Trends in Parasitology

CellPress
REVIEWS

Opinion

Importance of Sequence and Timing in Parasite Coinfections

Anssi Karvonen,[1,*] Jukka Jokela,[2,3] and Anna-Liisa Laine[4,5]

Coinfections by multiple parasites predominate in the wild. Interactions between parasites can be antagonistic, neutral, or facilitative, and they can have significant implications for epidemiology, disease dynamics, and evolution of virulence. Coinfections commonly result from sequential exposure of hosts to different parasites. We argue that the sequential nature of coinfections is important for the consequences of infection in both natural and man-made environments. Coinfections accumulate during host lifespan, determining the structure of the parasite infracommunity. Interactions within the parasite community and their joint effect on the host individual potentially shape evolution of parasite life-history traits and transmission biology. Overall, sequential coinfections have the potential to change evolutionary and epidemiological outcomes of host–parasite interactions widely across plant and animal systems.

Highlights

Parasite coinfections are common throughout plant and animal kingdoms. The resulting parasite–parasite interactions can potentially influence parasite traits such as infection success and virulence.

Coinfections of multiple parasites can occur simultaneously, but more often sequentially, with a gap of time between the infections. This can dramatically change the outcome of coinfection.

Sequential and repeated infection events are very common in nature. Regardless, research on coinfections has largely focused on simultaneous attack by multiple parasites.

Sequential coinfections have also implications for parasite epidemiology and prevention. Designing disease-prevention strategies that account for coinfections and their timing could significantly improve success of intervention efforts.

Temporal Sequence in Parasite Coinfections

During its life span, the same host individual encounters a multitude of different parasites. Indeed, **coinfection** (see Glossary) by multiple parasite species or strains/genotypes is proving to be the rule in both natural and man-made environments [1,2] (we use the term 'coinfection' to include scenarios with and without parasite coexistence (Box 1) unless noted otherwise). To date, the majority of research on coinfections assumes simultaneous arrival (or ignores arrival order), although in reality in most systems we expect different parasites to arrive sequentially. The arrival sequence of different parasites may be predictable, for example due to phenology/seasonality, or in many cases unpredictable because of haphazard contacts between hosts and infective propagules. In this opinion article, we argue that the arrival sequence of different parasites is an important determinant of parasite infection success and virulence in the wild. We review recent literature showing that a prior residency in a host can alter coinfection success across diverse host taxa such as plants [3–5], invertebrates [6,7], and vertebrates [8–11] (Figure 1).

Interactions among parasites sharing the same host can be antagonistic, facilitative, or neutral, but, in principle, coinfecting parasites can be considered as competitors that have conflicting interests in their use of host resources for growth and reproduction [12,13], to secure **transmission** to the next host [14,15], and even to affect the host's behavior in order to facilitate transmission [16]. Antagonistic interactions can take place directly in the form of competitive interference or exclusion between coinfecting parasites [17–19], or indirectly through resource competition or apparent competition mediated by cross-reactive host immune responses [20,21]. Facilitation, on the other hand, could follow from one parasite suppressing the immune function of the host [12] or from coinfection representing an additional challenge to the host immune system ([22,23]; reviewed in [24]). In theory, coinfection interactions should also be stronger between closely related parasites (strain or genotypes of one parasite species, or closely related parasite species) because of similarities in the transmission

[1]University of Jyvaskyla, Department of Biological and Environmental Science, P.O. Box 35, FI-40014 University of Jyvaskyla, Finland
[2]Eawag, Swiss Federal Institute of Aquatic Science and Technology, 8600 Dübendorf, Switzerland
[3]ETH Zürich, Institute of Integrative Biology (IBZ), 8092 Zürich, Switzerland
[4]Department of Evolutionary Biology and Environmental Studies, University of Zürich, 8057 Zürich, Switzerland
[5]Research Centre for Ecological Change, Organismal & Evolutionary Biology, P.O. Box 65 (Viikinkaari 1), FI-00014 University of Helsinki, Finland

*Correspondence:
anssi.t.karvonen@jyu.fi (A. Karvonen).

process, elicited immune recognition profiles, apparent and realized competition between the coinfecting partners etc. [25,26]. However, recent evidence also supports interactions between unrelated coinfecting parasites, at least in some taxa [27–31]. Overall, coinfections may change the **virulence** the host experiences, and interactions among parasites can directly affect their **fitness**. Therefore, coinfections can have significant implications for epidemiology, disease dynamics, and evolution of virulence (reviews in e.g., [32–34]).

Coinfections, like many other features of host–parasite interactions, are temporally dynamic. This means that two parasites are more likely to infect the host sequentially rather than simultaneously. The time gap between infections can vary from a few moments to a significant proportion of the host's lifespan, where the longer-term effects require the first infection to become chronic or to elicit a long-lasting host response. Further, the type of host exposure, simultaneous or sequential, depends on the specific details of the infection process and transmission of each of the parasites. For example, simultaneous infection of a host (Box 1) may be common when a disease vector such as a tick carries multiple viral and bacterial infections, and co-transmits these infections to the next host [35]. A more common co-transmission scenario may arise when coinfected **intermediate hosts** of trophically transmitted parasites are consumed by the predatory next host. Further, infective stages that penetrate host epithelium could, in theory, open a route to the host's body for other infections or act as carriers of microbes (see [31] for such an interaction). However, we argue that such circumstances are much less common than situations where host exposure to different parasites varies through time (Box 1). Such variation is driven by the significant spatiotemporal heterogeneity associated with host–parasite interactions in the wild [36]. More specifically, spatial aggregation of infected hosts and that of the infective stages [37–39], and the temporal variation in parasite transmission biology [40,41], result in a mosaic of hotter and colder spatiotemporal spots of infection, specific to each parasite [42]. Consequently, hosts become exposed to different parasite propagules at different times.

