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Outside-host predation as a biological control against an environmental opportunist disease

Ilona Merikanto[a,b,*], Jouni T. Laakso[a,b], Veijo Kaitala[a]

[a] Department of Biosciences, University of Helsinki, Helsinki, Finland
[b] Centre of Excellence in Biological Interactions, University of Jyväskylä, Finland

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ABSTRACT

Environmentally growing opportunist pathogens are a common threat to human health and food production. Due to environmental growth of the pathogen, these diseases are difficult to control with disinfectants and antibiotics. Thus, there is a need for sustainable and effective control methods against environmentally growing opportunist diseases. Predation is often a major limiting factor in the outside host environment. Here we propose that it could be used in the biological control of these diseases.

We introduce a novel epidemiological model for environmentally growing opportunists combining pathogen growth within-host (SI model) and outside-host into classical predator-prey model. We ask how the predation of the pathogens affects epidemiological dynamics, and whether outside-host predators can be used to control the epidemics. The model structure and parameterization are based on the columnaris disease that induces significant economical losses to aquaculture worldwide. The model is also suitable for other environmentally growing opportunist diseases.

In line with the classical predator-prey theory, increasing predation of the pathogen can produce cyclic dynamics (outbreaks). Predation can also clear the infection out of the host population and thereafter lead to the extinction of the pathogen. However, when using predators with poor ability to suppress the pathogen population and low inflow rate, the biological control of the disease might fail or counterintuitively lead to an increase in the density of infected individuals. The model demonstrates that environmentally growing opportunist pathogens can be heavily influenced by outside-host predation and this can effectively be utilized in biological control of infectious diseases.

1. Introduction

Many pathogens replicate in the environment, such as soil and water, independently of hosts, e.g. as saprotrophs. These pathogens can be referred to as environmentally growing opportunists as they can alternate between within-host and outside-host reproduction strategy (Casadevall, 2008; Veneault-Fourrey and Martin, 2011). Environmentally growing opportunists include well-known pathogens, some of which infect humans, such as *Vibrio cholera*, *Pseudomonas aeruginosa*, *Legionella pneumophila*, *Listeria monocytogenes*, *Cryptococcus neoformans* and many species from the genus *Mycobacterium*, *Flavobacterium*, *Serratia* and *Salmonella* (Casadevall, 2008; Veneault-Fourrey and Martin, 2011; Grimont and Grimont, 1978; Friedman et al., 2002; Leclerc et al., 2002; Hall-Stoodley and Stoodley, 2005; Hilbi et al., 2007; Rahman et al., 2008; Freitag et al., 2009; Kunttu et al., 2009; Mahlen 2011; Trivedi et al., 2011). Disease outbreaks caused by environmentally growing pathogens can be difficult to prevent with antimicrobials even if all the infected hosts were treated by antibiotics as environmentally growing pathogens gain their fitness from both within- and outside-host growth. Antimicrobials are in many cases targeted against the pathogen population living within host and not the pathogen population in the outside-host environment (Alanis, 2005). Thus, antimicrobial treatments do not eradicate disease agents from the environment even though all the hosts would be treated as these pathogens can survive and grow independently of hosts in the environment indefinitely, while obligate pathogens would eventually perish without available hosts as a resource (Merikanto et al., 2012).

Poor management of environmentally growing diseases by antibiotics has been seen for instance regarding cholera (Rahman et al., 2008) as well as columnaris disease, which is a freshwater fish disease presenting a major hazard in aquaculture worldwide

* Corresponding author at: Department of Biosciences, P.O. Box 65, 00014 University of Helsinki, Finland.
E-mail address: ilona.merikanto@helsinki.fi (I. Merikanto).

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(Kunttu et al., 2009; Pulkkinen et al., 2010; Declercq et al., 2013). In the case of columnaris disease, the severity of disease symptoms in fish farms has, in fact, increased after commencing antibiotic treatments in 1992 (Pulkkinen et al., 2010). Pulkkinen et al. (2010) suggest that this has resulted as antibiotics in fish farms have selected for pathogens with higher virulence that are also less affected by the antibiotic treatments by being fast killers of the infected fish. The use of antibiotics has also led to the evolution of multi-drug resistant bacteria strains (Oliveira et al., 2012). Furthermore, antibiotic treatment in aquaculture can be problematic as drugs are often administered in food mixtures and in many cases infected hosts cease feeding (Oliveira et al., 2012; Pulkkinen et al., 2010). Consequently, there is a need to develop efficient biocontrol methods for managing these diseases.

Previous disease theories have concentrated mostly on diseases caused by pathogens that grow only host-dependently and survive in the outside-host environment solely as a passive state or referred environment as a transmission stage in vectors (Anderson and May, 1978a,b, 1981; Read, 1994; Frank, 1996; Day, 2002; Keeling and Rohani, 2008; Boldin and Kisdi, 2012). This theoretical framework is only suitable for obligate pathogens that do not reproduce in the outside-host environment, e.g. in soil or aquatic environment. Traditional theory has therefore so far mostly neglected environmentally growing opportunist pathogens that are able to grow in the outside-host environment as well as opportunistically infect susceptible hosts as an alternative growth strategy (Casadevall, 2008; Veneault-Fourrey and Martin, 2011). Yet, antagonist interactions, such as inter-specific competition between microbes and predation, as well as outside-host growth of the pathogen are likely to influence disease dynamics. Only few modeling studies have considered outside-host growth and competition in controlling diseases (Merikanto et al., 2014; Godfray et al., 1999; Anttila et al., 2013). In our previous papers (Merikanto et al.2012, 2014), we showed that limiting the pathogen growth in the environment could prevent novel disease outbreaks. When considering columnaris disease, this could be achieved for instance by removing saprotrophic resources, such as dead fishes and fish feces from rearing tanks more efficiently (Merikanto et al., 2012). Also, increasing outside-host competition has been shown in theory to be a successful bio-control method limiting outside-host growth via resource competition (Godfray et al., 1999; Anttila et al., 2013; Merikanto et al., 2014). However, there are to our knowledge no modeling studies on how predation in the outside-host environment affects disease dynamics.

