Animal host-microbe interactions

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Abstract

The ecology of infectious diseases, as we currently recognise it, has been a major field of scientific research for over a century. Since the early work of John Snow, describing the epidemiology of cholera in 1850s London, and Ronald Ross, describing the transmission dynamics of malaria at the end of the 19th century, through the mathematical models of Kermack & McKendrick in the 1920s, and Anderson & May's revolutionary modelling of infectious disease dynamics in the late 1970s, the field of disease ecology has always sought to combine cutting-edge analytical and theoretical tools with observational and experimental data to understand the key drivers of infectious diseases. Through this body of work we now have a comprehensive understanding of many of the ecological factors underlying the transmission, spread and impact of infectious diseases, whether they be in wildlife, livestock or humans. In particular, we now recognise fundamental, unifying features of all infectious disease systems, such as the importance of the relationship between host density and transmission, the parasite's basic reproduction number (R0) and minimum threshold population sizes ('critical community sizes') below which the parasite cannot persist (Hudson, Rizzolli, Grenfell, Heesterbeek, & Dobson, 2002). We also understand that the heterogeneities between individual hosts that can, through the existence of superspreaders, dramatically alter parasite transmission potential (Paull et al., 2012). And we are increasingly aware of the potential for parasites to alter host behaviour (Adamo & Webster, 2013) and regulate host population sizes (Tompkins & Begon, 1999).

Disciplines

Medicine and Health Sciences | Social and Behavioral Sciences

Guest Editorial: Special feature on animal host-microbe interactions

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Introduction

The ecology of infectious diseases, as we currently recognise it, has been a major field of scientific research for over a century. Since the early work of John Snow, describing the epidemiology of cholera in 1850s London, and Ronald Ross, describing the transmission dynamics of malaria at the end of the 19th Century, through the mathematical models of Kermack & McKendrick in the 1920s, and Anderson & May's revolutionary modelling of infectious disease dynamics in the late 1970s, the field of disease ecology has always sought to combine cutting-edge analytical and theoretical tools with observational and experimental data to understand the key drivers of infectious diseases. Through this body of work we now have a comprehensive understanding of many of the ecological factors underlying the transmission, spread and impact of infectious diseases, whether they be in wildlife, livestock or humans. In particular, we now recognise fundamental, unifying features of all infectious disease systems, such as the importance of the relationship between host density and transmission, the parasite's basic reproduction number (R_0), and minimum threshold population sizes ('critical community sizes') below which the parasite cannot persist (Hudson et al. 2002). We also understand that the heterogeneities between individual hosts that can, through the existence of superspreaders, dramatically alter parasite transmission potential (Paull et al. 2012). And we are increasingly aware of the potential for parasites to alter host behaviour (Adamo and Webster 2013) and regulate host population sizes (Tompkins and Begon 1999).

Since that early seminal work, there has been a growing realisation of the importance of moving beyond the classical 'single-host-single-parasite' paradigm, recognising that parasites and pathogens do not exist in isolation, but typically interact with each other through co-infection of individual hosts (Pedersen and Fenton 2007), and circulate within reservoir communities comprising many potential host species (Haydon et al. 2002). The reality of 'multi-host-multi-parasite' systems, and their implications for host susceptibility, disease progression and onward transmission potential, has led to a surge of interest in the community ecology of disease; a field seeking to understand how ecological interactions between multiple parasites, and between multiple host species, can shape transmission dynamics in wider ecological communities (Johnson et al. 2015). The application of

these concepts to natural populations (including humans) has provided an invaluable opportunity to develop and test broader ecological theories. It has also had the practical benefit of informing the design and implementation of disease management strategies, such as threshold proportions to vaccinate, the likely impact of mass drug administration campaigns, and the success (or not) of culling to control disease spread.