Here, we focus primarily on ecological literature, but acknowledge the wealth of medical literature on the topic considering pathogen interactions, effects of vaccines etc. in the epidemiology of human diseases. We also mainly focus on the role of the host immune system in mediating sequential coinfections, although we acknowledge also other possible forms, such as direct interactions, between parasites. We first consider implications of sequential coinfections for virulence in the hosts, pointing out areas of research that have received less attention. Second, we consider how ecological and evolutionary consequences of simultaneous and sequential coinfection may differ for parasite epidemiology and transmission

Glossary

Coinfection: infection of a host by more than one parasite; syn. multiple infection, concomitant infection.
Fitness: number of descendants of an individual related to the number of descendants of other individuals in a population.
Intermediate host: a host that transmits the infection to the next host (another intermediate host or a definitive host) in a complex parasite life cycle. Parasites can use intermediate hosts for growth and/or asexual reproduction.
Transmission: movement of a parasite between host individuals; it can take place horizontally through direct contact between hosts (e.g., bacteria, viruses, free-living infective stages) or via vectors and intermediate hosts (e.g., many parasitic worms), or vertically from mother to offspring.
Virulence: the magnitude of negative impact of a parasite on its host, often measured as reduction in host fecundity or lifetime.

Box 1. Implications of Simultaneous versus Sequential Coinfections

Coinfecting parasites are generally considered competitors for limited host resources. These interactions can take place directly in the form of interference competition, or indirectly as competition for resources or through apparent host-immune-mediated competition. In sequential coinfections, one of the parasites invades the host first, and the timing between the two infections can vary from a few moments to years. This can modify the interactions, for example, the first parasite gaining a competitive advantage by taking over host resources before the second invader or eliciting cross-reactive host immune responses that suppress the parasite arriving later (Figure I). It is also important to note that the effects of infection sequence can depend on which parasite infects the host first, that is, the effects can be asymmetrical (in Figure I, the blue parasite can infect before the red, or vice versa). In general, sequential infection can result in competitive exclusion without coexistence (superinfection, see [32]) with only a small, or no, effect on the performance of the first invader. In a common scenario, sequentially establishing parasites coexist, but the first infection suppresses the second one, which typically results in lower virulence compared to a simultaneous coinfection (Figure I). Sequential infection effects can also arise when the first infection becomes cleared by the host, but cross-reactive immune responses elicited by the first parasite influence the success of the later infections in the absence of actual coexistence. Simultaneous coinfection can also facilitate parasite infection success, for example, if the genetically diverse infection represents a higher challenge to the host immune system compared to a single infection. In sequential coinfection, however, such facilitation may be reduced if the host has already mounted an immune response consequent to a previous infection from the same or a different parasite (Box 2). In an opposite scenario, sequential infection results – for example, in immunosuppression of the host, allowing higher replication of the second parasite [12]. Overall, these scenarios can also be influenced by parasite within-host dynamics (e.g., acute versus chronic and local versus systemic infections) as well as parasite taxonomic relatedness, which exemplifies the complexity of possible interactions in a coinfecting parasite community.

