Review

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Evolutionary Parasitology

Parasite adaptations to within-host competition

Nicole Mideo

Department of Biology, Queen's University, Kingston, ON K7L 3N6, Canada

Competition between parasite species or strains within hosts is a major evolutionary force in infections. In response, parasites exhibit a diverse array of strategies that improve their chances of growth or reproduction over competitors. This Review describes three types of competition that parasites face (exploitation, apparent and interference), identifies successful strategies for confronting these and discusses whether these strategies are true adaptations to competition. Although many studies of multiple infections have focused on disease outcomes (e.g. virulence), rather than on the particular parasite strategies that have adapted in response to the ensuing competitive interactions, these strategies are ultimately responsible for shaping disease outcomes of interest. A better understanding of parasite adaptations to competitive interactions will have important public health implications.

Competition driving evolution

Diversity in natural infections, whereby hosts are infected by multiple parasite species (see Glossary) or by multiple genotypes of the same species, is common [1]. For example, during a recent outbreak of dengue virus in India, nearly 20% of infections comprised multiple dengue serotypes [2], and in one community in Brazil, more than 73% of individuals infected by helminths harboured multiple species [3]. Experimental evidence of competition in these multiple infections (i.e. the sum total of the success of coinfecting parasites is less than their individual summed success in single infections) continues to mount and includes both interspecies competition (e.g. mixed-species helminth infections; for a review, see Ref. [4]) and intraspecies competition (e.g. genetically diverse malaria infections) [5,6]. Because of the ubiquity of multiple infections and their potential impact on disease outcomes and health protocols [1], empiricists and theorists alike have shown considerable interest in examining within-host competitive interactions between parasites.

Importantly, these competitive interactions will alter the evolutionary trajectory of parasite strategies for survival, growth or reproduction, and traits that are adaptive in competition might not be universally successful in its absence. Perhaps this is best explained by Chao *et al.* [7], who cite a story about being chased by a bear. One person alone might do best to get away from a bear by running as fast as possible, but when there are two people, one competitor need only run faster than the other (it is the relative speed that matters). Taking this analogy further, if a person with an odd habit of sticking out his leg were among a group of people being chased by a bear, he might enjoy relative success at escaping if his odd trait led to his competitors being tripped and their escape thwarted. However, were this fellow to be on his own, his trait would be a costly one because it would only serve to slow him down. Similarly, adaptations that make a parasite a good competitor in mixed infections might be costly in single infections (see, for example, Ref. [8]), although identifying these costs remains a key challenge.

In this Review, exploitation competition, apparent competition and interference competition are distinguished as three types of competitive interactions faced by parasites and strategies that have potentially evolved in response to these different interactions are described. Much emphasis has been placed on determining how within-host competition affects the evolution of virulence (Box 1), but virulence itself will be affected by the specific strategies parasites employ in competitive interactions, so understanding the details of these strategies is important. Finally, some surprising outcomes and potential applications of competitive interactions in the realm of public health are outlined.

In honour of Darwin, who observed that 'it is the most closely-allied forms, – varieties of the same species, and species of the same genus or related genera, which. . .generally come into the severest competition with each other' [9], it is these interactions that are the focus of this review. Details of the outcome of multiple infections involving more distantly related parasites can be found elsewhere (see, for example, Refs [10,11]).

Glossary

Bacteriocin: antimicrobial proteins that are produced by and toxic to bacteria.
Multiple infection: an infection in a single host that involves two or more parasite genotypes or species.
Parasite: this term is broadly defined here and refers to both microparasites (viruses, bacteria and protozoans) and macroparasitic worms and arthropods.
Siderophore: an iron-binding compound produced by bacteria that aids in iron acquisition, particularly when this resource is limiting.
Superinfection: refers to a host-cell-level process in which a virus infects an already productively infected cell. (Note that this is distinct from the host-level process of superinfection, assumed in some theoretical models of multiple infection, which is not explicitly discussed in this review.)
Virulence: the reduction in host fitness resulting from infection by a parasite, often equated with disease-induced host mortality rate.

Corresponding author: Mideo, N. (4nlm@queensu.ca).