As compared to outside-host competition, pathogen predation by protozoa may turn out to be a more efficient way of controlling bacteria population sizes, as predation is one of the leading causes of mortality in bacteria in the outside-host environment (Fenchel, 1980; Sherr and Sherr, 2002; Menon et al., 2003). Protozoan predation has been shown to e.g. effectively remove *V. cholerae* from environmental water samples (Martínez Pérez et al., 2004). Phage therapy has been discussed as another potential biological control method against environmentally growing opportunist diseases, such as cholera (Jensen et al., 2006).

Here, we introduce a novel environmentally growing opportunist disease model that considers outside-host predation of the pathogen. We analyze first how predation in the outside-host environment influences long-term disease dynamics. Secondly, we assess how external addition of predators to the system could function as a biological control method against environmentally growing opportunist diseases. Parameterization of our model is suitable for many environmentally growing opportunist diseases, even though a special consideration is given here to the columnaris disease caused by saprotrophic bacterium *Flavobacterium columnare*. The model assumes that the infected hosts are unable to grow or compete for resources with susceptible hosts. This assumption is suitable for host-sterilizing and highly virulent pathogenic diseases, such as columnaris disease (Pulkkinen et al., 2010). Model versions applicable to more benign environmentally growing diseases are presented in our previous study, which analyzes the effect of competition between the pathogenic and non-pathogenic strain in the outside-host environment on disease dynamics and invasion of novel diseases (Merikanto et al., 2014). Here, on the other hand, we concentrate on biological control of an acute and lethal environmentally growing opportunist disease. We show that outside-host predation can destabilize the epidemiological dynamics by causing cycles. Moreover, when the predators are continually added to the system, e.g. as a biological control measure, outside-host predation can be an efficient control method against environmentally growing opportunist diseases.

2. Methods

2.1. Modeling the biocontrol of an environmentally growing opportunist pathogen by predation

We consider a deterministic continuous time model combining environmentally growing opportunist pathogen-host interaction and outside-host predation. The model combines SI dynamics based on model G of Anderson and May (Anderson and May, 1981), pathogen outside-host growth and prey–predator model with predator saturation to describe changes in time (t) in the densities of susceptible hosts (S), infected hosts (I), pathogens (P) and pathogen predators (Z) in the environment outside-host. The model of biological control dynamics are given as follows:

$$\frac{dS}{dt} = r_S\left(1 - S_{(t)}\right)S_{(t)} - \beta S_{(t)}P_{(t)} - \mu_{SI}S_{(t)} \quad (1)$$

$$\frac{dI}{dt} = \beta S_{(t)}P_{(t)} - (\alpha + \mu_{SI})I_{(t)} \quad (2)$$

$$\frac{dP}{dt} = \Lambda\alpha I_{(t)} + r_P\left[1 - f_P P_{(t)}\right]P_{(t)} - \frac{aP_{(t)}}{1 + cP_{(t)}}Z_{(t)} - \mu_P P_{(t)} \quad (3)$$

$$\frac{dZ}{dt} = m + \left[\frac{ar_Z P_{(t)}}{1 + cP_{(t)}}\right]Z_{(t)} - \mu_Z Z_{(t)} \quad (4)$$

Eq. (1) describes the density change of the susceptible host population (S) in time (t). Susceptible host population grows density-dependently depending on the growth rate r_S. Host carrying capacity is chosen to be 1. Susceptible host population decreases as they die at rate μ_{SI} e.g. due to predation, which is the main cause of mortality for fishes in nature (Hixon and Jones, 2005), or are removed from the fish tank. Susceptible host population decreases also as they are infected at rate β. Population size of infected hosts (Eq. (2)) increases by environmental transmission rate β depending on population sizes of S and P. In many cases the infection inhibits reproduction of the hosts, as is the case in the columnaris disease, which we are basing our parameterization on. We thus assume that infection sterilizes infected hosts. Furthermore, for simplicity we do not consider resource competition between infected and susceptible hosts, as fishes infected by the columnaris disease generally cease feeding (Pulkkinen et al., 2010). Population size of infected hosts decreases as they die of infection at a rate α (indicating virulence) or due to other causes, e.g. due to predation at the same rate as S (μ_{SI}).

Outside-host population of pathogens (Eq. (3)) increases both by within-host growth and outside-host-growth. Within-host growth also affect the release of new pathogens to outside-host environment at rate Λ from infected hosts as they die to the infection. We assume that host mortality due to other reasons (μ_{SI}), indicating here predation or harvesting, is a dead-end for *F. columnare* that is an ectoparasite (Declercq et al., 2013). In saprotrophic pathogens,