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The role of pathogen shedding in linking within- and between-host pathogen dynamics

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ABSTRACT

A model linking within- and between-host pathogen dynamics via pathogen shedding (emission of pathogens throughout the course of infection) is developed, and several aspects of host availability and co-infection are considered. In this model, the rate of pathogen shedding affects both the pathogen population size within a host (also affecting host mortality) and the rate of infection of new hosts. Our goal is to ascertain how the rate of shedding is likely to evolve, and what factors permit coexistence of alternative shedding rates in a pathogen population. For a constant host population size (where an increase in infected hosts necessarily decreases susceptible hosts), important differences arise depending on whether pathogens compete only for susceptible (uninfected) hosts, or whether co-infection allows for competition for infected hosts. With no co-infection, the pathogen type that can persist with the lowest number of susceptible hosts will outcompete any other, which under the assumptions of the model is the pathogen with the highest basic reproduction number. This is often a pathogen with a relatively high shedding rate (s). If within-host competition is allowed, a trade-off develops due to the conflicting effects of shedding on within- and between-host pathogen dynamics, with within-host competition favoring clones with low shedding rates while between-host competition benefits clones with higher shedding rates. With within-host competition for the same host cells, low shedding rate clones should eliminate high-s clones in a co-infected host, if equilibrium is reached. With co-infection, but no within-host competition, pathogen clones still interact by affecting the mortality of co-infected hosts; here, coexistence is more likely. With co-infection, two clones can coexist if one is the superior competitor for uninfected hosts and the other for co-infected hosts.

1. Introduction

Our understanding of the ecology of infectious disease can be greatly enhanced by recognition of the similarities between models that link within- and between-host pathogen dynamics and models from classical spatial ecology. From the perspective of a pathogen, susceptible hosts are akin to patches of habitat that can be colonized [1–3]. After colonization, population sizes of microparasites such as bacteria, viruses, fungi, and protozoa can show dynamics within individual hosts, rising from an initial aliquot (of maybe just a very few infective propagules, see [4] and references therein) to very large, even astronomical, levels (for instance, titers of hepatitis B in the blood of human hosts can exceed 10^9 viruses per ml; [5]). Clearance of a pathogen by a host amounts to extinction within that habitat "patch." Death of a host is similar in a way to destruction of a patch in a dynamic metacommunity, and of course when the infected host dies the local pathogen population harbored by that individual host eventually goes extinct as well (although some pathogens may survive and multiply for some time after host death, and transmission during this period can be significant).

A rapidly developing arena of inquiry in infectious disease ecology and evolution focuses on linking within- and between-host levels of disease dynamics to arrive at more complex and realistic models of pathogen ecology and evolution [6–12]. The focus in our paper is to explore a potential analogue in infectious disease systems of a classic problem in population ecology, which is to understand how coupling between habitats by flows of individuals influences the population size in each, and the total population size over the entire landscape [13].

A population within a defined habitat patch can change in abundance in only four ways—birth, death, immigration, and emigration. If a patch is initially empty, for it to become occupied, there must be immigration from some occupied source patch—which implies the latter is experiencing emigration. Often (though not always, if populations have stage-structure dynamics or unstable population dynamics; see [14]), an increase in emigration will lead to a decline in

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local population growth rate (e.g., for an exponentially growing population) or in local population size (if the population settles to an equilibrium). If emigration is sufficiently great, a local population can even be vulnerable to extinction. In phytoplankton ecology, this phenomenon was the focus of the classic KISS model [15]. If individuals occupied a one-dimensional patch of suitable habitat surrounded by a hostile environment and passively diffused, this model predicts that population persistence required a minimum patch size, larger with a higher diffusion rate or smaller patch growth rate. This basic qualitative result from the KISS model is robust to many alternative assumptions [16].

Since emigration is required for immigration, colonization into empty patches may come only at a demographic cost to already occupied source patches. In this paper, we will explore a comparable trade-off that can conceivably arise in infectious disease systems. The basic idea is simply stated. If there is to be transmission to healthy hosts, this requires the emission of infective propagules from infected hosts, which can be viewed as a form of emigration. The greater this emigration (and hence transmission to other hosts), all else being equal, the greater the penalty one should observe, in terms of growth rates and population sizes of pathogens within infected hosts. This can be viewed in a way as a necessary expression of conservation of mass: any material put into infective propagules that exit an infected host is necessarily not available to contribute to further population growth, within that host. It can also be viewed as an allocation trade-off. For a genetically identical clone of pathogens occupying a focal host individual, as that clone grows in population size within that host, it can allocate a fraction of its production for export (needed to infect other hosts), retaining the remaining fraction for continued growth within the focal host.