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Box 1. Competition and the evolution of virulence

Current theory in the field of virulence evolution generally assumes that virulence (here, defined as disease-induced host mortality) is an unavoidable consequence of parasite replication and that the evolution of this trait is constrained by a trade-off with transmission (for a recent review, see Ref. [62]). Under this trade-off, at some point, the benefit to a parasite of increasing transmission is outweighed by the cost of increasing virulence, and intermediate levels of virulence are ultimately favoured. Parasites are predicted to exploit host resources less 'prudently' in multiple infections by increasing replication rates (e.g. Refs [63–65]). This prediction is explained by the fact that the benefit of this increased replication (increased relative transmission) accrues to the individual parasite, whereas the costs (faster exploitation of host resources, earlier host death and truncated transmission opportunities) are spread among all of the parasites in an infection – a so-called 'tragedy of the commons' [66].

Consistent with this prediction, recent experiments have shown that more virulent parasites have a competitive advantage in multiple infections (e.g. in malaria [5,67] and in a *Daphnia*–endoparasite system [8]). However, empirical support of this prediction is not overwhelming and higher virulence is not always favoured in multiple infection experiments (reviewed in Ref. [1]). Further theoretical work has refined expectations by demonstrating that the specific biological details of a given infection can greatly affect the predicted evolutionary outcome of multiple infections on virulence. Increased virulence might not be the predicted outcome depending on, for example, which other traits evolve in response to competition [7], the costs of other competitive interactions such as interference [68] and the precise details of how host exploitation is achieved [69] (Box 3).

Competitive interactions… and their interactions

Just as different adaptations are expected to evolve in the presence of competition as compared with its absence, different types of competitive interactions can also lead to different evolutionary outcomes. Competition between parasites within a host can occur by means of three different mechanisms: exploitation competition, apparent competition and interference competition [1]. First, conspecific parasite strains in most cases will have (and heterospecific parasites can sometimes have) overlapping ecological niches and, therefore, will compete in multiple infections for access to host resources (exploitation competition; Figure 1). Second, parasite strains or species can share a common enemy in the form of the nonspecific or cross-reactive host immune responses they elicit, leading to a situation in which the abundance of each parasite impacts the other through their effects on immune cell abundance (immune-mediated apparent competition [1]; Figure 2). Third, parasites might evolve strategies for directly inhibiting the growth, reproduction or transmission of competitors, either chemically or mechanically (interference competition; Figure 3).

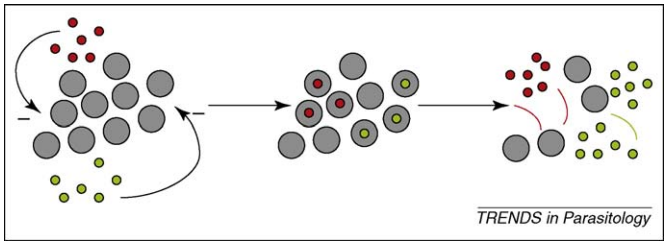

Figure 1. Exploitation competition. Two different parasite strains or species (small red and green circles) compete for access to the same pool of limited host resources (grey circles). '–' signs indicate a negative effect of parasites on host resources (i.e. depletion). Using malaria as an example, two strains are in competition for access to host red blood cells (RBCs). An infected RBC is programmed to produce either more asexual parasites (small circles), which can each infect another RBC, or a single transmission stage (gametocyte; curved lines). All else being equal, the green strain that converts fewer infected RBCs to gametocytes produces more of the competitive asexual stages and ultimately could infect a greater share of the host's RBCs. Exploitation competition can generate selection for low conversion rates in malaria [23].

