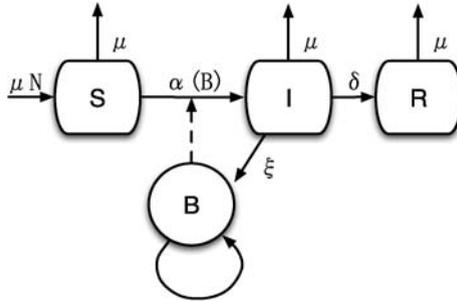


Fig. 1 Model diagram. S , I , and R are three compartments of human population denoted as the susceptible, the infected, and the recovered, respectively. The pathogen density in the reservoir is denoted as B .

Colwell et al., 1996). Below, we introduce a family of reservoir mediated SIR models with threshold pathogen density, which we refer to as iSIR models.

We use a three-compartment model consisting of susceptible, infected, and recovered individuals (see Fig. 1). Susceptible individuals are disease free. Once susceptible individuals become infected, they immediately become symptomatic and infectious. We assume that there is no infection-derived mortality and immunity, and that infected individuals eventually move into the recovered class. The assumption of zero mortality does not hold for some diseases, but it captures the essential dynamics of the infected subpopulation in a time scale of an epidemic outbreak. Our model and analysis can be easily modified to include various types of partial immunity allowing recovered individuals to become susceptible again.

Within the iSIR models presented here, transmission occurs via contact with reservoirs containing human pathogens, and not via direct person-to-person contact. We assume there is a minimum infectious dose (MID) of pathogens necessary to cause infection. The basis for explicitly modeling the MID is that the human innate immune system is capable of eliminating low levels of pathogens and staving off disease (Murphy et al., 2007). The innate immunity of individuals varies, but we assume all population members possess the same “average immunity.” Assuming the contact rate to the reservoir is identical for every individual, the minimum infectious dose can be rescaled as a threshold pathogen density for infection. If the in-reservoir pathogen density is above the threshold, susceptible individuals contact more pathogens than the infectious dose and become infected. We assume that infected individuals shed the pathogens back to the reservoir at a fixed rate, increasing the possibility that susceptible individuals contract the disease. Let S , I , and R be the numbers of the susceptible, the infected, and the recovered, respectively. We denote B as pathogen density in a reservoir. Our model can be described by a set of differential equations:

$$\frac{dS}{dt} = -\alpha(B)S - \mu S + \mu N, \quad (1)$$

$$\frac{dI}{dt} = \alpha(B)S - \mu I - \delta I, \quad (2)$$

$$\frac{dR}{dt} = \delta I - \mu R, \quad (3)$$

$$\frac{dB}{dt} = \pi(B) + \xi I. \quad (4)$$

The definitions of all parameters are presented in Table 1. Since $dS/dt + dI/dt + dR/dt = 0$, the total population of humans, denoted as N , is conserved. Thus, $R = N - S - I$, and we can focus on S , I , and B . Below, we describe the functional terms, $\alpha(B)$ and $\pi(B)$, corresponding to human-pathogen transmission rate and in-reservoir pathogen dynamics, respectively.

A key difference between this iSIR model and other SIR or indirect disease models is the explicit incorporation of a MID. For obvious reasons, higher pathogen density increases the chance that a susceptible individual becomes infected, so the transmissibility of the disease, $\alpha(B)$, is an increasing function of B . We define the threshold via the pathogen density c by requiring that $\alpha(B) = 0$ for $B \leq c$. The value c reflects a combination of immunological and ecological factors. We consider the natural family of transmissibility responses

$$\alpha(B) = \begin{cases} 0 & (B < c), \\ \frac{a(B-c)^n}{(B-c)^n + H^n} & (B \geq c), \end{cases} \quad (5)$$

where n is a positive integer. For any n , the function $\alpha(B)$ becomes saturated for sufficiently large B . In case of $n = 1$ and $n = 2$, it is almost linear and quadratic for values of B near c and known as Holling's type II and III functional response, respectively (Holling, 1959). Equation (5) is an extension of Holling's type III response and represents the gen-

Table 1 Model variables and parameters

Parameter	Description	Dimension
S	Number of the susceptible	
I	Number of the infected	
R	Number of the recovered	
N	Total population	
B	Pathogen density in a reservoir	cell liter ⁻¹
$\alpha(B)$	Transmissibility	day ⁻¹
$\pi(B)$	Pathogen growth rate	cell liter ⁻¹ day ⁻¹
μ	Per capita human birth or death rate	day ⁻¹
δ	Recovery rate	day ⁻¹
ξ	Pathogen shed rate	cell liter ⁻¹ day ⁻¹
a	Maximum rate of infection	day ⁻¹
c	Threshold pathogen density for infection	cell liter ⁻¹
r	Maximum per capita pathogen growth efficiency	day ⁻¹
K	Pathogen carrying capacity	cell liter ⁻¹
H	Half-saturation pathogen density	cell liter ⁻¹

eralized form of contact kinetics (Real, 1977). In this section, we analyze the threshold model with Holling's type II functional response

$$\alpha(B) = \begin{cases} 0 & (B < c), \\ \frac{a(B-c)}{(B-c)+H} & (B \geq c), \end{cases} \quad (6)$$

and in Appendix A, we extend our analysis to the full family of threshold models.

The growth rate of pathogen density, $\pi(B)$, is the natural in-reservoir growth rate of pathogens in the absence of human hosts. Pathogens might be free-living or exist on a variety of zoonotic hosts. The prevalence of pathogens in reservoirs suggests that there are stable steady states with positive pathogen densities but no infected individuals. We assume that pathogens exhibit the logistic growth, $\pi(B) = rB(1 - B/K)$ (Jensen et al., 2006). Without human hosts, the pathogen density will reach a constant level in the reservoir, generally referred to as the organism's carrying capacity.