While disease ecologists have primarily focused on parasites – organisms that have a negative effect on host performance – most interactions between animals and microorganisms do not result in disease (Hersh et al. 2014, Spencer and Zuk 2016). In fact, beneficial interactions between human hosts and their microbes have been known for more than a century (Dethlefsen et al. 2007). Yet, it was the advent of culture-independent molecular techniques in the early 2000s (e.g. Tyson et al. 2004, Venter et al. 2004) that revolutionised our understanding of host-microbe interactions, highlighting the importance of understanding the entire community of organisms living in and on eukaryotic hosts – their microbiota (Dethlefsen et al. 2007).

Over the last decade, the rise of next-generation sequencing methods and analytical technologies have resulted in unprecedented insight into host microbiotas (Koskella et al. 2017). Sequencing methods have identified a wide range of symbionts (including fungi, archaea, viruses, and macroparasites); however, bacteria are by far the most abundant and may have paramount influence over host-microbe interactions (Sommer and Bäckhed 2013). Bacteria also conserve the 16s RNA gene, such that 16S rRNA gene sequencing methods allow (near) complete characterization of these communities, allowing researchers to look beyond known parasites and pathogens and examine entire bacterial communities. It is now widely accepted that the microbiota have a profound impact on host development and function, influencing everything from host metabolism and nutrient acquisition, to stress responses and ability to fight both infectious and non-infectious diseases (Sommer and Bäckhed 2013). Pioneering work in this field has focused on humans, or standard laboratory model species (Amato Katherine 2013, Colston and Jackson 2016, Hird 2017).. Increasingly, ecologists are also turning their attention to this within-host ecosystem, both because of the demonstrated significance to host phenotype, and because issues relating to the study of community formation, diversity, and stability are inherently ecological (Costello et al. 2012). Importantly, ecologists are likely to take a different approach from clinicians, nutritionists, and immunologists working on humans. Moreover, ecologists are likely to use non-standard, non-model organisms - often in free-living settings. Ecological studies of host microbiota therefore have the potential to profoundly enhance our understanding of the processes that shape microbe-host interactions in natural systems (Amato Katherine 2013, Hird 2017).

In recognition of this recent surge of activity, the Journal of Animal Ecology launched an open call for papers investigating the ecology of host-microbe interactions, including (but not limited to) "the host gut microbiome, covert pathogens and endo-symbionts". This Special Feature represents a collection of the papers submitted in response to that call. Although only a subset of the work going on in this field, the breadth of questions, host taxa and approaches covered by these papers provide revealing insight into the current state of this burgeoning field, whilst also highlighting major knowledge gaps that may be fruitful avenues for future research.

Topics, systems and approaches covered in this Special Feature

Seventeen papers were accepted for this Special Feature, spanning host-microbe interactions in the broadest sense; some of the papers dealt with parasitic and pathogenic microbes, but the majority (10/17 papers) explored mutualistic- or commensal-host interactions focused on the host's gut microbiota. Indeed, all but three of the papers focussed on bacteria as their microbe of choice, with the others examining fungi or parasitic helminths, or presenting a meta-analysis across several different types of pathogens. Although a wide range of host taxa were incorporated into this Special Feature, individual papers were noticeably dominated by a single host taxa. Over half of the papers (10/17) utilised arthropod hosts (mostly insects, but also spiders) as convenient laboratory experimental systems, with the remaining papers tending to analyse data from field surveys of crustacean, mammalian, avian or amphibian hosts.

In terms of the research questions addressed, five major themes emerged. Several papers sought to assess how host behaviours influence the composition of their microbiota. Similar to a large body of work conducted in human and laboratory model-animals (e.g. David et al. 2014, Kurilshikov et al. 2017), a key theme was testing for effects of local environment, diet, or host genetic background on symbiont community composition, either between populations of a single species (Kohl et al. 2018, Näpflin and Schmid-Hempel 2018) or between cohabiting species (Muletz Wolz et al. 2018). Mihaljevic et al. (2018) extended this to also consider the role of alternate host species, in conjunction with environmental factors, in shaping symbiont communities across populations of a focal host species. Within a host species, the spatial and hierarchical structure of social interactions was also shown to shape the transmission of individual microbes (and disease susceptibility) in populations (Keiser et al. 2018a, Keiser et al. 2018b, Raulo 2018), as were several different types of indirect interactions. For instance, parents were found to play a role in shaping the gut microbiota of their offspring even when they were separated from them in space and time, through diapause (Mushegian et al. 2018), and to play an active role in modifying the microbiota on the external

