Modeling evolution of virulence and opportunistic disease dynamics of *Flavobacterium columnare*

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Abstract

Contrary to obligatory pathogens, opportunist pathogens can also grow in the outside-host environment [1–2]. Bacteria such as *Flavobacterium psychrophilum* and *F. columnare* replicate saprotrophically in environmental reservoirs and opportunistically infect fresh water fish [3–5]. They are capable of delaying their extinction or surviving indefinitely in the outside-host environment by using fish feed or dead fish material. Therefore the opportunists may thrive even though all susceptible hosts would either be treated or removed, making antibiotic treatments often inefficient. Also, high susceptible host density, lack of natural bacterial predators or competitors of *F. columnare* and high availability of dead fish material make fish tanks ideal places for the evolution of high virulence. It is thus no surprise that columnaris disease caused by *F. columnare* has become a major problem in fresh water fish farms worldwide [4–6]. Similarly, *F. psychrophilum* causing cold-water disease and rainbow trout fry syndrome is a great menace in fish farms [3].

Dynamics of opportunist pathogens and the evolution of opportunist virulence are currently poorly understood as the traditional epidemiological models consider only pathogens incapable of environmental growth. Traditional epidemiological models thus do not adequately describe disease dynamics of opportunistic pathogens, such as *Vibrio cholera, Pseudomonas aeruginosa, F. columnare, F. psychrophilum* etc. Also, theory on how opportunist virulence develops in the first hand is lacking. Yet, it has been suggested that obligatory pathogenicity develops logically through opportunist pathogenicity [1]. As microbes adapt to within-cell environment, genes and potentially metabolic pathways related to free-living life history are lost due to trade-offs with within-cell adaptation [7], possibly promoting shifting from opportunism to obligatory in time. Therefore, development of a proper model on evolution of virulence and opportunistic disease dynamics is crucial so that columnaris disease and other opportunist disease outbreaks could be more efficiently predicted and suppressed.

We developed a model that couples density-dependent growth and competition between pathogen and non-pathogenic bacteria in the outside-host environment to host-pathogen dynamics. Stability analysis and numerical simulations were used to analyze how outside-host growth and competition affects the dynamics of the host and the parasite. Evolution of opportunist virulence was studied using invasion analyses. Model was parameterized to suite for *F. columnare* and its potential hosts.

The model produces stable or cyclic outbreak dynamics and in some situations outside-host growth can drive the host extinct. We found out, that our model is capable of generating

disease dynamics that can strongly differ from the traditional epidemiological models [8–9]. Interestingly, the outside-host density-dependent growth has a strong stabilizing effect, as has increased pathogen mortality, while the outside-host competition can destabilise disease dynamics. Opportunist pathogens are also able to remain in the outside-host environment by using outside-host replication when the density of susceptible hosts is too low for host-dependent persistence, or in the absence of the hosts. Thus, outside-host growth is a potential ecological mechanism for disease outbreaks. Increased density-dependency and higher pathogen mortality outside hosts makes pathogen growth more restricted. This on the other hand decreases pathogens' regulatory effect on susceptible hosts and explains why increased density-dependency and higher pathogen mortality outside hosts are likely to be stabilizing. When a superior non-pathogenic competitor is present, the model generates cyclic dynamics because as pathogen population increases outside hosts, competition outside host increases as well pushing thus pathogen population down. Strong enough competition can also lead to extinction of the pathogen. We also demonstrate that a novel pathogen can evolve if the fitness advantage due to within-host growth exceeds the cost of virulence traits when competing with the non-pathogenic competitors in the outside-host environment.

Thus, our analysis demonstrates that the coupling of outside-host growth and competition to the traditional host-pathogen dynamics has profound influence on disease evolution, prevalence and dynamics. The model could also be applied to disease control. We suggest that the efficacy of columnaris disease treatment in fish farms could be increased by a more efficient removal of saprotrophic resources, such as dead fish material and faeces, from the tanks decreasing the pathogen's ability to grow outside the host. By increasing the diversity of natural bacterial enemies in fish tanks, e.g. by presenting a superior non-pathogenic competitor, disease outbreaks could also be prevented more effectively.

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