The nondimensionalized versions of Eqs. (1–4) are

$$\frac{dS}{d\tau} = -\bar{\alpha}(B)S - S + 1, \quad (7)$$

$$\frac{dI}{d\tau} = \bar{\alpha}(B)S - pI, \quad (8)$$

$$\frac{dB}{d\tau} = \mathcal{R}B(1 - B) + qI, \quad (9)$$

where $S = S/N$, $I = I/N$, $B = B/K$, $\tau = \mu t$, $\mathcal{A} \equiv a/\mu$, $\mathcal{C} \equiv c/K$, $p \equiv (\mu + \delta)/\mu$, $q \equiv \xi N/\mu K$, $\mathcal{R} \equiv r/\mu$, $\lambda = H/K$ and

$$\bar{\alpha}(B) \equiv \begin{cases} 0 & (B < C), \\ \frac{\mathcal{A}(B-C)}{(B-C)+\lambda} & (B \geq C). \end{cases} \quad (10)$$

Note that I can increase in two ways: (i) pathogen density becomes higher than the threshold for infection, then subsequently there is a chance of transmission for each contact with the reservoir (Fig. 2(a)) (ii) introduction of infected individuals into the community, then pathogen density becomes higher due to shedding from infected individuals. If the fraction of infected individuals is sufficiently high, then shedding can cause B to become greater than C , which can cause further infection of the susceptible (Fig. 2(b)). In this case, the basic reproductive number, R_0 , would be less than 1, even though the number of infected individuals increases after a period of initial decline. Thus, we need alternative measures other than R_0 to determine if there will be an outbreak and the extent of such outbreaks when they occur.

3. Analysis of the model

3.1. Equilibrium points and asymptotic behavior

Recall that C is the ratio of the re-scaled minimum infectious dose to the reservoir carrying capacity. We will now show that if $C < 1$ there are two equilibrium points, and if $C > 1$,

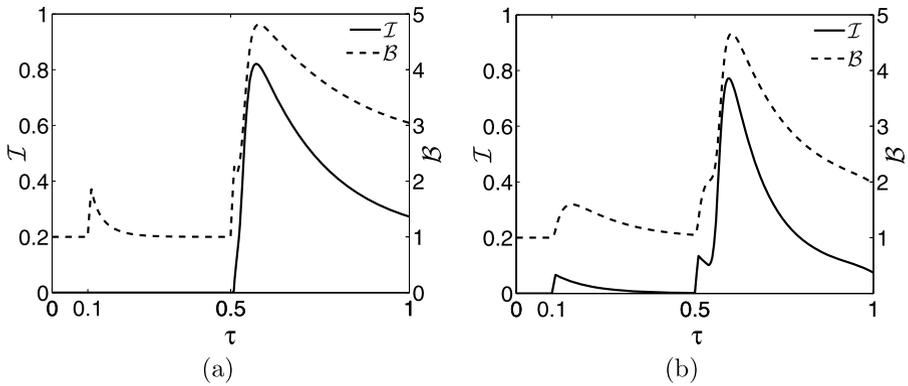


Fig. 2 Dynamics of \mathcal{I} and \mathcal{B} when \mathcal{I} or \mathcal{B} is are perturbed suddenly at two distinct times, $\tau = 0.1$ and $\tau = 0.5$. (a) An outbreak induced by pathogen density fluctuation in the reservoir. \mathcal{B} was increased suddenly at $\tau = 0.1$ and $\tau = 0.5$. (b) An outbreak initiated by the introduction of infected individuals. \mathcal{I} was increased suddenly at $\tau = 0.1$ and $\tau = 0.5$. Parameters are $\mathcal{A} = 100$, $\mathcal{C} = 2$, $p = 10$, $q = 450$, $\mathcal{R} = 20$, and $\lambda = 1$.

there are either two, three, or four equilibrium points. The case of $\mathcal{C} < 1$ implies that the in-reservoir carrying capacity exceeds the rescaled MID, and $\mathcal{C} > 1$ denotes the opposite.

Let $(S^*, \mathcal{I}^*, \mathcal{B}^*)$ be an equilibrium point for the system in Eqs. (7–9). Equation (10) shows that $\bar{\alpha}(\mathcal{B})$ is positive only when $\mathcal{B} > \mathcal{C}$. Thus, if the pathogen density \mathcal{B} is above the threshold \mathcal{C} , susceptible individuals become infected; otherwise, there is no further infection. We first consider both cases separately and then combine them to obtain Proposition 2.

For $\mathcal{B}^* < \mathcal{C}$, $\bar{\alpha}(\mathcal{B}^*) = 0$, and thus $S^* = 1$ and $\mathcal{I}^* = 0$. From Eq. (9), \mathcal{B}^* corresponds to the roots of the quadratic equation

$$\mathcal{R}\mathcal{B}^*(\mathcal{B}^* - 1) = 0. \tag{11}$$

The root $\mathcal{B}^* = 0$ corresponds to the equilibrium point $(1, 0, 0)_u$ and, provided $\mathcal{C} > 1$, the root $\mathcal{B}^* = 1$, corresponds to the equilibrium point $(1, 0, 1)_s$. The equilibrium point $(1, 0, 0)_u$ is a saddle, and $(1, 0, 1)_s$ is stable. Thus, for $\mathcal{C} < 1$, there is a single unstable equilibrium point $(1, 0, 0)_u$, and for $\mathcal{C} \geq 1$, there are two equilibrium points: $(1, 0, 0)_u$ and $(1, 0, 1)_s$. There are no infected individuals corresponding to either equilibrium point.