surface of other (dead) animals in preparing a carcass for their larval offspring (Duarte et al. 2018). Migratory behaviour, associated with extreme physiological demands on host metabolism, energy storage, and endurance, was also correlated with distinct bacterial communities, indicating potential direct and indirect interactions between host behaviour and their microbiota (Risely et al. 2018).

The second research theme centred on understanding interactions between microbes and the role of the host immune system in mediating these interactions. New analytical approaches to quantify the interactions between microbes and assess how they influence the composition of a host's microbiota were developed by Aivelo and Norberg (2018), drawing on the ecological tools developed to investigate parasite co-infections. To better understand host regulation of microbe-microbe interactions, Dhinaut et al. (2018) examined host immune priming by microbes. Although immune priming is increasingly well understood for pathogen-specific immune responses (e.g. Tate 2016), the mechanisms underpinning immune priming by the diverse host microbiota, and the reciprocal influence of immune responses on interactions between microbes, is just starting to be investigated. Dhinaut et al. (2018) shed some light in this area by experimentally testing how initial exposure to microbes – either directly or via maternal exposure - shaped later interactions between host and microbes, which have been found elsewhere to influence microbiota composition (e.g. Schwarz et al. 2016).

One of the major areas of microbiota research to date has involved assessing the functional importance of these within-host communities. However, although several (groups of) bacteria have known function in human and lab animal models, wildlife studies often find that a large proportion of the bacterial DNA they find is new to science, with very limited understanding of its function within the host, let alone functional similarities or redundancies between bacterial groups (Koskella et al. 2017). Within this issue, several papers make novel advances in our understanding of the functional importance of certain host-microbe interactions. For instance, following on from extensive work on microbiota-pathogen interactions in humans (reviewed by Pickard et al. 2017), Martinez et al. (2018) demonstrate that different bacterial symbionts have vastly different effects on the susceptibility of aphid hosts to wasp parasitism. In a different species of aphid, interactions between bacterial strains or species within the host were also shown to influence the outcome of symbiosis for both symbiont and host (McLean et al. 2018), suggesting complex fitness landscapes and selection pressures. Adding to this complexity, it appears that the microbiota composition most relevant to infection susceptibility may not always be the microbiota within the host at the time of infection, with Knutie et al. (2018) demonstrating that early-life experiences may be more important in some systems. Microbiota composition was also suggested to enhance the accessibility of certain

foraging resources (Kohl et al. 2018), and alter host metabolism and/or energy harvest in relation to host migration (Risely et al. 2018).

A number of studies also demonstrated that although host microbiota are generally not considered pathogenic, there can be costs associated with hosting symbionts (Martinez et al. 2018, McLean et al. 2018). Any benefits, such as reduced susceptibility to or enhanced tolerance of infection, or increased energy harvested from available food resources, must therefore be assessed in light of the costs of hosting these microbes. Notably, these costs may differ depending on host factors, such as diet (Miller and Cotter 2018), as well as environmental factors such as temperature (Russell and Moran 2006).

Finally, some studies touched on the potential for anthropogenic processes to alter host-microbe interactions. For instance, conservation actions such as supplemental provisioning were found to alter the transmission of pathogens within wildlife species, depending on host behaviour and parasite type (Becker et al. 2018). Whilst other anthropogenic processes, including those that alter host susceptibility to infection (such as the herbicide atrazine in frogs exposed to *Batrachochytrium dendrobatidis*) did not show appreciable effects on the diversity or composition of the gut microbiota of hosts (Knutie et al. 2018).