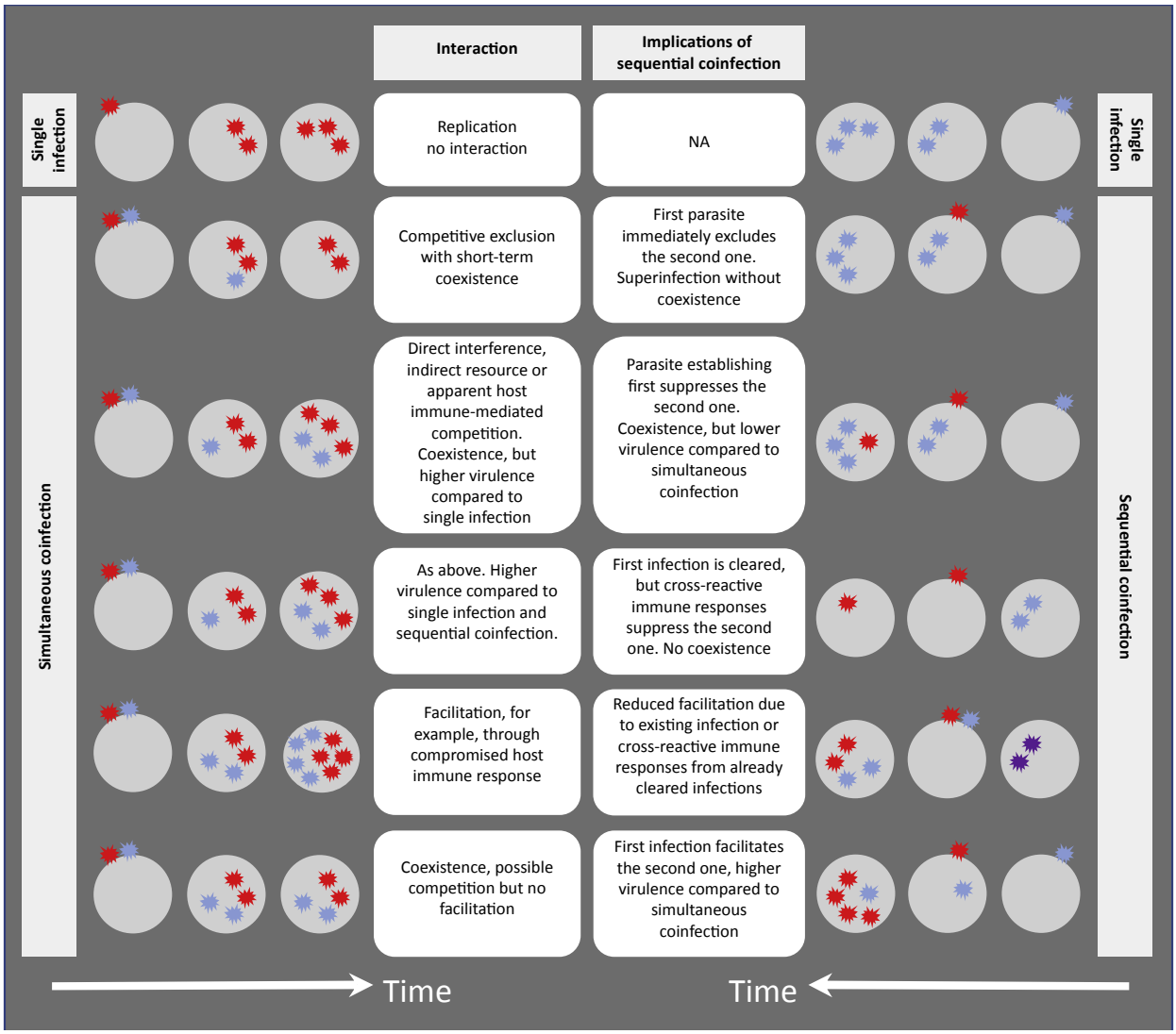
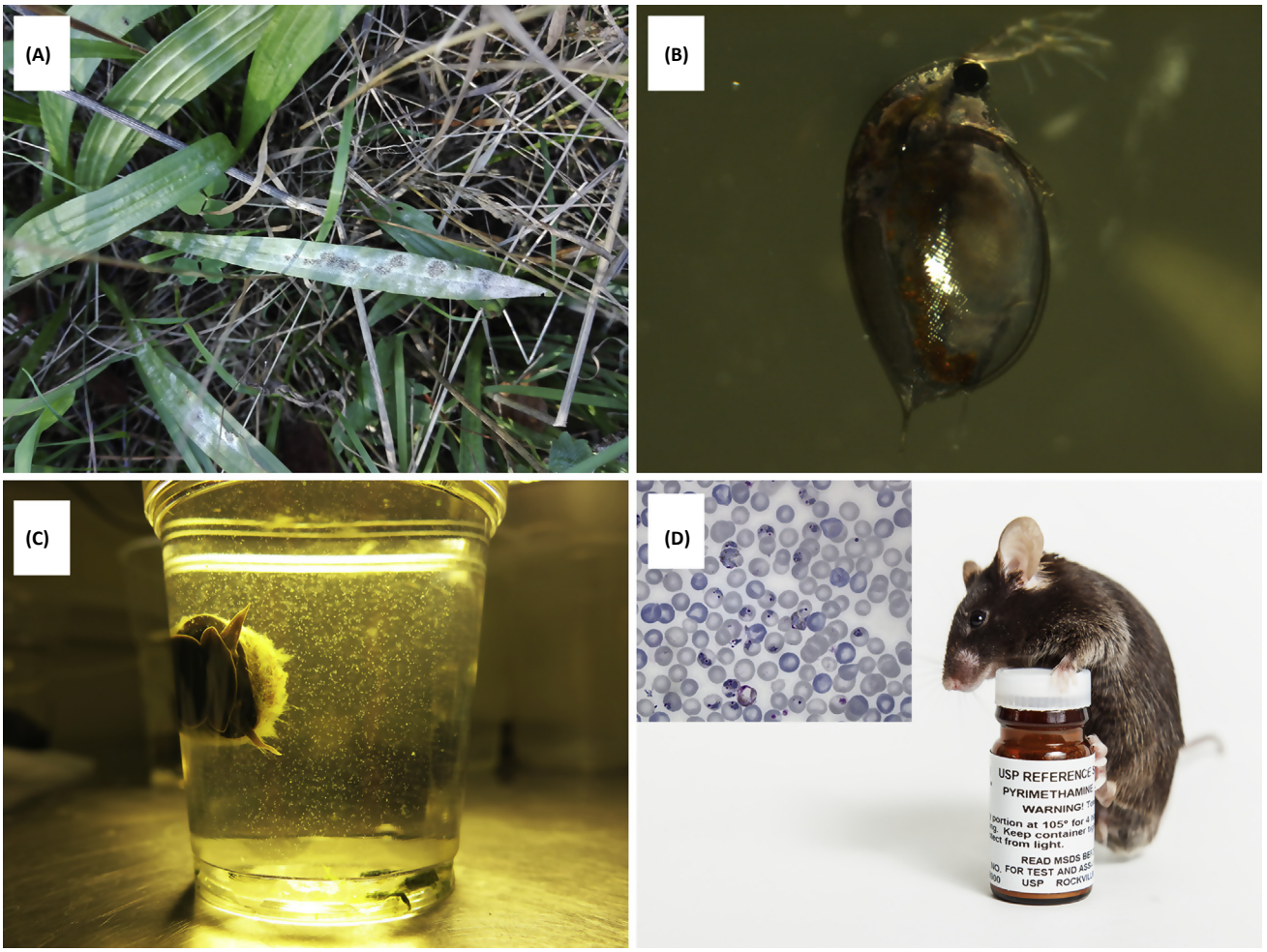


Figure I. Schematic Presentation of Possible Interactions and Implications of Simultaneous (Left) and Sequential (Right) Parasite Coinfections in a Host. Parasite strains/genotypes are denoted in different colors.

strategies. Overall, we propose that sequential processes of coinfection may influence many, if not most, host–parasite–parasite interactions in nature.

Sequential Coinfections and Implications for Virulence

Theoretically, coinfecting parasite species and individuals can interact to a degree that drives evolution of virulence (reviews in [1,32]) and maintains fitness variation in parasite populations (review in [43]). Many of these predictions still await comprehensive empirical support.