For $\mathcal{B}^* \geq \mathcal{C}$, Eqs. (7–9) at equilibrium yield

$$S^* = \frac{\mathcal{B}^* - \mathcal{C} + \lambda}{(\mathcal{A} + 1)(\mathcal{B}^* - \mathcal{C}) + \lambda}, \tag{12}$$

$$\mathcal{I}^* = \frac{1}{p} \left(\frac{\mathcal{A}(\mathcal{B}^* - \mathcal{C})}{(\mathcal{A} + 1)(\mathcal{B}^* - \mathcal{C}) + \lambda} \right) \tag{13}$$

$$= \frac{\mathcal{R}}{q} \mathcal{B}^*(\mathcal{B}^* - 1). \tag{14}$$

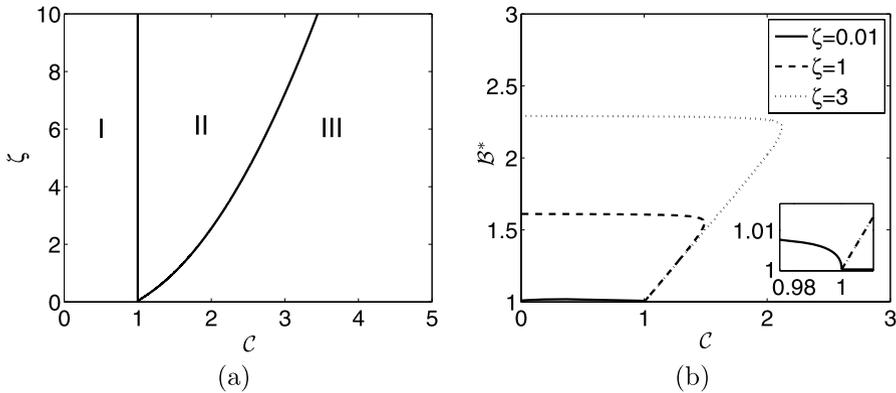


Fig. 3 (a) Bifurcation diagram for $\mathcal{A} = 100$ and $\lambda = 1$. For $C > 1$, the saddle node bifurcation locus separates the parameter space into two components. (b) Relationship between nontrivial steady state pathogen density and C for various ζ . For sufficiently small ζ , there is no saddle node bifurcation by changing C .

Equations (13–14) can be combined as

$$B^*(B^* - 1) \left(B^* - \left(C - \frac{\lambda}{\mathcal{A} + 1} \right) \right) = \zeta \frac{\mathcal{A}}{\mathcal{A} + 1} (B^* - C), \tag{15}$$

where $\zeta \equiv q/pR$. The number of roots of the cubic equation, Eq. (15), depends of the values of ζ , \mathcal{A} , λ , and C . One can easily analyze the roots by graphing the left- and right-hand sides of the equation and counting intersection points.

If $C < 1$, there is one root $B^* \geq C$, that corresponds to a attracting equilibrium point $(\hat{S}_0, \hat{\mathcal{I}}_0, \hat{B}_0)_s$ with $\hat{\mathcal{I}}_0 > 0$.

If $C > 1$, there are either zero, one, or two roots with $B^* \geq C$. The existence of additional equilibrium points depends on the choice of parameters: the relation between ζ and C is crucial (see Figs. 3 and 4). For sufficiently small ζ , there are no additional equilibrium points, and as ζ increases, there is a saddle-node bifurcation (Strogatz, 1994) that creates a saddle equilibrium point $(\hat{S}_1, \hat{\mathcal{I}}_1, \hat{B}_1)_u$ and an attracting equilibrium point $(\hat{S}_2, \hat{\mathcal{I}}_2, \hat{B}_2)_s$ with $\hat{\mathcal{I}}_2 > \hat{\mathcal{I}}_1 > 0$ (see Fig. 5). In Appendix B, we derive the exact algebraic conditions for the bifurcation.

Definition 1. For a given initial condition, a disease is *endemic* if $I(\infty) > 0$.

We now combine and summarize these calculation on the existence and stability of equilibrium points.

Proposition 2 (Equilibrium Points and Asymptotic Behavior of Solutions).

- (1) If $C < 1$, there are two equilibrium points: $(1, 0, 0)_u$ is a saddle and $(\hat{S}_0, \hat{\mathcal{I}}_0, \hat{B}_0)_s$ is attracting with $\hat{\mathcal{I}}_0 > 0$. It follows that the solution for almost every initial condition converges to $(\hat{S}_0, \hat{\mathcal{I}}_0, \hat{B}_0)_s$. Hence, for almost all initial conditions, the disease becomes endemic.

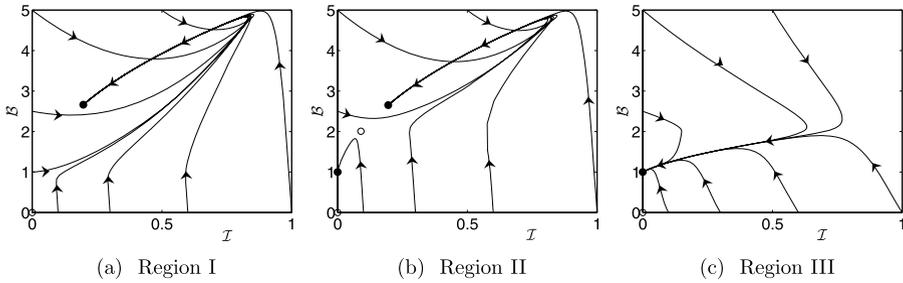


Fig. 4 Schematic diagram of phase portraits projected into the IB plane. Note that the trajectories can cross in the projected representation. Stable equilibria are marked as \bullet , while \circ represents an unstable equilibrium. (a) Region I: $C < 1$ ($C = 0.8$ and $\zeta = 4.5$). For almost every solution, the number of infected individuals does not go to zero. (b) Region II: $C > 1$ and sufficiently large ζ ($C = 2$ and $\zeta = 4.5$). The system becomes bistable with two stable equilibrium points, and asymptotic behavior is determined by initial conditions. (c) Region III: $C > 1$ and small ζ ($C = 2$ and $\zeta = 0.5$). The number of the infected goes to zero as $t \rightarrow \infty$. The parameter ζ is defined as $q/p\mathcal{R}$.