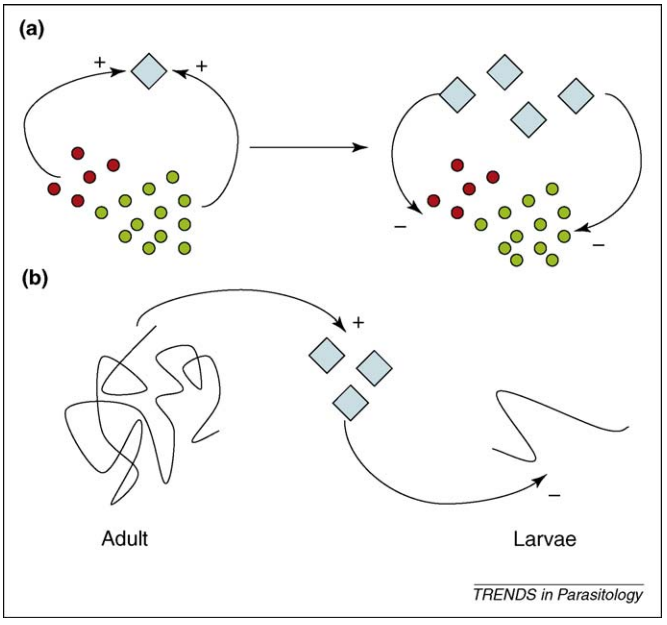

Figure 2. Immune-mediated apparent competition and immune response manipulation. **(a)** Immune-mediated apparent competition. Two different parasite strains or species (small red and green circles) compete to evade the immune responses they elicit (blue diamonds; '+' indicates a stimulatory effect of parasite densities on immune responses and '–' signs indicate an inhibitory effect of immune responses on parasite survival or growth). In the case of nonspecific or crossreactive immune responses, these will target both parasites, regardless of which one stimulated the response. Here, by sheer force of numbers, the green parasite might have an advantage in eluding immune capture. **(b)** Immune response manipulation. As a slight variation on this theme, adult filarial nematodes induce a host immune response to which they are immune but which targets larval stages [37]. This could be an adaptation of adult worms to prevent further competition for host resources.

Teasing apart which sources of competition are at play in any given system is non-trivial. Consider the wealth of data available from experimental *Plasmodium chabaudi* (rodent malaria) infections in mice. In multiple infections, more virulent *P. chabaudi* clones (i.e. ones that induce greater red blood cell [RBC] loss and reach higher peak densities) can competitively suppress less virulent clones [5,6]. This result might be explained by a competitive advantage of virulence in exploitation competition: winning clones cause the greatest target-cell loss and, thus, have a stronger exploitation strategy and obtain a greater share of host resources. But this result could equally be explained by a competitive advantage of virulence in immune-mediated apparent competition: the winning clones are those that are able to reach higher densities, thus build up a bigger stock of parasites and are more likely to overcome nonspecific immune responses by sheer force of numbers. (Of course, other traits could also be playing a part in these competitive interactions.)

Experiments have attempted to disentangle the roles of different types of competition in *P. chabaudi* infections. The data suggest that multiple forms of competition are at

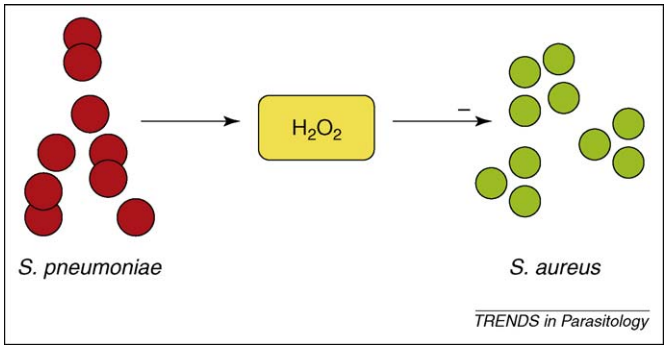

Figure 3. Interference competition. Some parasites interfere directly with the growth or reproduction of competitors, most commonly by releasing toxic compounds. Largely known to involve bacteria, one example is the production of hydrogen peroxide (H_2O_2) by *Streptococcus pneumoniae*. This compound has no effect on *S. pneumoniae* but is lethal to *Staphylococcus aureus* (denoted by the '–' sign) [48], which can co-occur in the upper respiratory tract of human hosts.

play, with the relative importance of each alternating throughout the course of infection [12] and with some forms of competition possibly serving to alleviate others [13] (Figure 4). Differentiating parasite adaptations according to the type of competitive interaction that stimulated their evolution (the selective force) might be difficult for two reasons: the adaptations can be common among different types of competition, and the selective force can be obscured by interactions between sources of competition. What follows is an attempt at such categorization with a handful of putative parasite adaptations to competition.