Trends in Parasitology

Figure 1. Examples of Systems Where the Effects of Sequential Parasite Coinfections Have Been Explored. (A) Sequential infection of *Plantago lanceolata* with a strain of the powdery mildew *Podosphaera plantaginis* can provide protection against strains of the same pathogen arriving later during the early growing season [3]. The photograph shows whitish fungal lesions on the leaves of *P. lanceolata*. (Photograph by Anna-Liisa Laine.) (B) A prior residency of low-virulent strains of *Pasteuria ramosa* in *Daphnia* decreases the virulence of high-virulence strains [53]. The photograph shows infection of *P. ramosa* in *Daphnia longispina*, seen as whitish formations behind and under the eye. (Photograph courtesy of Katja Pulkkinen.) (C) Two genotypes of *Diplostomum pseudospathaceum* clonal cercariae released from the same snail intermediate hosts are more infectious than single genotypes, but only if the host has not encountered the parasite earlier [9]. The photograph shows a dense swarm of cercariae released from an infected snail. (Photograph by Anssi Karvonen.) (D) The photograph shows gametocytes of *Plasmodium chabaudi* in mouse. Competitively inferior strains of the rodent malaria parasite *P. chabaudi* can gain a competitive advantage over competitively superior strains by infecting the mouse host first [11]. (Photographs courtesy of Andrew Read and Sarah Reece.)

Multiple parasite infections, simultaneous and sequential, have traditionally been approached through models of coinfection (here coexistence of two parasite strains of one species or two different species) and superinfection (total exclusion of one strain by another without coexistence), showing that the order of arrival can significantly change the outcome of virulence [32]. However, as recently pointed out by Sofonea *et al*. [44], the complexity of multiple parasite infections is unlikely to be captured by the coinfection–superinfection dichotomy alone. First, many coinfection models do not consider host recovery (or parasite clearance) [32], which is important if the first (sequential) infection elicits a long-lasting, cross-reactive immune

response that prevails after clearance and influences subsequent parasites (Box 1). Second, infections can be chronic and prevail in hosts for years (e.g., helminths), which can influence outcomes of many other (acute) infections that emerge and pass rapidly in an epidemic manner [12]. Similarly, the order of sequential infection can be important with the outcome being different when parasite A infects before B, compared to B before A (Box 1). Third, these scenarios can be influenced by whether infections are local or systemic; that is, not all parasites interact, but this depends, for example, on the resources extracted, site of infection, and type of host immune responses. Consequently, interactions in sequential infections and in multiple infections in general are more likely between related parasite species. Finally, host demography is important; young hosts can provide fewer resources, but can also show weaker immune responses after birth compared to older individuals that have already been exposed (repeatedly) to the same or different parasites. We argue that incorporating such dynamics into models of (sequential) coinfections would make them more realistic, but, inevitably, also more complex.

Empirical examples of sequential coinfections in plants (e.g., [3–5,45]) suggest that the arrival sequence of pathogen strains may be a key determinant of infection outcomes. There are examples in which strains arriving later have a lower success in establishment, and this is attributed to induced host resistance, as the pathogen arriving first triggers host defenses that are effective against pathogens arriving later ('cross-protection', Table 1). Thus, the sequence of arrival can have strong effects for within-host pathogen dynamics. Indeed, simultaneous infections are often significantly more damaging to hosts than sequential coinfections [4]. Similar to plants, examples from invertebrate and vertebrate hosts suggest that the temporal sequence between two parasites can influence the infection outcome, mostly by mechanisms of resource competition and/or apparent host-immune-mediated competition (Figure 1 and Table 1). In many cases, these effects are asymmetric [7,10] and depend on the species and transmission mode of the parasite that infects first. Overall, the current evidence strongly highlights negative effects for the parasite that arrives later (Table 1).

There are currently three major gaps in knowledge regarding the effect of sequential infections on virulence. First, to draw conclusions on the evolution of virulence, studies should not only compare virulence in simultaneous and sequential coinfections, but also look into genotype ($G \times G$) interactions between the coinfecting parasites. This is necessary to gain an understanding of which virulence genotypes are favored by selection [26,32]. Recent studies on simultaneous infection of two parasites have shown the complexity of such interactions (e.g., [31,46]), but similar approaches are lacking in sequential infections. We argue that empirical tests addressing $G \times G$ interactions and virulence in a sequential coinfection framework are necessary to gain a comprehensive understanding of virulence evolution in different infection backgrounds of hosts. Second, mechanisms underlying effects of sequential infections are generally poorly known. In most cases, they likely involve both direct interactions (e.g., interference competition) and indirect interactions (resource competition, host-immune-mediated apparent competition), but their relative contribution is often unknown (Table 1). We argue that elucidating such mechanisms is important as they underlie evolution of virulence in many, if not most, systems [32]. These mechanisms are also likely influenced by within-host dynamics (e.g., local versus systemic, acute versus chronic infections), as well as taxonomic relatedness of the parasites. Finally, while research on coinfections, simultaneous and sequential, is heavily based on strains of single species or closely related parasites, we propose that interactions between completely unrelated parasites are probably more common than previously anticipated. Thus, we encourage more research towards community-level patterns and processes of sequential coinfections to elucidate the breadth of possible direct and indirect interactions.