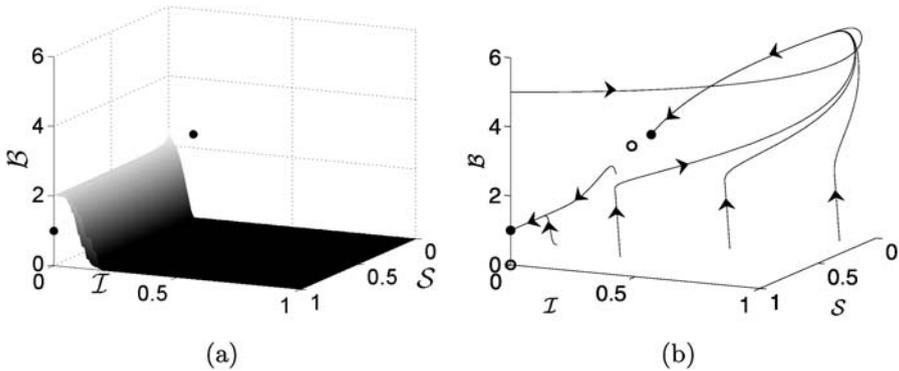


Fig. 5 Phase portrait for $C > 1$ and large ζ . There are two stable equilibrium points that attract almost all solutions and asymptotic behaviors depend on the choices of initial conditions. (a) The surface represents the boundary of two attracting basins. (b) Trajectories in the phase space with attracting equilibrium points. Stable equilibria are marked as \bullet , while \circ represents an unstable equilibrium. Parameters are $\mathcal{A} = 10^3$, $C = 2$, $p = 10$, $q = 10^3$, $\mathcal{R} = 30$, and $\lambda = 1$.

(2) If $C > 1$, the equilibrium point $(1, 0, 0)_u$ is a saddle, $(1, 0, 1)_s$ is attracting, and there exist up to two additional equilibrium points. For sufficiently small ζ , there are no additional equilibrium points, and the solution for almost every initial condition converges to $(1, 0, 1)_s$. Thus, $I(\infty) = 0$, and the population becomes asymptotically disease free.

If there are two additional equilibrium points, $(\hat{S}_1, \hat{I}_1, \hat{B}_1)_u$ is a saddle, and $(\hat{S}_2, \hat{I}_2, \hat{B}_2)_s$ is attracting with $\hat{I}_2 > \hat{I}_1 > 0$. In this case, the solution for almost every initial condition converges to one of the two attracting equilibrium points, and asymptotically the population becomes either disease free or the disease becomes endemic (depending on initial conditions).

Corollary 3 (Zero threshold case). *The special case where there is no threshold occurs when $C = 0$. It follows from Proposition 2 that for almost all initial conditions, the disease becomes endemic.*

Remark 4 (Biological interpretation of ζ). In the original variables, ζ can be written as

$$\zeta = \left(\frac{\xi N}{\mu + \delta} \right) \left(\frac{\mu}{rK} \right). \tag{16}$$

From Eq. (4), ξN is the pathogen shed rate when all individuals are infected and $1/(\mu + \delta)$ is the average duration of infection. The first term, $\xi N/(\mu + \delta)$, represents the total number of pathogens shed into the reservoir during the average period of infectiousness assuming all individuals were infected and there were no feedback. The term rK is the in-reservoir pathogen birth rate in the absence of shedding and $1/\mu$ is the average life-span of a susceptible individual. Hence, we interpret this dimensionless number as the ratio of two factors: (i) the average number of pathogens shed over the time course of infection if all individuals were infected; (ii) the average number of pathogens reproduced in the reservoir over the time course of an uninfected individual. We term this the pathogen enhancement ratio and expect that endemic outbreaks rather than epidemic outbreaks will be favored for increasing values of ζ .

3.2. Epidemics

We use the following definition of an epidemic.

Definition 5. For an initial condition, an *epidemic* occurs if $dI/dt(t_0) > 0$ at some time t_0 , i.e., the number of infected individuals is increasing at some time $t_0 > 0$.

As is the case for SIR models, an initial condition can lead to a disease that is both epidemic and endemic.

In our model, an epidemic or endemic can result from the introduction of infected individuals into the population or sufficiently large fluctuations of pathogen density in the reservoir. Thus, unlike most disease models, pathogens are able to maintain a foot-hold in a reservoir and persist stably without causing infections. Starting with the disease free equilibrium with the pathogen density in the reservoir at its carrying capacity, $(1, 0, 1)_s$, we represent the density fluctuation of pathogens within the reservoir by $(1, 0, 1)_s \rightarrow (1, 0, \mathcal{B}_0)$, and the introduction of infected individuals into the population by $(1, 0, 1)_s \rightarrow (1 - \mathcal{I}_0, \mathcal{I}_0, 1)$. If $\mathcal{B}_0 > C$, the number of new infected individuals starts increasing.

How then can we determine the criterion for when an epidemic does or does not occur? If \mathcal{I}_0 is sufficiently large, there exists $\tau_0 > 0$ such that $\mathcal{B}(\tau_0) = C$. If the pathogen density is increasing at this instant, i.e.,

$$\frac{d\mathcal{B}}{d\tau}(\mathcal{B}(\tau_0) = C) > 0, \tag{17}$$

then \mathcal{B} will increase and more susceptible individuals will become infected. From Eq. (9), this can be written as

$$\mathcal{I}(\tau_0) = \mathcal{I}_0 e^{-p\tau_0} > \frac{\mathcal{R}C(C - 1)}{q}. \tag{18}$$

For the pathogen density to increase over its threshold requires that $d\mathcal{B}/d\tau(\tau_0) > 0$, which implies $\bar{\alpha}(\tau) > 0$ immediately after τ_0 , and thus some susceptible individuals start getting infected. It follows that Eq. (18) is a necessary condition for an infection. It is not a sufficient condition because the first term on the RHS of Eq. (8) could be larger than the second term. However, if the product of the recovery rate and the number of infected individuals is small, then this necessary condition is close to being sufficient. We cannot yet prove this result, but it holds for the cases we have considered.