Future directions

This collection of papers demonstrate that across the animal kingdom, research into host-microbe interactions is gathering pace. It is clear from these and related studies that recent advances in sequencing technologies now make it possible to describe and characterise vast quantities of information relating to microbial species richness, diversity and dynamics, and those abilities are only likely to increase into the future. However, the papers in this issue also indicate that this field is still very much in the early stages of development, primarily seeking to characterise microbiota composition, or explore underlying drivers using simplified, single-factor experiments. This is an exciting phase in any emerging research field, as relatively simple studies can often reveal tantalising patterns and generate intriguing hypotheses that can be tested as the field progresses and expands to a broader range of scenarios. Increasing our understanding of host-microbe interactions is of profound importance to our understanding of animal ecology (Spencer and Zuk 2016). Yet our ability to make predictions about these dynamic, highly complex communities is limited, hindering our capacity to manage them effectively (Widder et al. 2016). Building predictive frameworks in this field will require creative, integrative extensions to the work presented here. In addition to carefully designed comparative studies (e.g. Risely et al. 2018), one promising avenue for future research may

be to bridge the gap between laboratory experiments and field observations. Extending experimental approaches from lab studies to field settings may help overcome the captivity-induced curtailment of natural microbiota, and allow researchers to embrace the full complexity found in natural ecosystems (Amato Katherine 2013, Colston and Jackson 2016, Hird 2017). Field experiments, such as translocations, cross-fostering, and targeted manipulations of host microbiota in natural settings may prove especially useful in uncovering important patterns and processes.

One of the major barriers to predicting and managing host-microbe interactions stems from a limited understanding of microbiota function (Widder et al. 2016). Because of the vast number of uncharacterised species, current next-gen sequencing approaches are limited to describing members of a host's microbiota in terms of their sequence identity, rather than function (Koskella et al. 2017). Yet taxonomic composition of the microbiota is likely to be far less important than its function *in situ*. A promising approach may be to compare metagenomics profiles (using DNA sequence identity, as in most studies) with metatranscriptomic profiles (using RNA transcript data) to reveal patterns of expression and hence functional importance of certain genes or pathways (Koskella et al. 2017). Pairing these data with information on host physiological profiles (e.g. Sommer et al. 2016) and modern improvements to traditional culture-based methods (e.g. Lau et al. 2016) will greatly enhance the determination of microbiota function.

With increased understanding of the functional relationships between hosts and their microbiota, the field will be poised to begin unravelling broader questions along the lines of classical disease ecology. For instance, the transmission of microbes (between hosts), their spread (across the landscape), their maintenance (as populations in their own right), potential interactions between them, and the environmental factors that influence these processes, are all important considerations in the conservation of microbiota, and their hosts (Spencer and Zuk 2016). These processes also aid in understanding the scaling relationships and feedback loops occurring across multiple levels of biological organisation (within-host dynamics, among-host dynamics, across host community dynamics). Extensions of metacommunity theory, modified for organisms living on or in eukaryotic hosts (Mihaljevic et al. 2018), may be particularly useful in addressing these questions. Likewise, unravelling the impact of microbiota on host physiology, behaviour, and population dynamics, particularly in the context of environmental stressors, are key issues for future research. Such insights may have the potential to spur additional fields of research, such as the evolutionary implications of stable (or unstable) interactions between hosts and their microbiota.

In recognition of the pervasive influence of host microbiota, data cataloguing these communities is accumulating on an unprecedented scale. Rapidly evolving sequencing (and other 'omics)