Table 1. Examples of Plant, Invertebrate, and Vertebrate Systems Demonstrating the Effects of Sequential Parasite Coinfections

Host	Coinfecting parasites	Outcome of sequential coinfection	Possible mechanism	Refs
White campion, *Silene latifolia*	Strains of anther smut fungus, *Microbotryum violaceum*	First-arriving strain has an advantage over strains arriving later	Competitive exclusion by an unknown mechanism	[5]
Ribwort plantain, *Plantago lanceolata*	Strains of powdery mildew, *Podosphaera plantaginis*	First infection provides protection against later strains, but results in higher infection later in the season	Apparent (host-immune-mediated) competition	[3]
Tomato plant (*Solanum* sp.) epidermal cells	Strains of powdery mildew, *Oidium neolycopersici*	An avirulent strain suppresses a virulent strain	Hypersensitive reaction at the scale of single cells	[51]
Brown mustard, *Brassica juncea*	Compatible and incompatible strains of oomycete, *Albugo candida*	Incompatible strain induces protection against the compatible strain	Durable, systemic immune response	[52]
Barley, *Hordeum vulgare*	Barley stripe mosaic virus and barley yellow dwarf virus	Lower virulence compared to simultaneous infection; lower concentration of the virus arriving later	Apparent (host-immune-mediated) or interference competition, details unknown	[4]
Waterflea, *Daphnia magna*	Strains of the bacterium *Pasteuria ramosa*	More competitive and virulent strains dominate, except when a less-virulent strain infects first	Apparent (host-immune-mediated) or interference competition, details unknown	[53]
Waterflea, *Daphnia magna*	Bacterium *Pasteuria ramosa* and microsporidium *Octosporea bayeri*	No effect, but *O. bayeri* is able to withstand competition when it first infected the host vertically	Competition by an unknown mechanism	[28]
Waterflea, *Daphnia galeata*	Protozoan *Caullerya mesnili* and fungus *Metschnikowia* sp.	Higher prevalence of coinfection, *C. mesnili* suppressing *Metschnikowia* sp.	Apparent (host-immune-mediated) or interference competition, details unknown	[6]
Honeybee, *Apis mellifera*	Microsporidia *Nosema apis* and *N. ceranae*	Species infecting first inhabits the second; magnitude of the effect depends on the species	Apparent (host-immune-mediated) or resource competition, details unknown	[7]
Pacific chorus frog, *Pseudacris regilla*	Trematodes *Ribeiroia ondatrae* and *Echinostoma trivolvis*	Success of *R. ondatrae* is reduced by *E. trivolvis*; no effect in opposite order of infections	Apparent (host-immune-mediated) or resource competition, details unknown	[10]
Laboratory mouse	Strains of rodent malaria, *Plasmodium chabaudi*	Reduction in density of the later-arriving strains with the length of sequence between infections	Apparent (host-immune-mediated) or resource competition, details unknown	[11]
Laboratory mouse (meta-analysis on 54 studies)	Metazoan parasitic worms and microparasites	No effect of infection interval; decreased or increased microparasite densities in coinfection	Anemia and immune suppression of the host, resulting in decreased or increased microparasite densities, respectively	[12]
African buffalo, *Syncerus caffer*	Gastrointestinal nematode and bovine tuberculosis (*Mycobacterium bovis*)	Prior nematode infection facilitates the invasion of bovine tuberculosis	Nematode-induced immune suppression	[48]

Implications of Sequential Coinfections for Parasite Transmission Strategies and Epidemiology

Coinfections can represent opportunities or challenges also for parasites. Coinfection scenarios are typically unpredictable for the coinfecting parasites in terms of background of the target host (species, resistance genotype) and the identity of the coinfecting partner (genetic interaction between the parasite individuals; see [31,46] for examples of simultaneous coinfections). Sequential infections add yet another component to the unpredictable 'host environment' that newly arriving parasites must face. In general, an uninfected host is a first-come-first-served resource, where sequential host exposure can result in direct competitive interference/exclusion, or indirect resource or host-immune-mediated competition that the second invader needs to deal with (Box 1). An interesting question is whether evolution of parasite traits has been responding to the probability of coinfection, simultaneous or sequential.

In theory, host heterogeneity (uninfected/infected) could result in selection (evolutionary branching) towards specialized parasite strains, ones targeting uninfected hosts and others targeting those already infected [25,47]. However, given the wide spectrum of possible interactions in a coinfecting parasite infracommunity and parasite within-host dynamics (see above), we argue that these interactions probably are orders of magnitude more diverse in nature. Sequential exposure of hosts to one or several parasites could nevertheless influence evolution of transmission strategies. For example, the first infection could result in suppression of host immune function, allowing higher replication for the second one [12]. A simultaneous coinfection could also result in higher infection success for parasites in an immunologically naïve host compared to single infection if the infection diversity represented a higher challenge for the host immune system ([22]; reviewed in [24]). However, such benefits of co-exposure could disappear following sequential exposure and activation of the host immune system (Box 2). In theory, the latter scenario could select for co-transmission strategies aiming at naïve hosts with lower resistance and the possibility for facilitation in coinfection success. This could be possible, for example, if the release of infective stages of parasites coincided with the emergence of young, susceptible host cohorts. However, facilitation requires that there is little or no competition between parasites, which is why such interactions are likely to be system specific. Overall, more research on facilitative interactions in sequential coinfections and transmission is needed in different systems.

Sequential host exposure to multiple parasites can have important implications also for parasite epidemiology. For example, a significant proportion of the host population being already infected, or showing cross-reactive immune responses from previous infections, can alter the success of the parasites arriving later (Box 1), thus potentially changing the course of an epidemic [48]. This is