Exploitation competition

The abundance of host resources required by parasites is probably a limiting factor in many competitive interactions. Theory has shown, for example, that infection dynamics can be explained (at least in part) by the availability of susceptible $CD4^+$ T cells in HIV infections [14,15] and the availability of uninfected RBCs in malaria infections (see, for example, Refs [16,17]). A key theoretical result from the broader field of evolutionary ecology is that exploitation competition is predicted to lead to selection either for divergence in resource use between organisms (character displacement; for a review, see Ref. [18]) when suitable resource alternatives are available or for adaptations that improve an organism's ability to acquire those shared resources when there are no alternatives (see, for example, Ref. [19]). Evidence to support both evolutionary routes can be found in parasites.

Divergence in host resource use was recently studied in sympatric, congeneric trematode parasites [20,21], which have complex life cycles that include an avian definitive host and two intermediate hosts (snails and fish), providing many opportunities for niche overlap and competition for resources. The trematodes specialize on different host species and their exploitation strategies also diverge at an even finer scale; each species infects a particular portion of the avian intestine [20] and different eye tissues of the fish host [21]. The tissue tropism in fish was maintained when parasites were exposed individually to a novel fish species, suggesting that this specialization is an evolved strategy [21]. Although other explanations for these results are possible [20], they are suggestive of adaptations to exploitation competition. Support for this hypothesis could be found by looking at the tissue preferences of these species (or related species) in areas where coinfections are rare. Under these conditions, tissue preferences might be expected to be less specific (depending on the quality of different tissue patches) because the benefit of decreasing interspecific competition would be diminished and site specialization could carry a cost of increasing intraspecific competition.