3.3. Two measures of distance to an epidemic

We use the observations in the previous subsection to define two new measures of how likely it is that a disease-free equilibrium subject to perturbations will exhibit endemic or epidemic behavior. Since an epidemic or endemic can result from either an introduction of infected individuals or a density fluctuation of pathogens within the reservoir, we must account for both components.

The first measure is $\Delta\mathcal{B}$, the minimum magnitude of pathogen density fluctuations required to initiate an epidemic, starting at the disease free equilibrium with the pathogen density in the reservoir at its carrying capacity. The fluctuation of pathogen density can be represented as $(1, 0, 1 + \delta\mathcal{B}_0)$, and if $\delta\mathcal{B}_0 > \Delta\mathcal{B}$, an epidemic will occur. It immediately follows from Eq. (10) that

$$\Delta\mathcal{B} = \mathcal{C} - 1. \quad (19)$$

The second measure is $\Delta\mathcal{I}$, the minimum proportion of infected individuals required to initiate an epidemic, starting at the disease free equilibrium with the pathogen density in the reservoir at its carrying capacity. The addition of infected individuals can be represented as $(1 - \delta\mathcal{I}, \delta\mathcal{I}, 1)$. If $\delta\mathcal{I} > \Delta\mathcal{I}$, then there will be an epidemic, otherwise the disease will die out asymptotically.

Often, the time scale of epidemiological dynamics is considerably slower than the average duration of infection (Mourino-Pérez et al., 2003), that is, the number of infected individuals changes slowly relative to the pathogen generation time. In this case, we make the approximation that $d\mathcal{I}/dt = 0$, and thus from Eq. (18), $\Delta\mathcal{I}$ can be written as

$$\Delta\mathcal{I} = \frac{\mathcal{R}\mathcal{C}(\mathcal{C} - 1)}{q}. \quad (20)$$

There will be an epidemic if the proportion of added infected individuals is greater than $\Delta\mathcal{I}$.

Above we only considered two types of changes to the initial conditions. Of course, one can perturb the equilibrium state $(1, 0, 1)_s$ by changing both the number of infected individuals and pathogen density. Taken together, $\Delta\mathcal{I}$ and $\Delta\mathcal{B}$ provide significant insight into opportunities for control and prevention of disease outbreaks (see Fig. 6). If the minimum ratio of infected individuals to cause an epidemic or endemic condition is small, then emphasis should be placed on minimizing new infected cases. Public education and quick diagnosis would be important to suppress disease transmission. Further, variation in the disease threshold due to heterogeneity in innate immune systems may also play a key role in facilitating movement of pathogens from reservoirs to humans. On the other hand, if the

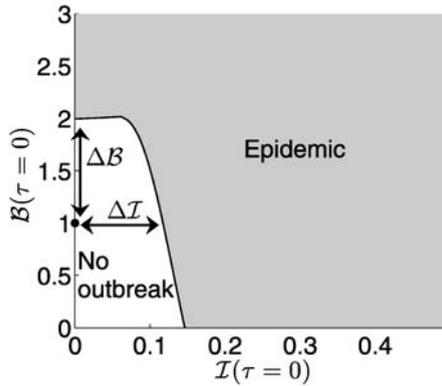


Fig. 6 Graphic representation of ΔI and ΔB . Each point on the plane represents an initial condition given as $(S, I, B) = (1 - I(0), I(0), B(0))$ and there is an epidemic if $dI/d\tau > 0$. Parameters are same as Fig. 5.

Table 2 Order of magnitude estimations of ΔB and ΔI for waterborne diseases. Estimation of parameters is given in Appendix C

Disease	Number of pathogens shed by an infected/day (pathogen/day)	Infectious dose (pathogen)	Typical concentration (pathogen/liter)
Cholera	10^{11} – 10^{12} (Kaper et al., 1995)	10^3 – 10^6 (Levine et al., 1981; Colwell et al., 1996)	10 – 10^3 (Brayton et al., 1987)
Cryptosporidiosis	10^8	100 – 300 (DuPont et al., 1995)	1 – 5 (LeChevallier et al., 1991)
Giardiasis	10^8 – 10^9 (Rendtorff, 1954)	10 – 100 (Rendtorff, 1954)	1 – 5 (LeChevallier et al., 1991)
Rotavirus disease	10^{12} – 10^{13} (White and Fenner, 1994)	100	10 – 1000 (Ward et al., 1986)

Disease	ΔB	ΔI
Cholera	10 – 100	0.001 – 1
Cryptosporidiosis	20 – 300	0.01 – 1
Giardiasis	1 – 100	0.01 – 0.1
Rotavirus disease	< 10	NA

minimum pathogen density fluctuation to cause an epidemic or endemic is small, maintaining or lowering in- reservoir pathogen density will prevent the disease. For diseases with nonhuman alternative hosts, controlling alternative zoonotic hosts for pathogens can be an effective approach. For bacterial diseases, introducing phage into bacterially contaminated reservoirs might regulate bacterial density at lower levels (Jensen et al., 2006). Given sufficient resources, multiple modes of control are likely to be most effective. The point of the two measures, ΔI and ΔB is to provide additional context for prioritization.

Table 2 shows the estimation of ΔB and ΔI for waterborne diseases. We preface any such discussion of quantitative comparisons with the caveat that additional research on

MID and carrying capacities would dramatically improve these estimates. Nonetheless, we estimate that the infectious dose for giardiasis is slightly higher than the typical density in natural water reservoirs (Rendtorff, 1954; LeChevallier et al., 1991). The MID would be much lower for the immuno-compromised, thus lower than the density in aquatic reservoirs. Giardiasis is known for several epidemic outbreaks as well as an endemic for the immuno-compromised (Webster, 1980), which is consistent with our model prediction.

Depending on the pathogen, we find that ΔI may be very small for some cases, but even sudden immigration and/or infection of 1% of total population does not happen often. In contrast, pathogen/parasite density often varies several orders of magnitude, and thus would be responsible for the majority of outbreaks. This analysis suggests that control of pathogen density in reservoirs would be more effective than minimizing the number of infected individuals for indirectly transmitted infectious diseases.