Box 2. Dynamics of Host Exposure in a Trematode–Fish System

Trematodes of the genus *Diplostomum* are ubiquitous parasites of freshwater fishes, with several species [2] and genotypes [54] of the parasites typically coinfecting a host. Different coinfecting species interact in fish in a genotype-specific and dose-dependent manner, which changes the infection success of the parasites [46]. Cercariae are released into the water in high numbers from the first intermediate freshwater snail hosts after asexual reproduction. One snail can harbor and release more than one clonal parasite genotype, which can result in simultaneous coexposure of the fish to two genotypes. Similarly, a fish can be simultaneously coexposed to two parasite genotypes emerging from two different snails if the snails are in close proximity (Figure I). These scenarios are possible in the wild because of aggregation of snail intermediate hosts that release the infective stages (cercariae) in shallow areas of a lake, high prevalence of infection in some populations, and aggregation (coinfection) of parasite genotypes to certain snail intermediate host individuals [55]. Simultaneous coexposure of a previously unexposed fish to two genotypes (Figure I) results in higher infection success compared to single-genotype exposures. This is likely as a result of exposure heterogeneity representing an additional challenge to the host immune system in the naïve hosts [23]. The results

suggest that coexposing the fish host could be beneficial to the parasite. However, the benefit is reduced or even eroded if the fish host has been previously exposed [9] (Figure I), presumably following development of specific immune responses in the fish (the immunization process itself is not specific to parasite genotypes [56]). Thus, after likely activation of the host adaptive immune system following the first exposure, parasites no longer benefit from coexposing a host.

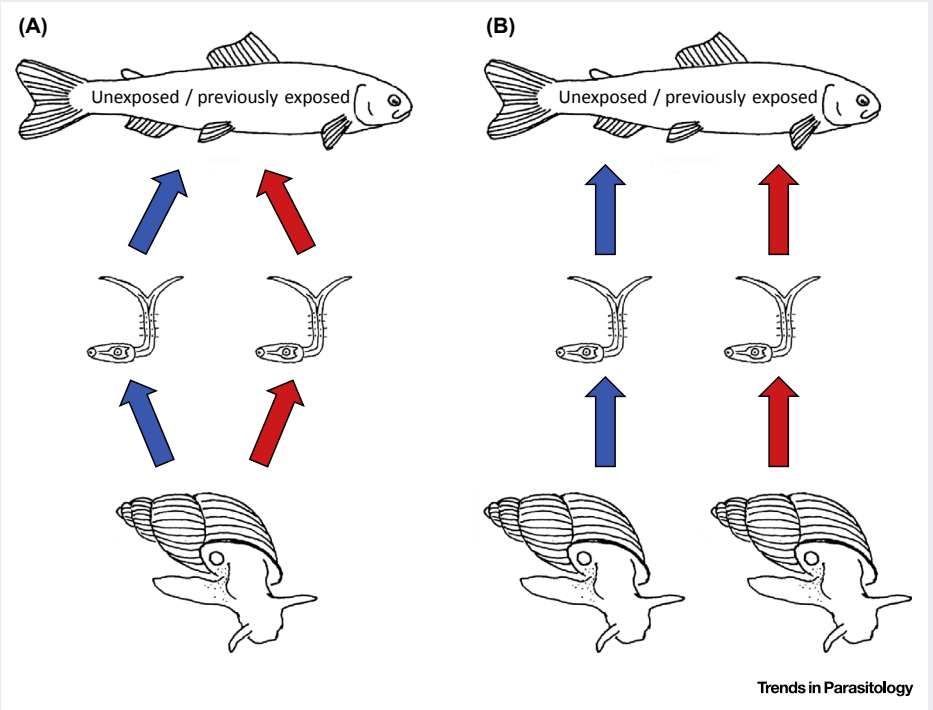


Figure I. Scenarios of Simultaneous and Sequential Coinfections of a Fish Host by *Diplostomum pseudospathaceum* Trematode Cercariae. Simultaneous coexposure of fish can result from one snail releasing two parasite genotypes (denoted by different colors) (A), or from two different snails releasing single genotypes in close proximity (B). Infection success and facilitation of the genotypes depend on whether the fish is unexposed or has been previously exposed (sequential exposure). Drawings courtesy of Sven Nikander.

the fundamental element, for example, in vaccination programs, where a sequential administration of attenuated pathogens of one type can prevent epidemics of virulent strains through cross-reactive immune responses. However, most of the evidence on sequential coinfections outside the medical realm comes from laboratory experiments (Table 1), where conditions often do not correspond to nature in terms of infection dose (unnaturally high doses) or pattern of exposure (the order and administration of infection is forced). Thus, exploring the actual epidemiological consequences of sequential exposure requires approaches in the field. Recent investigations manipulating the order (sequence, priority effects) of infections have demonstrated significant changes in the epidemiology [45] and community structure [49] of parasites in natural conditions. For example, Halliday *et al*. [45] elegantly took advantage of the natural sequence of multiple infections driven by environmental conditions and showed how the sequence and interactions between parasites influenced the epidemics.

We propose that many more experiments in natural conditions are needed to understand the general epidemiological consequences of sequentially occurring infections. It would be important also from an evolutionary perspective to implement ecological conditions of parasite

coinfections that resemble better the natural patterns of parasite exposure and resulting interactions. Epidemiological implications of sequential infections have relevance also for the prevention of diseases of humans and livestock. For instance, if previous or existing other infections could modulate the outcome of a target infection this could represent a challenge for effective disease mitigation strategies [12,50]. This is well illustrated in intensive production units, where epidemics are commonly treated with little consideration of the presence or history of other infections. In general, we argue that coinfections, simultaneous or sequential, can contribute to disease-related management failures and are important components of disease epidemiology in production environments.