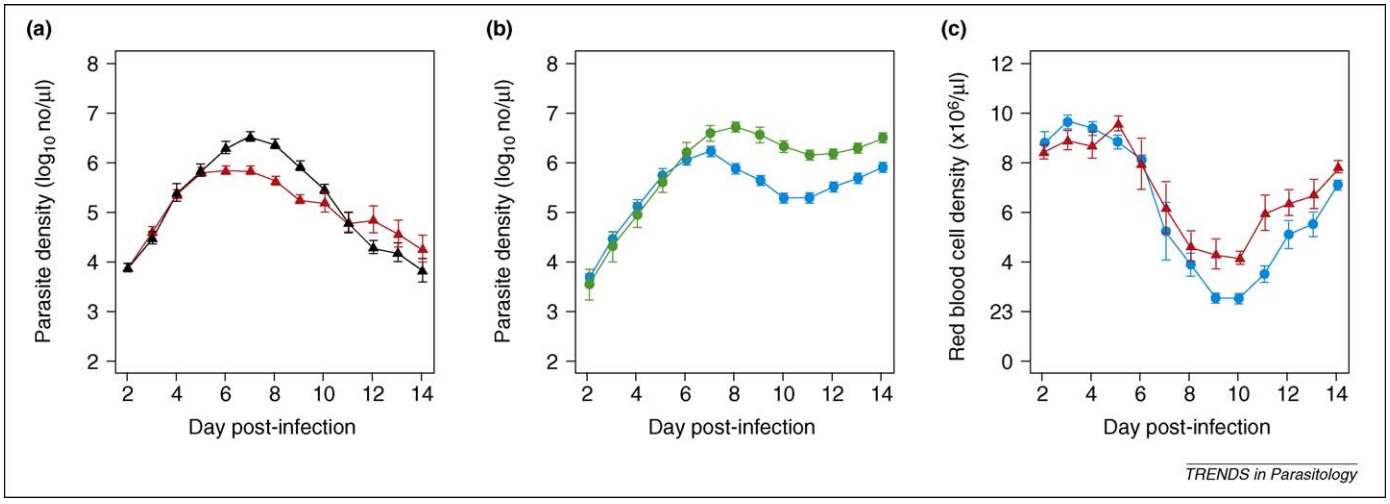

Figure 4. Interactions between types of competition in a rodent malaria system (*Plasmodium chabaudi*). Malaria infections composed of multiple clones might be regulated by both exploitation and apparent competition. Experimentally depleting host $CD4^+$ T cells should alleviate the observed competitive suppression of a less virulent clone in multiple infections, if this suppression is, in part, due to $CD4^+$ T-cell-mediated apparent competition. **(a)** Average parasite densities (±1 standard error of the mean, or s.e.m.) of a particular malaria clone (DK) in single infections (black line) and in coinfections with a more virulent clone (red line) in normal mice. DK is competitively suppressed in mixed infections over the course of the initial peak of parasites. After day 9, there is no evidence of competitive suppression. **(b)** Average parasite densities (±1 s.e.m.) of the DK clone in single infections (green line) and in coinfections with a more virulent clone (blue line) in $CD4^+$ T-cell-depleted mice. Immune depletion did not alleviate competitive suppression of DK in coinfections; rather, DK continues to be suppressed throughout the infection, unlike in normal mice. **(c)** Average densities (±1 s.e.m.) of target red blood cells (RBCs) are lower for mixed infections in $CD4^+$-depleted mice (blue line, circles) than in immune-intact mice (red line, triangles) owing to higher parasite densities and subsequently greater host exploitation. A main limiting factor in the infections of $CD4^+$-depleted mice is access to uninfected RBCs [16]. In normal mice, parasite densities seem to be limited by $CD4^+$ T-cell-dependent immune responses leading to competition for evading these responses and, also, less severe host exploitation, potentially mitigating any effects of resource competition. This could explain why competitive suppression continues in (b) but not in (a). Modified, with permission, from Ref. [13].

When switching resources in response to exploitation competition is not possible, parasites could evolve strategies for gaining a bigger share of limited host resources. Malaria parasites offer two different examples of such adaptations.

First, a competitive advantage in resource acquisition might come in the form of how a parasite invests those resources. Malaria parasites face a trade-off in resource expenditure between asexual growth and transmission: an infected RBC is programmed to produce either multiple asexual parasite stages (merozoites), each of which can subsequently infect another RBC, or a single sexually differentiated stage (gametocyte), which is responsible for transmission to mosquitoes. Generally, few infected RBCs are converted into gametocytes in malaria infections, which seems paradoxical given their crucial role in generating new infections [22], but recent theoretical results suggest that competition for RBCs can lead to selection for low rates of conversion to gametocytes [23]. The theory shows that in the absence of competition, high conversion rates could evolve, but the presence of competition for RBCs drives the gametocyte conversion rate to lower levels to produce a greater number of the competitive (and host-damaging) asexual forms. Experimental evidence to support this theory has so far been limited [24], but further investigation is warranted.

Second, along with adaptations for obtaining host resources as quickly as possible, or hoarding resources in time, malaria parasites seem to hoard resources in space by displaying a rosetting phenotype whereby uninfected RBCs adhere to infected ones. This phenomenon has been found in all human malaria species [25] but not all isolates [26]. One advantage of this strategy could be that it enables more efficient invasion of RBCs after progeny parasites burst from the central infected cell [26], although evidence does not seem to support invasion specifically targeting RBCs in rosettes [27,28]. An alternative advantage could be that resources are less accessible to competitors. Experiments have yet to compete rosetting and non-rosetting parasites directly in multiple infections to test the adaptive value of this trait. Rosetting is costly for the host because it is correlated with disease severity [29], but whether this translates to relative fitness costs for rosetting parasites in single infections remains unresolved. Such resource hoarding might have analogues in other taxa. For instance, in zebrafish, *Mycobacterium* reportedly stimulates recruitment of macrophages to developing granulomas where, instead of performing a host-protective role, they can become infected and facilitate the spread of the bacteria [30].

Immune-mediated apparent competition (and variations thereof)

Host immune responses present a great challenge to parasite survival. Numerous immune-evasion strategies have evolved but, among them, few seem explicitly adapted to dealing with the dual challenge of immunity and competition. As described earlier, adaptations that make parasites successful in exploitation competition might similarly be advantageous in apparent competition (e.g. strategies that lead to higher parasite densities could ensure a particular parasite line access to a greater share of host resources and a greater probability of overcoming immune responses). One example of this overlap in successful strategies is low gametocyte conversion rates in malaria. Theory shows that this strategy is also advantageous in multiple infections in response to immune-mediated apparent competition and in the absence of competition for resources [31]. The roles of apparent and exploitation competition in shaping gametocyte conversion rates of malaria parasites could be illuminated by further experimental work with a model system in which the host immune response can be manipulated.