4. Discussion

Preventive methods for a disease are usually focused on the dynamics of human populations and emphasize minimizing transmission via direct contacts and prompt diagnosis upon detectable signs of illness. However, ecological dynamics of human pathogens within natural reservoirs also play an important role for many types of diseases. The dynamics of human pathogens are closely linked to climate pattern (Pascual et al., 2000) and the typical concentration of human pathogens varies substantially with seasonality. In addition, rapid climate change by global warming is altering the ecosystem of microorganisms and regions with an endemic or epidemic might shift drastically (Yoganathan and Rom, 2001). The study of the emergence of infectious diseases is likely to become increasingly important with increases in human and livestock population (Wolfe et al., 2007) and increasing stress placed on aquatic reservoirs (Häder et al., 1998).

Here, we presented a family of iSIR models which couple in-reservoir pathogen dynamics to epidemiological dynamics. For reservoir-mediated diseases, the minimal infectious dose is crucial for disease transmission. The likelihood of an epidemic or an endemic outbreak can be expressed in terms of two dimensionless parameters: $\Delta \mathcal{I}$, the minimum ratio of infected individuals, and $\Delta \mathcal{B}$, the minimum pathogen density fluctuation to initiate an epidemic or endemic. The relative magnitude of $\Delta \mathcal{I}$ and $\Delta \mathcal{B}$ can serve as guidelines in disease risk assessments and the need to implement control measures. Further, when an outbreak does occur, we defined an additional measure, the pathogen enhancement ratio, that determines whether the outbreak leads to an epidemic or endemic disease state. Note that our pathogen enhancement ratio is similar to R_0 of Hartley et al. (2006).

The iSIR model presented in this paper is generalizable and can be applied to diseases other than cholera. The model can be modified with short or no memory infection-derived immunity for parasitic diseases and share many of the qualitative features. Also, the model can describe diseases with indirect transmission via reservoirs, but without feedback from infected individuals. The dynamics of such models reflects strict source-sink dynamics of pathogens. Examples include legionellosis (Fields et al., 2002) by bacteria *Legionella pneumophila* and hantavirus pulmonary syndrome (Zaki et al., 1995). In such cases, pathogen dynamics are largely decoupled from within-human dynamics, thus the control of pathogen density within the reservoirs is central to their prevention.

There are many challenges to confront in this and related models of indirect transmission. First, the basic assumption of models is homogeneity in the immunological state of susceptible individuals and in the distribution of environmental pathogens. In reality, pathogens are distributed heterogeneously and some highly contaminated reservoirs may be responsible for most incidences of infection. Also, the average number of contacts with contaminated reservoirs as well as the minimum infectious dose differs among individuals. Second, there are many factors that limit our ability to determine $\Delta\mathcal{I}$ and $\Delta\mathcal{B}$. It is necessary to understand the dynamics of free-living stages and alternative hosts as well as to develop accurate detection schemes to measure the pathogen density in reservoirs. Here we used a logistic growth model of in-reservoir pathogen dynamics for simplicity, but the model can be improved by using more realistic behaviors of pathogen dynamics. Vector-borne models in which the vector is known and can be monitored have been of exceptional utility, as in studies of links between mosquito densities and malaria dynamics (Craig and Snow, 1999). However, for diseases in which pathogen densities are undetectable because the zoonotic host is unknown, or for cases in which pathogens possess a free-living stage, the present framework is likely to be highly relevant. Further, by explicitly incorporating an immunological threshold, we are able to show how low levels of environmental pathogens can, given suitably large fluctuations, lead to occasional emergence of epidemic and endemic disease.

Acknowledgements

We are pleased to acknowledge the support of the Defense Advanced Research Projects Agency under grant HR0011-05-1-0057. Joshua S. Weitz, Ph.D., holds a Career Award at the Scientific Interface from the Burroughs Wellcome Fund.

Appendix A: Analysis for generalized functional responses

A.1 Linear response

A linear functional response, known as Holling's type I response with threshold can be written as

$$\alpha(B) = \begin{cases} 0 & (B < c), \\ a(B - c) & (B \geq c). \end{cases} \quad (\text{A.1})$$

Then Eq. (15) becomes

$$\mathcal{B}^*(\mathcal{B} - 1) \left(\mathcal{B}^* - \left(c - \frac{1}{\mathcal{A}} \right) \right) = \zeta(\mathcal{B}^* - c), \quad (\text{A.2})$$

where $\mathcal{A} \equiv aK/\mu$ and all other constants are defined as before. Hence, the asymptotic behavior is identical to the type II response.

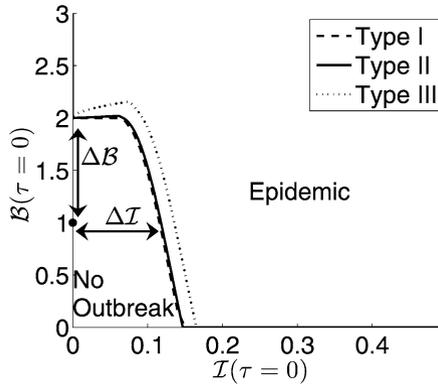


Fig. A.1 Comparison of ΔI and ΔB for Holling’s three types of functional responses. Note that ΔI is larger for type III functional response than type I or II functions. Parameters are same as Fig. 5.