Concluding Remarks

Parasite coinfections predominate in host populations in the wild and can have significant implications for key parasite traits such as virulence [1]. Most coinfections, however, do not occur simultaneously, but sequentially with one parasite establishing first, which can change the outcome of infection and epidemiology of a disease. We argue that the prevalence and significance of sequential coinfections for ecological and evolutionary dynamics of host–parasite interactions is probably largely underestimated in the wild. While interactions are generally considered more likely between related parasites, recent evidence has begun to reveal sequential coinfection interactions also between taxonomically distant parasites. This could significantly increase the complexity of possible interactions within the parasite community of one host. However, the magnitude of possible interactions is still largely unknown (see Outstanding Questions). Sequential coinfection interactions are also influenced by different types of direct and indirect interactions between the parasites. In most cases, however, detailed mechanisms have remained unknown. Particularly the role of specific immune responses of vertebrates is still poorly understood, although these responses probably shape subsequent parasite interactions long after the primary infection itself has been cleared. It would also be important to explore the evolutionary implications of sequential coinfections in detail. For example, a sequence between two infections generally attenuates virulence, but the variation associated in specific genotype interactions (G $\times$ G) between the coinfecting parasites is largely unknown. Such information could help to elucidate which virulence genotypes are favored by selection. Further, simultaneous coinfections could facilitate transmission of the coinfecting partners. This could impose selection on transmission strategies, but also depend on the sequential infection history and immunological status of the hosts. In general, aspects of sequential host exposure are important also from an applied perspective as sequential epidemics of different pathogens are common also in intensive production environments. Acknowledgement and integration of dynamics of infections in implementation of management practices would be essential in the fight against emerging parasitic diseases and drug resistance.

Outstanding Questions

How widely do effects of sequential coinfections extend across different parasite taxa? Do these operate on the scale of the entire parasite community of one host?

What are the detailed mechanisms by which sequentially coinfecting parasites interact within a host? How do these differ across different hosts such as plants, invertebrates, and vertebrates, and between different components of the host immune system?

Are sequential coinfections important for the evolution of parasite virulence and transmission strategies?

What is the significance of coinfections and sequential coinfections for disease severity in production environments? Can knowledge of ecology and evolution of sequential infections provide tools for disease control?

Acknowledgments

We thank I. Klemme and K.-R. Louhi for fruitful discussions and three anonymous reviewers for their constructive comments. The work was supported by the Academy of Finland for A.K. (grants 263864, 292736 and 310632). A.-L.L. was funded by grants from the Academy of Finland (296686), and the European Research Council (Consolidator Grant RESISTANCE 724508).

References

1. Read, A.F. and Taylor, L.H. (2001) The ecology of genetically diverse infections. *Science* 292, 1099–1102
2. Rellstab, C. *et al.* (2011) Analysis of trematode parasite communities in fish eye lenses by pyrosequencing of naturally pooled DNA. *Infect. Genet. Evol.* 11, 1276–1286
3. Laine, A.L. (2011) Context-dependent effects of induced resistance under co-infection in a plant–pathogen interaction. *Evol. Appl.* 4, 696–707
4. Marchetto, K.M. and Power, A.G. (2018) Coinfection timing drives host population dynamics through changes in virulence. *Am. Nat.* 191, 173–183
5. Hood, M.E. (2003) Dynamics of multiple infection and within-host competition by the anther-smut pathogen. *Am. Nat.* 162, 122–133
6. Lohr, J.N. *et al.* (2010) Prior residency does not always pay off – co-infections in *Daphnia*. *Parasitology* 137, 1493–1500