Immune responses elicited by a parasite alter the in-host environment, and these changes have a well-documented impact on a host's ability to resist subsequent infections by different parasite species through either suppression or facilitation of infection and growth (see, for example, Ref. [32]). Immune responses generated by resident infections also decrease the likelihood of a subsequent infection by conspecifics, as suggested by sequential experimental infections of schistosomes in mice [33] and malaria in both mice [6] and lizards [34]. This effect of limiting a competitor's access to host resources could merely be an advantageous byproduct of natural host responses, and although it is at least theoretically plausible that parasites could evolve to manipulate hosts for their benefit [35], whether this has occurred is an open question.

Probably the best evidence in support of the hypothesis that parasites adapt to co-opt host immune mechanisms in response to competition comes from worms. More than 40 years ago, experiments showed that exposure to adult schistosomes led to resistance of subsequent infection by larval stages [36]. More recently, similar results were found in filarial nematode worm infections [37]. Given that the adult worms were not cleared in these infections, the results suggest that adult worms are able to induce host immune responses that target larval stages and to which they are immune. Because these responses are, again, beneficial for both the host and the parasite – they protect the host from subsequent infections and the resident parasites from further competition – it is unclear which organism is ultimately responsible for generating them (Box 2).

Such manipulation of host immunity by parasites need not be limited to interactions occurring between life stages. Recent theoretical work suggests that parasites could improve their ability to invade a host possessing a resident infection by modifying the host environment through the elicitation of immune responses to which the invading parasites are adapted but the resident parasites are not [38]. Although the theory is framed for a pathogenic species that invades a population of commensals, it could be applied more widely to competing parasitic species or strains, and it is supported by some empirical data. For example, innate immune responses elicited specifically by *Haemophilus influenzae* led to clearance and competitive exclusion of *Streptococcus pneumoniae* in mice that were simultaneously inoculated with both bacteria, whereas co-inoculation had no negative effect on *H. influenzae* [39].

Box 2. Outstanding questions and major challenges

Are these even strategies of the parasite?
In cases involving host immunity, it is not clear whether the parasite actually plays any part in limiting the success of competitors. When hosts produce immune responses that target larval but not adult nematodes [37], are adult worms inducing a particular (adult-worm-adaptive) immune response from the host? Alternatively, is the host employing a host-adaptive strategy by protecting itself from a greater parasite burden? When multiple infections are rare, it would be disadvantageous for worms to elicit these immune responses, assuming there is some cost to doing so. Similarly, there would be selection against the host producing these responses under the reasonable assumption that the most important target of a host's immune response is a current infection and energy directed away from this target and towards future threats would be wasted when no such threats exist. Assuming these costs are real, the question of whether elicitation of these immune responses is an adaptation of the host or parasite could potentially be answered by an experimental approach that infected hosts from areas of rare multiple infection with nematodes from areas of common multiple infection and vice versa. In the first case, the generation of these larvae-specific immune responses would suggest a parasite adaptation and in the second case, a host adaptation.

Do these parasite strategies indicate evolutionary change or plasticity?
Looking for costs associated with parasite strategies in the absence of competition assumes that these strategies are static across within-host environments; however, evolution could have favoured plasticity. Indeed, some parasites alter life-history traits according to within-host environmental factors, including competition, in ways that are adaptive (see, for example, Refs [70,71]). The value of plastic versus evolved (static) traits as research subjects is debatable. At the level of understanding basic biology, identifying plastic traits is probably easier: expose a parasite of a given genotype to different within-host environments (absence versus presence of competition) and observe any phenotypic changes. Contrast this with looking at related taxa with different known evolutionary histories (common versus rare exposure to competition) and observing any differences in traits, which might be indicative of evolved strategies. Linking the two routes of investigation would be beneficial because a trait that is plastic in a given parasite would be a good starting place to look for adaptations to competition in a related parasite.

Understanding the difference between evolved and plastic strategies is likely to be very important at more applied levels. Plasticity makes any discussion about the implications of competitive interactions on health interventions confusing at best and potentially irrelevant. If, for example, drug-resistant parasites were able to exploit non-preferred host resources or alter other traits to mitigate the effects of competition, then attempts to harness competitive interactions with superior strains to slow the spread of drug resistance would fail. More generally, interventions alter the within-host environment, and parasites with plastic strategies could respond to these changes in unpredictable ways and, more importantly, on short time-scales.