A.2 General responses

The more general form of $\alpha(B)$ is given by

$$\alpha(B) = \begin{cases} 0 & (B < c), \\ \frac{a(B-c)^n}{(B-c)^n + K^n} & (B \geq c), \end{cases} \tag{A.3}$$

where n is a positive integer. Holling’s type II and III functional responses correspond to $n = 1$ and $n = 2$, respectively. Equation (A.3) is an extension of Holling’s type III response and is a generalized form of Michaelis–Menton enzyme kinetics. In this case, Eq. (15) becomes

$$B^*(B^* - 1)((A + 1)(B^* - C)^n + 1) = \zeta A(B^* - C)^n, \tag{A.4}$$

which is easily shown to have two solution for sufficiently large ζ . Thus, the asymptotic behavior is unchanged. Large n implies that the functional response is changing sharply depending on the pathogen density. As n increases, the transmissibility near the threshold becomes smaller, thus $dI/d\tau$ becomes smaller. Therefore, to induce an epidemic, a higher ratio of the infected is necessary and ΔI becomes larger for higher n (see Fig. A.1).

Appendix B: Condition for bifurcation

Let $f(B^*) \equiv \zeta A(B^* - C)/(A + 1)$ and $g(B^*) \equiv B^*(B^* - 1)(B^* - (C - (1/A + 1)))$, representing the RHS and LHS of Eq. (15). Then a saddle node bifurcation occurs when there is a point B^* satisfying $f(B^*) = g(B^*)$ and $f'(B^*) = g'(B^*)$. Note that there is a point where

$$\frac{dg(B^*)}{dB^*} = \frac{df(B^*)}{dB^*}. \tag{B.1}$$

Let the value of \mathcal{B}^* satisfying Eq. (B.1) be \mathcal{B}^\dagger . Then \mathcal{B}^\dagger can be expressed in terms of other parameters as

$$\mathcal{B}^\dagger = -\frac{1}{3(\mathcal{A}+1)} + \frac{1+C}{3} + \frac{\sqrt{2 + \mathcal{A} - 2(\mathcal{A}+1)\mathcal{C} + (\mathcal{A}+1)^2(1-\mathcal{C} + \mathcal{C}^2 + 3\zeta\frac{\mathcal{A}}{\mathcal{A}+1})}}{3(\mathcal{A}+1)}. \quad (\text{B.2})$$

Since $dg(\mathcal{B}^*)/d\mathcal{B}^*$ is an increasing function when $\mathcal{B}^* > \mathcal{C}$, $\mathcal{B}^\dagger > \mathcal{C}$ if

$$g'(\mathcal{B}^* = \mathcal{C}) < f' = \zeta \frac{\mathcal{A}}{\mathcal{A}+1}. \quad (\text{B.3})$$

Therefore, two conditions for saddle-node bifurcation become

$$\begin{aligned} \zeta &> \frac{\mathcal{A}+1}{\mathcal{A}} g'(\mathcal{B}^* = \mathcal{C}) \\ &= \frac{\mathcal{A}+1}{\mathcal{A}} \left(\mathcal{C}^2 + \left(\frac{2}{\mathcal{A}+1} - 1 \right) \mathcal{C} - \frac{1}{\mathcal{A}+1} \right), \end{aligned} \quad (\text{B.4})$$

$$f(\mathcal{B}^\dagger) = g(\mathcal{B}^\dagger). \quad (\text{B.5})$$

Appendix C: Estimation of $\Delta\mathcal{I}$

In the nonrescaled variables, $\Delta\mathcal{I}$ is expressed as

$$\Delta\mathcal{I} = \frac{rc}{\xi N} \frac{c-K}{K}. \quad (\text{C.1})$$

The average daily intake of water varies in the order of 1–10 liters, but much of it is via food and heated before intake. Therefore, we assume the average daily intake of untreated water is 1 liter; i.e., the amount of water taken directly from aquatic reservoirs. A susceptible individual becomes infected if the number of pathogens within 1 liter exceeds the minimum infectious dose. Therefore, the threshold pathogen density for infection, c , becomes

$$c = \frac{\text{infectious dose}}{1 \text{ liter}}. \quad (\text{C.2})$$

The growth rate, r , is known for cholera as 0.3–14.3/day (Mourino-Pérez et al., 2003). For other diseases, it is not known because the pathogen(parasite) density is regulated by nonhuman hosts and the time scale of density regulation would be smaller than that of free-living bacteria. Thus, we set $r = 0.1/\text{day}$ for other diseases, which is lower than growth rate of cholera.

Let η be the total number of pathogens shed by an infected individual per day and V_{res} be the total volume of the reservoir. Then we can estimate the shed rate, ξ , as

$$\xi = \frac{\eta}{V_{\text{res}}}. \quad (\text{C.3})$$

We assume the volume of the reservoir, V_{res} , would be proportional to the total population, N . A estimation would be that the reservoir typically contains enough water for 100 days and a person would utilize about 100 liters/day via drinking, food processing, washing, etc. Thus, we can assume

$$\frac{V_{\text{res}}}{N} \approx 10^4 \text{ liter.} \quad (\text{C.4})$$

Combing all these estimations, Eq. (C.1) can be rewritten as

$$\Delta \mathcal{I} = 10^3 \text{ (liter/day)} \times \frac{c(c - K)}{\eta K}. \quad (\text{C.5})$$

