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Review

Multiple-genotype infections and their complex effect on virulence☆

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ABSTRACT

Multiple infections are common. Although in recent years our understanding of multiple infections has increased significantly, it has also become clear that a diversity of aspects has to be considered to understand the interplay between co-infecting parasite genotypes of the same species and its implications for virulence and epidemiology, resulting in high complexity. Here, we review different interaction mechanisms described for multiple infections ranging from competition to cooperation. We also list factors influencing the interaction between co-infecting parasite genotypes and their influence on virulence. Finally, we emphasise the importance of between-host effects and their evolution for understanding multiple infections and their implications.

Contents

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1. Introduction

Host–parasite coevolution is associated with high selection dynamics and has manifold consequences for hosts and parasites (defined in this article *sensu lato*, including viruses, prokaryotes and eukaryotes). However, parasites may not only interact with their coevolving host, but also with co-infecting parasites. In this article, we focus on co-infections by different parasite genotypes of the same species, although co-infections by different species are doubtlessly relevant as well. Actually, most infections in nature consist of multiple parasite genotypes (Read and Taylor, 2001). In recent years, multiple-strain infections attracted considerable attention because of their prevalence in naturally infected hosts (Petney and Andrews, 1998; Cox, 2001; Balmer and Tanner, 2011; Louhi et al., 2013). Advances in methods of genotyping revealed that several life threatening diseases are likely to consist of infections by multiple parasite genotypes (Arnot, 1998; Read and Taylor, 2001). For instance, a recent outbreak of dengue fever in India revealed that 20% of infections comprised multiple dengue serotypes (Bharaj et al., 2008). Similarly, in the case of human malaria, infected adults were simultaneously infected by more than five *Plasmodium falciparum* strains (Lord et al., 1999). Moreover, it has been well documented that irrespective of geographical regions, prevalence of parasite infection is positively correlated with mixed genotype frequencies (Louhi et al., 2013).Host-Parasite Coevolution

Most studies on multiple infections, both theoretical and empirical ones, have focused on the consequences of multiple infections on virulence. This is doubtlessly essential for predictions about consequences for host populations and epidemiology. While theoretical models initially assumed a specific type of competition between co-infecting parasite genotypes resulting in increased virulence, nowadays a diversity of theories and models exist. They reveal that manifold interaction mechanisms between co-infecting parasites are possible and that their consequences for epidemiologically relevant factors like virulence are rather complex.

Even though the importance of diverse infections has often been acknowledged, our understanding of virulence evolution in multiple infections is still limited (Read and Taylor, 2001; Rigaud et al., 2010; Garbutt et al., 2011). Disentangling the virulence evolution among single and multiple parasite infections is essential for the management of disease severity, epidemiology and also in our dealing with emerging drug resistance (Read and Taylor, 2001; Alizon et al., 2011).

This review focusses on infections by multiple parasite genotypes of the same species. First, we summarise theories about multiple infections with a focus on their effect on virulence. For this, we first introduce virulence and the concept of optimal virulence. We then explain why different interaction mechanisms between co-infecting strains may change virulence and list further parameters which can influence virulence. Finally, we suggest directions which future research on multiple infections should take. We point out that although virulence is an important measure and is without doubt crucial for epidemiology, it is impossible to understand the interaction between co-infecting parasites from simply measuring virulence.

2. Virulence

2.1. What is virulence?

Parasites per definition harm their hosts by decreasing their fitness (Read, 1994). This harm is referred to as virulence, the prime factor describing parasites. Virulence is frequently measured as reduction in host reproduction, host death rate or time to death, but any other measure which correlates with the reduction in host fitness such as the decline in red blood cells in vertebrates infected with *Plasmodium* (Mackinnon and Read, 1999) is valid. Although parasites have to cause harm to access host resources, this harm can feed back negatively on the parasite. For example, due to a parasite attack a host population may drop in number which in return results in a drop of parasite number.

In most theoretical models, virulence is considered as increase in host mortality due to the infection. For some models, this assumption is essential (see Section 2.2). If empirical studies use a different measure for virulence, comparisons between empirical results and theoretical expectations may not be straightforward, since different measures for virulence can behave differently (Alizon and Michalakis, 2015).

2.2. Why should virulence be optimal?

From an evolutionary perspective, the degree of virulence which maximises parasite fitness is optimal and should be selected. However, parasite virulence and fitness do not necessarily need to be linked; the association can be random (Fig. 1a) and virulence can be a non-adaptive trait (Schmid-Hempel, 2011). This is, for example, the case in bacterial meningitis (Levin and Bull, 1994). Bacteria like *Streptococcus pneumoniae* usually colonise the respiratory tract. Sometimes, however, they colonise the cerebrospinal fluid instead, causing severe damage to the central nervous system. This infection route is a dead-end; no transmission occurs from here. Thus, virulence is uncoupled from parasite fitness. Alternatively, parasites may depend on host survival for replication and transmission. In such a case, any increase in virulence may lead to an earlier host death which would in turn reduce parasite fitness (Fig. 1b). This scenario is also known as the avirulence theory (Ball, 1943) since low virulence is selected. Here, parasitism might easily evolve to commensalism or mutualism if the parasite offers some advantage to the host. Conversely, parasites may depend on host death for replication and transmission. Then, virulence and parasite fitness are positively correlated (Fig. 1c) and high virulence is optimal. If parasites, however, depend on host survival for replication and on host death for transmission, an intermediate level of virulence can be optimal (Fig. 1d). If the host dies too early, parasite replication will be low. If it dies too late, transmission rate, i.e. the number of transmitted parasite particles to a new host per duration of infection, will be low. In both extremes, parasite fitness is reduced and the virulence-maximising fitness is intermediate. This scenario is described in the trade-off hypothesis (Anderson and May, 1982; Ewald, 1983). It is perhaps the best-studied theory for the evolution of virulence using models (Bremermann and Pickering, 1983; Massad, 1987; van Baalen and Sabelis, 1995b; Ebert and Bull, 2003; Alizon et al., 2009; Alizon and Michalakis, 2015) and empirical studies (Dwyer et al., 1990; Mackinnon and Read, 2004; Jensen et al., 2006; Fraser et al., 2007; Doumayrou et al., 2013; Williams et al., 2014). However, the trade-off hypothesis makes specific assumptions (parasite reproduction correlates with virulence, it depends on host survival and parasites can only be transmitted by living hosts) which are not fulfilled in all parasite–host systems. While an optimal level of virulence is likely in many systems, the underlying reasons can differ to those proposed by the trade-off hypothesis.

2.3. Virulence is not static

Virulence can be influenced by a variety of factors. First of all, virulence is characterised by both the host and the parasite genotype (Read, 1994). Depending on which parasite genotype encounters which host genotype, the virulence might differ dramatically. This has been shown by genotype-specific interactions between hosts and parasites (e.g., Webster and Woolhouse, 1998; Schulenburg