Interference competition

Superinfection resistance by viruses such as HIV is often referred to as 'interference' (see, for example, Ref. [40]), although this strategy lacks the defining quality of being a direct interaction between parasites and is instead mediated by host cells. Multiple HIV gene products stimulate the downregulation of both CD4 receptors and various co-receptors on the target cell (lymphocyte) surface that are required for cell entry, subsequently decreasing the susceptibility of the cell to further infection by another virion (see, for example, Refs [41–43]). In addition to limiting the access of a competitor to target cells, viruses benefit from resisting superinfection because it is associated with both increased cell death [41] and decreased virion production [44]. Although other hypotheses have been offered to explain the downregulation of crucial HIV receptors (for a review, see Ref. [45]), superinfection resistance is a compelling theory, given the costs to a virus of being in a multiply-infected cell. Because superinfection resistance blocks the access of competitors to resources at the level of the host cell, it is likely that this type of strategy exists outside of the viral domain, wherever parasites require resources within target cells for replication or growth.

The arguably archetypal example of interference competition is allelopathy, whereby organisms produce toxic compounds that directly kill or hinder the growth of competitors. For example, cestodes release substances (termed 'crowding factors') that inhibit worm growth, such that the size of worms in an infection is inversely proportional to the number of worms within a host [46]. Injections of putative crowding factors from the cestode *Hymenolepis diminuta* into rat hosts resulted in reduced worm growth, even in the absence of competition [47]. Although there is adaptive value in moderating the growth of competitors when resources are limited, these crowding factors could be explained as a passive accumulation of the end products of metabolism that serve as a signal for worms to slow growth rather than being an outright interference strategy. Work on worm-crowding factors has been slow to progress in the past [46] and current research seems lacking, so a resolution to this uncertainty remains elusive.

Interference competition in bacteria, by contrast, continues to receive considerable attention. One example is the production of hydrogen peroxide by *Streptococcus pneumoniae* to eliminate competitors in the upper respiratory tract of hosts. Although this toxin has no effect on *S. pneumoniae*, it is lethal to *Staphylococcus aureus* by inducing lysis [48]. Bacteriocins are another group of compounds that are ubiquitous in prokaryotes and operate through numerous modes of action to kill closely related bacteria (for a review, see Ref. [49]). A bacteriocin-producing bacterium is immune to its toxic effects owing to the expression of a genetically linked immunity gene, but production and transport of these toxic compounds is not without costs [49]. Despite these costs, bacteriocins are widely held to be the 'weapon of choice' for bacteria. A recent study of *Escherichia coli* has shown that many strains produce more than one bacteriocin [50], and given that most bacteriocins are toxic only to closely related strains, this could be a strategy for expanding the range of competitors that a particular bacterial strain can kill [50]. Some bacteriocins have wider killing ranges encompassing different species [51], suggesting that bacteriocin production is an adaptation to both intra- and inter-specific competition. Indeed, *in vivo* experiments have shown that bacteriocins determine the outcome of competition both between strains [52] and between species [53]. Because bacteriocin production benefits all genetically related strains that share the same immunity gene within an infection, it can give rise to an interesting type of social

Box 3. Competition, spite and cooperation

The production of bacteriocins to defeat competitors in multiple infections represents a case in which the benefit of producing these substances can be shared by many coinfecting parasites but the cost is borne by individual producers. A similar example is the production of siderophores that facilitate iron uptake in bacteria and improve growth (see Ref. [72] and references therein). These two scenarios are related but represent different types of interactions, and both contrast with the 'tragedy of the commons' described above (Box 1). Although production of either bacteriocins or siderophores is costly, bacteriocin production is considered a spiteful strategy because these substances serve only to kill competitors [68], whereas siderophores improve growth and are instead equated with public goods [73]. In both cases, multiple infections can lead to decreased virulence but for different reasons. (These predictions are also influenced by relatedness within an infection [74].)

