Trends in Parasitology

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Review

Parasite–Parasite Interactions in the Wild: How To Detect Them?

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Inter-specific interactions between parasites impact on parasite intra-host dynamics, host health, and disease management. Identifying and understanding interaction mechanisms in the wild is crucial for wildlife disease management. It is however complex because several scales are interlaced. Parasite–parasite interactions are likely to occur via mechanisms at the within-host level, but also at upper levels (host population and community). Furthermore, interactions occurring at one level of organization spread to upper levels through cascade effects. Even if cascade effects are important confounding factors, we argue that we can also benefit from them because upper scales often provide a way to survey a wider range of parasites at lower cost. New protocols and theoretical studies (especially across scales) are necessary to take advantage of this opportunity.

Parasite–Parasite Interactions: From The Lab to the Field

Parasites (see Glossary) are ubiquitous in the living world. Largely considered as agents of disease and death, parasites are now recognized as integral parts of ecosystems [1,2] and as major driving forces for biological evolution [3,4].

However, research into host–parasite interactions remains dominated by the study of 'one host–one parasite' systems. Such studies ignore three important aspects that are emerging questions [2]. First, many potentially pathogenic agents silently circulate within host populations (e.g., [5]). Second, many parasites infect several host species (e.g., generalist parasites), with consequences for disease epidemiology and the selective pressures acting on each parasite and host [6]. Third, hosts can simultaneously carry several agents, with consequences for the dynamics of each parasite and for host health (e.g., [7,8]). In addition, understanding the spatiotemporal dynamics of diseases and the evolution of hosts and parasites requires integrating processes at different scales of ecological organization, space, and time from the within-host level (e.g., interactions of parasites with the host immune system, host resources, and coinfecting parasites) to the ecosystem or landscape level (e.g., influence of environmental variables and of host community composition on parasite dynamics); it implies moving from 'one host–one parasite' systems towards an ecosystem view of host–parasite interactions, embracing the real complexity of natural systems, one of the most exciting and challenging tasks for disease ecologists today [2,9–11].

In this paper we focus on interactions between different species of parasites in wild hosts. Within a host, these parasites can interact with each other, modifying the intra-host and/or inter-host dynamics (spatial and/or temporal) of each other. Such parasite–parasite interactions increase

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Hosts are often infected by more than one parasite species. Numerous experimental and clinical studies carried out at the host individual level have revealed that interactions between parasite species impact on parasite dynamics, host health, and disease management.

Field studies are still in their infancy and robust methods to detect parasite–parasite interactions in complex natural systems are lacking.

In the wild, parasite–parasite interactions can occur not only through processes at the host individual level but also at population and community levels, stressing the need to investigate interaction mechanisms at various ecological scales.

Interactions occurring at one level can cascade up, translating into the epidemiological patterns observed at higher levels of organization.

We propose to use cascade effects to detect parasite–parasite interactions in the wild.

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 http://dx.doi.org/10.1016/j.pt.2015.07.005

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(synergy) or decrease (antagonism) the **susceptibility** of the host to other agents, the inter-host transmission rate of the interacting parasites, and/or the severity of the disease symptoms they induce. They may also greatly influence the evolution of the parasites themselves, in particular the evolution of their virulence (reviewed in [12]). Many examples of parasite–parasite interactions have been identified, and there is now strong evidence of their impact on host health, parasite circulation, and pathogen management [8,13–17]. Despite this, few studies have looked at parasite interactions in wild populations (e.g., [15]). Considering the impact they can have on wildlife populations [18], that over 60% of human diseases may have a zoonotic origin [19,20], and that a substantially higher percentage of livestock diseases are probably shared with other wild-ranging hosts [21], more work on parasite–parasite interactions in wild populations is needed. Their better detection and understanding are crucial to prevent and manage infectious diseases. The identification of synergies between different parasite species may help to prevent population declines or extinctions. By contrast, where interactions are antagonistic, measures targeting only one parasite species may result in unexpected increases in a second co-circulating parasite species [22,23]. Recent studies suggest that antagonist parasites may also help in fighting problematic pathogens in natural populations, as exemplified by the protective effect of *Janthinobacterium lividum* against chytridiomycosis in amphibians [24] and of diverse microbial enemies of nematodes in dune plants [25].

Current knowledge of parasite–parasite interactions largely results from animal models and from experimental and clinical studies with an individual-based approach. These studies are biased towards human pathogens and suspected interactions (e.g., following the observation of increased mortality in a population). They also focus on mechanisms occurring at the within-host level (e.g., mediated by the host immune system, Table 1), whereas, as will be developed further, interactions between parasites can also occur via mechanisms occurring at the host population [26] and probably higher levels of organization. Interaction mechanisms resulting in particular from host behavior have been largely ignored, despite its crucial role in transmission processes [27]. A mechanistic approach, aiming at deciphering the underlying processes of parasite–parasite interactions, is necessary to go beyond the simple description of parasite associations patterns. Community ecology already proved to be useful to understand processes shaping within-host parasite communities (e.g., top-down and bottom-up regulation of parasite population size, via host immune system and resources, respectively) [9,11,28], but so far no framework includes higher scales.

Studies are now beginning to be extended to natural populations (e.g., [15]), but detecting and identifying parasite–parasite interactions and their underlying mechanisms represent a methodological challenge in complex food webs [29]. The difficulty resides in the existence of multiple confounding factors (e.g., parasites transmitted by a similar vector or a similar behavior, and environmental factors exposing hosts to several parasites simultaneously) and possible mismatches between the level of organization under study and the level of organization at which the interaction occurs. Long-term field studies are rare and costly and an increasing effort is also put on developing methods to deal with more usual empirical epidemiological data such as presence/absence data obtained in cross-sectional studies, that is, sampling multiple host individuals, populations, or communities at one time [29,30]. Other questions have been poorly investigated and represent interesting avenues of research. Are there traces of within-host interactions at higher levels of organization (i.e., do parasite–parasite interactions cascade up?). In other words, can we detect parasite–parasite interactions by examining patterns at levels higher than the level of their underlying mechanism? What types of patterns can be expected? – or, put differently – what are the consequences of within-host interactions for the spatiotemporal dynamics of interacting parasites within host populations, communities, or at the regional scale? Being able to interpret epidemiological patterns obtained in the field at different scales, and to link the observed patterns to different types of parasite–parasite interactions and their mechanisms,

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