7. Natsopoulou, M.E. *et al.* (2015) Interspecific competition in honeybee intracellular gut parasites is asymmetric and favours the spread of an emerging infectious disease. *Proc. R. Soc. B* 282, 20141896
8. Karvonen, A. *et al.* (2009) Host immunization shapes interspecific associations in trematode parasites. *J. Anim. Ecol.* 78, 945–952
9. Klemme, I. *et al.* (2016) Host infection history modifies co-infection success of multiple parasite genotypes. *J. Anim. Ecol.* 85, 591–597
10. Hoverman, J.T. *et al.* (2013) Does timing matter? How priority effects influence the outcome of parasite interactions within hosts. *Oecologia* 173, 1471–1480
11. de Roode, J.C. *et al.* (2005) Dynamics of multiple infection and within-host competition in genetically diverse malaria infections. *Am. Nat.* 166, 531–542
12. Graham, A.L. (2008) Ecological rules governing helminth-microparasite coinfection. *Proc. Natl. Acad. Sci. U. S. A.* 105, 566–570
13. Griffiths, E.C. *et al.* (2015) Bottom-up regulation of malaria population dynamics in mice co-infected with lung-migratory nematodes. *Ecol. Lett.* 18, 1387–1396
14. Wargo, A.R. *et al.* (2007) Transmission stage investment of malaria parasites in response to in-host competition. *Proc. R. Soc. B* 274, 2629–2638
15. Mideo, N. and Day, T. (2008) On the evolution of reproductive restraint in malaria. *Proc. R. Soc. B* 275, 1217–1224
16. Hafer, N. and Milinski, M. (2016) Inter- and intraspecific conflicts between parasites over host manipulation. *Proc. R. Soc. B* 283, 20152870
17. Bashey, F. *et al.* (2012) Spiteful interactions between sympatric natural isolates of *Xenorhabdus bovienii* benefit kin and reduce virulence. *J. Evol. Biol.* 25, 431–437
18. Poulin, R. (2001) Interactions between species and the structure of helminth communities. *Parasitology* 122, S3–S11
19. Gold, A. *et al.* (2009) Within-host competitive exclusion among species of the anther smut pathogen. *BMC Ecol.* 9, 11
20. Cox, F.E.G. (2001) Concomitant infections, parasites and immune responses. *Parasitology* 122, S23–S38
21. Cui, J. *et al.* (2005) *Pseudomonas syringae* manipulates systemic plant defenses against pathogens and herbivores. *Proc. Natl. Acad. Sci. U. S. A.* 102, 1791–1796
22. Jokela, J. *et al.* (2000) Dr. Pangloss restrained by the Red Queen – steps towards a unified defence theory. *Oikos* 89, 267–274
23. Karvonen, A. *et al.* (2012) Synchronous attack is advantageous: mixed genotype infections lead to higher infection success in trematode parasites. *Proc. R. Soc. B* 279, 171–176
24. Zélé, F. *et al.* (2018) Ecology and evolution of facilitation among symbionts. *Nat. Commun.* 9, 4869
25. Alizon, S. and van Baalen, M. (2008) Multiple infections, immune dynamics, and the evolution of virulence. *Am. Nat.* 172, E150–E168
26. Choisy, M. and de Roode, J.C. (2010) Mixed infections and the evolution of virulence: Effects of resource competition, parasite plasticity, and impaired host immunity. *Am. Nat.* 175, E105–E118
27. Fellous, S. and Koella, J.C. (2009) Infectious dose affects the outcome of the within-host competition between parasites. *Am. Nat.* 173, E177–E184
28. Ben-Ami, F. *et al.* (2011) The expression of virulence during double infections by different parasites with conflicting host exploitation and transmission strategies. *J. Evol. Biol.* 24, 1307–1316
29. Vojvodic, S. *et al.* (2012) Virulence of mixed fungal infections in honey bee brood. *Front. Zool.* 9, 5
30. Duncan, A.B. *et al.* (2015) The consequences of co-infections for parasite transmission in the mosquito *Aedes aegypti*. *J. Anim. Ecol.* 84, 498–508
31. Louhi, K.-R. *et al.* (2015) Interactions among bacterial strains and fluke genotypes shape virulence of co-infection. *Proc. R. Soc. B* 282, 20152097
32. Alizon, S. *et al.* (2013) Multiple infections and the evolution of virulence. *Ecol. Lett.* 16, 556–567
33. Bose, J. *et al.* (2016) Multiple-genotype infections and their complex effect on virulence. *Zoology* 119, 339–349
34. Tollenaere, C. *et al.* (2016) Evolutionary and epidemiological implications of multiple infection in plants. *Trends Plant Sci.* 21, 80–90
35. Swanson, S.J. *et al.* (2006) Coinfections acquired from *Ixodes* ticks. *Clin. Microbiol. Rev.* 19, 708–727
36. Jousimo, J. *et al.* (2014) Ecological and evolutionary effects of fragmentation on infectious disease dynamics. *Science* 344, 1289–1293
37. Byers, J.E. *et al.* (2008) Controls of spatial variation in the prevalence of trematode parasites infecting a marine snail. *Ecology* 89, 439–451
38. Jokela, J. and Lively, C.M. (1995) Spatial variation in infection by digenetic trematodes in a population of fresh-water snails (*Potamopyrgus antipodarum*). *Oecologia* 103, 509–517
39. Combes, C. *et al.* (1994) Behaviors in trematode cercariae that enhance parasite transmission – patterns and processes. *Parasitology* 109, S3–S13
40. Karvonen, A. *et al.* (2004) Parasite resistance and avoidance behaviour in preventing eye fluke infections in fish. *Parasitology* 129, 159–164
41. Taskinen, J. *et al.* (1994) Quantity of sporocysts and seasonality of two *Rhipidocotyle* species (Digenea: Bucephalidae) in *Anodonta piscinalis* (Mollusca: Bivalvia). *Int. J. Parasitol.* 24, 877–886
42. Thompson, J.N. (2005) *The Geographic Mosaic of Coevolution,* University of Chicago Press
43. Seppälä, O. and Jokela, J. (2016) Do coinfections maintain genetic variation in parasites? *Trends Parasitol.* 32, 930–938
44. Sofonea, M.T. *et al.* (2017) Exposing the diversity of multiple infection patterns. *J. Theor. Biol.* 419, 278–289
45. Halliday, F.W. *et al.* (2017) Interactions among symbionts operate across scales to influence parasite epidemics. *Ecol. Lett.* 20, 1285–1294
46. Seppälä, O. *et al.* (2012) Reciprocal interaction matrix reveals complex genetic and dose-dependent specificity among coinfecting parasites. *Am. Nat.* 180, 306–315
47. Gandon, S. *et al.* (2002) The evolution of parasite virulence, superinfection, and host resistance. *Am. Nat.* 159, 658–669
48. Ezenwa, V.O. *et al.* (2010) Hidden consequences of living in a wormy world: nematode-induced immune suppression facilitates tuberculosis invasion in African buffalo. *Am. Nat.* 176, 613–624
49. Benesh, D.P. and Kalbe, M. (2016) Experimental parasite community ecology: intraspecific variation in a large tapeworm affects community assembly. *J. Anim. Ecol.* 85, 1004–1013
50. Hartgers, F.C. and Yazdanbakhsh, M. (2006) Co-infection of helminths and malaria: modulation of the immune responses to malaria. *Parasite Immunol.* 28, 497–506
51. Seifi, A. *et al.* (2012) An avirulent tomato powdery mildew isolate induces localized acquired resistance to a virulent isolate in a spatiotemporal manner. *Mol. Plant Microbe Interact.* 25, 372–378
52. Singh, U.S. *et al.* (1999) Induction of systemic resistance to *Albugo candida* in *Brassica juncea* by pre- or coinoculation with an incompatible isolate. *Phytopathology* 89, 1226–1232
53. Ben-Ami, F. *et al.* (2008) The effects of multiple infections on the expression and evolution of virulence in a *Daphnia*–endoparasite system. *Evolution* 62, 1700–1711
54. Rauch, G. *et al.* (2005) How a complex life cycle can improve a parasite's sex life. *J. Evol. Biol.* 18, 1069–1075
55. Louhi, K.-R. *et al.* (2013) Prevalence of infection as a predictor of multiple genotype infection frequency in parasites with multiple-host life cycle. *J. Anim. Ecol.* 82, 191–200
56. Rellstab, C. *et al.* (2013) Genotype-specific vs. cross-reactive host immunity against a macroparasite. *PLoS One* 8, e78427