Bacteriocins directly hinder the growth of competitors; thus, multiple infections with bacteriocin-producing bacteria could lead to decreased host exploitation and, subsequently, lower overall virulence in multiple infections [68]. Indeed, recent experiments have shown that multiple infections composed of two bacterial species that produce mutually lethal bacteriocins resulted in lower virulence in caterpillars than did either single-species infection [53] and that lower virulence also resulted from single-species, mixed-strain infections when conditions favoured bacteriocin production [75]. With public goods, such as siderophores, cooperation between parasites to produce these substances could lead to mutual parasite benefit and improved host exploitation (see, for example, Refs [76,77]); however, diverse infections are prone to generating selection for cheater strategies (i.e. non-producers that would bear no production costs while exploiting the beneficial products of others). Thus, when cooperation enhances host exploitation, multiple infections could result in lower virulence through decreased cooperation (see, for example, Refs [69,72]). Experimental evidence from siderophore-producing bacteria supports these predictions, demonstrating that mixed infections with cheaters and cooperators result in a benefit to cheaters and lower virulence overall than infections composed strictly of cooperators [78]. An interesting wrinkle in these cooperative scenarios is that, as before, interactions between types of social interactions (e.g. public goods cooperation and competition) might be important; for example, when required resources are at higher densities and exploitation competition, therefore, is decreased, the costs of cooperation are reduced and the advantage of cheating is mitigated [79]. For a review of cooperation in microbes, see Ref. [73].

interaction among microbes that could even be called 'cooperation' (Box 3).

Competitive interactions and public health

The outcome of competitive interactions between parasites has the potential to both inform and affect public health interventions. It is clear that how pathogenic and non-pathogenic parasite strains fare in direct competition has implications for vaccine design. Less obvious are the unintended negative consequences that vaccination could have, such as increasing the prevalence of non-vaccine strains or species that are otherwise competitively excluded from infections. For example, pneumococcal vaccination has reportedly led to the increased incidence of both non-vaccine *S. pneumoniae* serotypes and *S. aureus* infections [54,55].

Parasite competitive interactions can also be harnessed for our benefit and already are: when we take supplements of non-pathogenic bacteria to prevent parasitic infections [56], for example. For fighting bacterial infections, bacteriocins offer promise and their diversity provides a vast arsenal from which to draw treatment options [57]. Owing to their specificity, bacteriocins are attractive as potential drugs because, in contrast to some traditional antibiotics, they are unlikely to harm a patient either directly through toxic effects or indirectly by indiscriminately killing non-target beneficial bacteria.

Competition between drug-sensitive and drug-resistant parasites determines 'the clinically useful life-span of a drug' [1], and these interactions could potentially be co-opted to manage drug resistance [56]. In a recent experiment involving rodent malaria [58], drug-resistant clones were suppressed by competitively superior drug-sensitive clones in the absence of drugs. Curative drug treatment led to 'competitive release' of the resistant clone (i.e. its growth was enhanced and it achieved higher densities than in single infections, potentially risking greater transmission of the drug-resistant clone). A subcurative drug treatment led to less substantial competitive release, raising the question of whether the spread of drug resistance could be slowed by not completely eliminating competitively superior drug-sensitive parasites. A definitive answer to this question will prove hugely important, with the potential to alter current thinking on the evolution and proliferation of drug resistance and treatment protocols [58,59].

Concluding remarks

The strategies discussed in this review might provide competitive advantages to parasites in multiple infections, but whether these truly represent adaptations to competition is not always clear (Box 2). Bacteriocin production is arguably the least ambiguous example: there would be no discernable benefit to toxin production in the absence of competitors, and producing these substances is costly – at the very least it uses energy and resources that could otherwise be allocated to parasite growth or replication (and in the extreme it can result in parasite death, when lysis is required for toxin release) [49]. This example highlights a key question for determining whether a given trait is an adaptation to competition: what are the costs associated with the trait and how do these costs impact parasite fitness in the absence of competition? (But see Box 2.) Would a pneumococcal strain that was unable to produce hydrogen peroxide perform better than a wild-type competitor in the absence of other infections? Does a malaria strain that converts a high proportion of asexuals to gametocytes have greater fitness than one that converts less when alone in a host? Theory has suggested some answers (see, for example, Ref. [31]) but experimental work has lagged behind, and for good reason. Quantifying the costs associated with parasite traits is a major challenge and necessitates a reliable measure of parasite fitness, which is complicated by the fact that this measure includes transmission to new hosts. This can make for very challenging experiments. Furthermore, this review has focused on the adaptive value of parasite strategies within hosts, but between-host processes will also shape these strategies (see, for example, Refs [60,61]). Whatever the difficulties

with identifying veritable adaptations to within-host competition, the study of parasite strategies in competitive interactions remains important because they continue to transform our understanding of disease outcomes and, potentially, our public health interventions.

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