We will call this a “shedding” model for infection; shedding will be quantified by a per capita shedding rate *s*, the fraction of pathogens leaving the host per unit time. Individual multicellular hosts can of course have highly complex internal spatial structures, and within a host, different tissues can in effect represent different habitats [4,17–19]. The same type of model developed below can also be applied to the dynamics *within* a multi-cellular host individual. In this case, the “host” in the models is then reinterpreted as an individual cell that is either uninfected or infected by an intra-cellular parasite, for example, a virus. In this paper, however, we will not deal with this issue of internal host heterogeneity (while recognizing its importance).

In the long run, given that hosts are not immortal, for a pathogen to persist in the host population, some pathogen individuals must leave infected hosts and infect new hosts. Increased loss of the pathogen from infected hosts can have several intertwined effects. The instantaneous rate of transmission from a given infected host should be larger when a greater number of pathogen individuals are shed and so have the opportunity to seek new hosts. However, if such shedding reduces future population sizes of the pathogens, this could depress transmission in the future. The models we present will couple increased transmission to new hosts to reduced growth rates for the pathogens within infected hosts, which can ultimately reduce net transmission to susceptible hosts from infected hosts due to fewer pathogens in those hosts. Our models also allow the death rate of a host to be affected by the load of pathogens it carries. Alternative scenarios one could imagine would be to have the death rate of the host depend instead on the rate of increase of the pathogen or on its rate of exit (since the precise methods a pathogen uses to increase its emigration rate can be harmful to the host). We will not consider these alternative influences of pathogens on host mortality here, but recognize their potential importance.

The particular content of our paper builds upon our previous work [20], where we linked within-host dynamics to the dynamics of the pathogen in the entire host population via shedding or bursting models of pathogen transmission (in a bursting model, pathogens are not released until host death). Holt and Barfield [20] assumed that the number of susceptible hosts was fixed (which may be approximately true in the early phases of an epidemic, for instance). Here, we relax this assumption by assuming the kind of density dependence usually assumed in classical epidemiology, e.g. [21–23], in which the total host population size remains constant (by an unspecified mechanism), while the relative numbers of infected and uninfected (susceptible) hosts are dynamic. We also for simplicity assume that hosts, once infected, do not develop acquired immunity if they recover; therefore, an individual who loses the infection re-enters the susceptible class (i.e., an SI model). Also, again for simplicity, we ignore demographic structure (e.g., age-dependent infection or mortality) in the host. Our model formulation does permit host mortality to depend upon the within-host abundance of pathogen, which can vary with time since infection, and can also implicitly incorporate the impacts of host immune responses on pathogen loads.

Pathogens are assumed to be emitted from an infected host at a constant per pathogen rate throughout the course of infection (shedding), rather than in a “burst” at the time of host death. We start by sketching the basic model for a single pathogen clone infecting the host population (summarizing the main pertinent results of [20]). We then examine competition between clones differing in their shedding rates, which is a necessary ingredient for understanding pathogen evolutionary dynamics. This is first examined under the assumption that no individual host can be infected by more than one pathogen clone, so that pathogens only indirectly compete for susceptible hosts. For this scenario, we show that the clone with the highest basic reproduction number R_0 can eliminate all others. Assumptions about within-host dynamics influence the shedding rate that maximizes R_0 and thus the ultimate outcome of competitive evolution among pathogen strains, as well as the effect of such evolution on virulence experienced by the host.

Next, we consider the case in which two pathogen clones can infect the same host, and within the host the clones use the same resource (e.g., they infect the same cell types). In this case, there is also direct competition within co-infected hosts. Finally, we consider the case in which two clones can attack a single host, but within the host they use different resources (e.g., the pathogen strains might occupy different tissue types). There is in this case no direct within-host competition, but within a co-infected host the two clones can affect each other by affecting the host’s mortality rate. In this last case, there may be differences between clones, other than just their shedding rates. We examine these last two scenarios first under the assumption that the pathogen numbers quickly reach their positive equilibrium values within individual infected hosts and are fixed there until the point of host death. Then, we use simulations to determine the result of clonal competition with more realistic within-host population dynamics, using a differential equation model commonly used for viral infection within hosts (from [24], based on models in [25] and references therein) coupled with an individual-based model of hosts including stochastic between-host transmission and host death (within-host dynamics were deterministic, however).

In all cases, we examine competition of clones differing only in shedding rate (even when co-infecting clones are assumed to attack different cell types, the parameters used are the same, so that the two clones compete for different, but equivalent, sets of cells). Within the discussion, we provide ideas for future extensions of this work to encompass a richer array of life history effects.

2. Models and results with equilibrium within-host pathogen numbers

2.1. Shedding model with a limited population of hosts—no co-infection

In [20], we considered the effect of within-host dynamics on the spread of a pathogen within a population of hosts, including the