References

- Bove, F.J., Fulcomer, M.C., Klotz, J.B., Esmart, J., Dufficy, E.M., Savrin, J.E., 1995. Public drinking water contamination and birth outcomes. *Am. J. Epidemiol.* 141, 850–862.
- Brayton, P.R., Tamplin, M.L., Huq, A., Colwell, R.R., 1987. Enumeration of *vibrio cholerae* O1 in Bangladesh waters by fluorescent-antibody direct viable count. *Appl. Environ. Microbiol.* 53, 2862–2865.
- Capasso, V., Paveri-Fontana, S.L., 1979. A mathematical model for the 1973 cholera epidemic in the European Mediterranean region. *Rev. Epidém. Santé Pub.* 27, 121–132.
- Chitsulo, L., Engles, D., Montresor, A., Savioli, L., 2000. The global status of schistosomiasis and its control. *Acta Trop.* 77, 41–51.
- Codeço, C.T., 2001. Endemic and epidemic dynamics of cholera: the role of the aquatic reservoir. *BMC Infect. Dis.* 1, 1.
- Colwell, R.R., Bryatton, P., Herrington, D., Tall, B., Huq, A., Levine, M.M., 1996. Viable but nonculturable *vibrio cholerae* revert to a cultivable state in the human intestine. *World J. Microbiol. Biotechnol.* 12, 28–31.
- Craig, M.H., Snow, R.W., le Sueur, D., 1999. A climate-based distribution model of malaria transmission in sub-Saharan Africa. *Parasitol. Today* 15, 105–111.
- Dietz, K., 1993. The estimation of the basic reproduction number for infectious diseases. *Stat. Meth. Med. Res.* 2, 23–41.
- DuPont, H.L., Chappell, C.L., Sterling, C.R., Okhuysen, P.C., Rose, J.B., Jakubowski, W., 1995. The infectivity of *cryptosporidium parvum* in healthy volunteers. *N. Eng. J. Med.* 332, 855–859.
- Estes, M.K., Palmer, E.L., Obijeski, J.F., 1983. Rotavirus: a review. *Curr. Top. Microbiol. Immunol.* 105, 123–184.
- Fields, B.S., Benson, R.F., Besser, R.E., 2002. *Legionella* and legionnaires' disease: 25 years of investigation. *Clin. Microbiol. Rev.* 15, 506–526.
- Häder, D.P., Kumar, H.D., Smith, R.C., Worrest, R.C., 1998. Effects on aquatic ecosystems. *J. Photochem. Photobiol. B: Biol.* 46, 53–68.
- Hartley, D.M., Morris, J.G., Smith, D.L., 2006. Hyperinfectivity: A critical element in the ability of *v. cholerae* to cause epidemics? *PLoS Med.* 3, e7.
- Holling, C.S., 1959. The components of predation as revealed by a study of small-mammal predation of the European pine sawfly. *Can. Entomol.* 91, 293–320.
- Jensen, P.K., Ensink, J.H.J., Jayasinghe, G., van de Hoek, W., Cairncross, S., Dalsgaard, A., 2002. Domestic transmission routes of pathogens: the problem of in-house contamination of drinking water during storage in developing countries. *Trop. Med. Int. Health* 7, 604–609.
- Jensen, M.A., Faruque, S.M., Mekalanos, J.J., Levin, B.R., 2006. Modeling the role of bacteriophage in the control of cholera outbreaks. *Proc. Natl. Acad. Sci. USA* 103, 4652–4657.
- Kaper, J.B., Morris Jr., J.G., Levine, M.M., 1995. Cholera. *Clin. Microbiol. Rev.* 8, 48–86.
- Kermack, W.O., McKendrick, A.G., 1927. A contribution to the mathematical theory of epidemics. *Proc. R. Soc. Lond. A* 115, 700–721.
- LeChevallier, M.W., Norton, W.D., Lee, R.G., 1991. *Giardia* and *cryptosporidium* spp. in filtered drinking water supplies. *Appl. Environ. Microbiol.* 57, 2617–2621.

- Levine, M.M., Black, R.E., Clements, M.L., Nalin, D.R., Cisneros, L., Finkelstein, R.A., 1981. Volunteer studies in development of vaccines against cholera and enterotoxigenic *escherichia coli*: a review. In: Holme, T., Holmgren, J., Merson, M.H., Mollby, R. (Eds.), *Acute Enteric Infections in Children. New Prospects for Treatment and Prevention*, pp. 443–459. Elsevier/North-Holland Biomedical Press, Amsterdam.
- Macdonald, G., 1952. The analysis of equilibrium in malaria epidemiology. *Trop. Dis. Bull.* 49, 813–829.
- Mourino-Pérez, R.R., Worden, A.Z., Azam, F., 2003. Growth of *vibrio cholerae* O1 in red tide waters off California. *Appl. Environ. Microbiol.* 69, 6923–6931.
- Murphy, K.M., Travers, P., Walport, M., 2007. *Janeway's Immunobiology*, 7th edn. Garland Science.
- Pascual, M., Rodó, X., Ellner, S.P., Colwell, R., Bouma, M.J., 2000. Cholera dynamics and El Niño–Southern oscillation. *Science* 289, 1766–1769.
- Real, L., 1977. The kinetics of functional response. *Am. Nat.* 111, 289–300.
- Rendtorff, R.C., 1954. The experimental transmission of human intestinal protozoan parasites: *Giardia lamblia* cysts given in capsules. *Am. J. Hyg.* 59, 209–220.
- Rose, J.B., 1997. Environmental ecology of *crptosporidium* and public health implications. *Annu. Rev. Public Health* 18, 135–161.
- Ross, R., 1908. Report on the Prevention of Maralaria in Mauritius. Waterlow and Sons Ltd.
- Strogatz, S.H., 1994. *Nonlinear Dynamics and Chaos: With Applications to Physics, Biology, Chemistry, and Engineering*. Perseus Books.
- Ward, R.L., Bernstein, D.I., Young, E.C., Sherwood, J.R., Knowlton, D.R., Shiff, G.M., 1986. Human rotavirus studies in volunteers: determination of infectious dose and serological response to infection. *J. Infectious Dis.* 154, 871–880.
- Webster, A.D., 1980. Giardiasis and immunodeficiency diseases. *Trans. R. Soc. Trop. Med. Hyg.* 74, 440–443.
- White, P.O., Fenner, F.J., 1994. *Medical Virology*, 4th edn. Academic, San Diego.
- Wolfe, M.S., 1992. Giardiasis. *Clin. Microbiol. Rev.* 5, 93–100.
- Wolfe, N.D., Dunovan, C.P., Diamond, J., 2007. Origins of major human infectious diseases. *Nature* 447, 279–283.
- Yoganathan, D., Rom, W.N., 2001. Medical aspects of global warming. *Am. J. Ind. Med.* 40, 199–210.
- Zaki, S.R., et al., 1995. Hantavirus pulmonary syndrome—pathogenesis of an emerging infectious disease. *Am. J. Pathol.* 146, 552–579.