technologies has been paralleled by a surge in the development of statistical and computational tools to analyse these data, including network analysis pipelines, machine learning, neural net algorithms, etc. However, perhaps the greatest challenge to the field remains the development of simple, general theories about the processes that govern within-host ecosystems. Although concepts of assembly, complexity, and stability are grounded in general ecological theory (e.g. Costello et al. 2012), applying these concepts to host microbiota presents several challenges. In particular, microbiota fundamentally differ from their free-living counterparts on the basis of relative time scales (ecological and evolutionary), mechanisms for generating genetic diversity (including direct transfer of genes between microbes), pervasive ecosystem engineering by microbes, and host control (Koskella et al. 2017). For instance, the prevailing approach to assessing the response of microbiota to perturbation assumes a shift from one stable state to another (Turnbaugh et al. 2007), similar to the alternative stable states theory for free-living organisms (Scheffer et al. 2001). Yet, evidence from a wide range of systems indicates that perturbations tend to result in stochastic shifts in microbial community composition, with increased variability between hosts following perturbation (Zaneveld et al. 2017). Developing predictive statements in microbiota research, and judiciously contrasting these with theories developed for free-living communities therefore presents an unprecedented opportunity to probe, evaluate, and advance our understanding of ecology and evolution more generally.

Disease ecology has always pioneered the development of simple theory to help understand potentially complex systems. We would encourage this field to capitalise on the data generated by microbial sequencing technologies in order to develop, test and advance ecological theory more generally. The papers presented in this Special Feature provide an excellent foundation on which this field can build into the future.

References

Adamo, S. A., and J. P. Webster. 2013. Neural parasitology: how parasites manipulate host behaviour. Journal of Experimental Biology **216**:1-2.

Aivelo, T., and A. Norberg. 2018. Parasite–microbiota interactions potentially affect intestinal communities in wild mammals. Journal of Animal Ecology:n/a-n/a.

Amato Katherine, R. 2013. Co-evolution in context: The importance of studying gut microbiomes in wild animals. Microbiome Science and Medicine.

Becker, D. J., D. G. Streicker, and S. Altizer. 2018. Using host species traits to understand the consequences of resource provisioning for host–parasite interactions. Journal of Animal Ecology:n/a-n/a.

Colston, T. J., and C. R. Jackson. 2016. Microbiome evolution along divergent branches of the vertebrate tree of life: what is known and unknown. Molecular Ecology **25**:3776-3800.

Costello, E. K., K. Stagaman, L. Dethlefsen, B. J. M. Bohannan, and D. A. Relman. 2012. The Application of Ecological Theory Toward an Understanding of the Human Microbiome. Science **336**:1255-1262.

David, L. A., A. C. Materna, J. Friedman, M. I. Campos-Baptista, M. C. Blackburn, A. Perrotta, S. E. Erdman, and E. J. Alm. 2014. Host lifestyle affects human microbiota on daily timescales. Genome Biology **15**:R89.

Dethlefsen, L., M. McFall-Ngai, and D. A. Relman. 2007. An ecological and evolutionary perspective on human–microbe mutualism and disease. Nature **449**:811.

Dhinaut, J., M. Chogne, and Y. Moret. 2018. Immune priming specificity within and across generations reveals the range of pathogens affecting evolution of immunity in an insect. Journal of Animal Ecology:n/a-n/a.

Duarte, A., M. Welch, C. Swannack, J. Wagner, and R. M. Kilner. 2018. Strategies for managing rival bacterial communities: Lessons from burying beetles. Journal of Animal Ecology:n/a-n/a.

Haydon, D. T., S. Cleaveland, L. H. Taylor, and M. K. Laurenson. 2002. Identifying reservoirs of infection: A conceptual and practical challenge. Emerging Infectious Diseases **8**:1468-1473.

Hersh, M. H., S. L. LaDeau, M. A. Previtali, and R. S. Ostfeld. 2014. When is a parasite not a parasite? Effects of larval tick burdens on white-footed mouse survival. Ecology **95**:1360-1369.

Hird, S. M. 2017. Evolutionary Biology Needs Wild Microbiomes. Frontiers in Microbiology **8**:725.

Hudson, P., A. Rizzolli, B. Grenfell, J. Heesterbeek, and A. Dobson, editors. 2002. The Ecology of Wildlife Diseases. Oxford University Press, Oxford.

Johnson, P. T. J., J. C. de Roode, and A. Fenton. 2015. Why infectious disease research needs community ecology. Science **349**.

Keiser, C. N., N. Pinter-Wollman, M. J. Ziemba, K. S. Kothamasu, and J. N. Pruitt. 2018a. The index case is not enough: Variation among individuals, groups and social networks modify bacterial transmission dynamics. Journal of Animal Ecology:n/a-n/a.

Keiser, C. N., S. Vojvodic, I. O. Butler, E. Sartain, V. H. W. Rudolf, and J. B. Saltz. 2018b. Queen presence mediates the relationship between collective behaviour and disease susceptibility in ant colonies. Journal of Animal Ecology:n/a-n/a.

Knutie, S. A., C. R. Gabor, K. D. Kohl, and J. R. Rohr. 2018. Do host-associated gut microbiota mediate the effect of an herbicide on disease risk in frogs? Journal of Animal Ecology:n/a-n/a.

Kohl, K. D., J. Varner, J. L. Wilkening, and M. D. Dearing. 2018. Gut microbial communities of American pikas (Ochotona princeps): Evidence for phylosymbiosis and adaptations to novel diets. Journal of Animal Ecology:n/a-n/a.

Koskella, B., L. J. Hall, and C. J. E. Metcalf. 2017. The microbiome beyond the horizon of ecological and evolutionary theory. Nature Ecology & Evolution **1**:1606-1615.

Kurilshikov, A., C. Wijmenga, J. Fu, and A. Zhernakova. 2017. Host Genetics and Gut Microbiome: Challenges and Perspectives. Trends in Immunology **38**:633-647.

Lau, J. T., F. J. Whelan, I. Herath, C. H. Lee, S. M. Collins, P. Bercik, and M. G. Surette. 2016. Capturing the diversity of the human gut microbiota through culture-enriched molecular profiling. Genome Medicine **8**:72.

Martinez, A. J., M. R. Doremus, L. J. Kraft, K. L. Kim, and K. M. Oliver. 2018. Multi-modal defences in aphids offer redundant protection and increased costs likely impeding a protective mutualism. Journal of Animal Ecology:n/a-n/a.

McLean, A. H. C., B. J. Parker, J. Hrček, J. C. Kavanagh, P. A. D. Wellham, and H. C. J. Godfray. 2018. Consequences of symbiont co-infections for insect host phenotypes. Journal of Animal Ecology:n/a-n/a.

Mihaljevic, J. R., B. J. Hoye, and P. T. J. Johnson. 2018. Parasite metacommunities: Evaluating the roles of host community composition and environmental gradients in structuring symbiont communities within amphibians. Journal of Animal Ecology:n/a-n/a.

Miller, C. V. L., and S. C. Cotter. 2018. Resistance and tolerance: The role of nutrients on pathogen dynamics and infection outcomes in an insect host. Journal of Animal Ecology:n/a-n/a.

Muletz Wolz, C. R., S. A. Yarwood, E. H. Campbell Grant, R. C. Fleischer, and K. R. Lips. 2018. Effects of host species and environment on the skin microbiome of Plethodontid salamanders. Journal of Animal Ecology:n/a-n/a.

Mushegian, A. A., J.-C. Walser, K. E. Sullam, and D. Ebert. 2018. The microbiota of diapause: How host–microbe associations are formed after dormancy in an aquatic crustacean. Journal of Animal Ecology:n/a-n/a.

Näpflin, K., and P. Schmid-Hempel. 2018. Host effects on microbiota community assembly. Journal of Animal Ecology:n/a-n/a.

Paull, S. H., S. Song, K. M. McClure, L. C. Sackett, A. M. Kilpatrick, and P. T. J. Johnson. 2012. From superspreaders to disease hotspots: linking transmission across hosts and space. Frontiers in Ecology and the Environment **10**:75-82.

Pedersen, A. B., and A. Fenton. 2007. Emphasizing the ecology in parasite community ecology. Trends in Ecology & Evolution **22**:133-139.

Pickard, J. M., M. Y. Zeng, R. Caruso, and G. Núñez. 2017. Gut microbiota: Role in pathogen colonization, immune responses, and inflammatory disease. Immunological Reviews **279**:70-89.

Raulo, A. 2018. Social behavior and gut microbiota in red-bellied lemurs (Eulemur rubriventer): In search of the role of immunity in the evolution of sociality. Journal of Animal Ecology.

Risely, A., D. Waite, B. Ujvari, B. Hoye, and M. Klaassen. 2018. Active migration is associated with specific and consistent changes to gut microbiota in Calidris shorebirds. Journal of Animal Ecology:n/a-n/a.

Russell, J. A., and N. A. Moran. 2006. Costs and benefits of symbiont infection in aphids: variation among symbionts and across temperatures. Proceedings of the Royal Society B: Biological Sciences **273**:603-610.

Scheffer, M., S. Carpenter, J. A. Foley, C. Folke, and B. Walker. 2001. Catastrophic shifts in ecosystems. Nature **413**:591.

Schwarz, R. S., N. A. Moran, and J. D. Evans. 2016. Early gut colonizers shape parasite susceptibility and microbiota composition in honey bee workers. Proceedings of the National Academy of Sciences **113**:9345-9350.

Sommer, F., and F. Bäckhed. 2013. The gut microbiota — masters of host development and physiology. Nature Reviews Microbiology **11**:227.

Sommer, F., M. Ståhlman, O. Ilkayeva, J. M. Arnemo, J. Kindberg, J. Josefsson, C. B. Newgard, O. Fröbert, and F. Bäckhed. 2016. The Gut Microbiota Modulates Energy Metabolism in the Hibernating Brown Bear Ursus arctos. Cell Reports **14**:1655-1661.

Spencer, H. G., and M. Zuk. 2016. For Host's Sake: The Pluses of Parasite Preservation. Trends in Ecology & Evolution **31**:341-343.

Tate, A. T. 2016. The Interaction of Immune Priming with Different Modes of Disease Transmission. Frontiers in Microbiology **7**.

Tompkins, D. M., and M. Begon. 1999. Parasites Can Regulate Wildlife Populations. Parasitology Today **15**:311-313.

Turnbaugh, P. J., R. E. Ley, M. Hamady, C. M. Fraser-Liggett, R. Knight, and J. I. Gordon. 2007. The Human Microbiome Project. Nature **449**:804.

Tyson, G. W., J. Chapman, P. Hugenholtz, E. E. Allen, R. J. Ram, P. M. Richardson, V. V. Solovyev, E. M. Rubin, D. S. Rokhsar, and J. F. Banfield. 2004. Community structure and metabolism through reconstruction of microbial genomes from the environment. Nature **428**:37.

Venter, J. C., K. Remington, J. F. Heidelberg, A. L. Halpern, D. Rusch, J. A. Eisen, D. Wu, I. Paulsen, K. E. Nelson, W. Nelson, D. E. Fouts, S. Levy, A. H. Knap, M. W. Lomas, K. Nealson, O. White, J. Peterson, J. Hoffman, R. Parsons, H. Baden-Tillson, C. Pfannkoch, Y.-H. Rogers, and H. O. Smith. 2004. Environmental Genome Shotgun Sequencing of the Sargasso Sea. Science **304**:66-74.

Widder, S., R. J. Allen, T. Pfeiffer, T. P. Curtis, C. Wiuf, W. T. Sloan, O. X. Cordero, S. P. Brown, B. Momeni, W. Shou, H. Kettle, H. J. Flint, A. F. Haas, B. Laroche, J. U. Kreft, P. B. Rainey, S. Freilich, S. Schuster, K. Milferstedt, J. R. van der Meer, T. Grobetakopf, J. Huisman, A. Free, C. Picioreanu, C. Quince, I. Klapper, S. Labarthe, B. F. Smets, H. Wang, and O. S. Soyer. 2016. Challenges in microbial ecology: building predictive understanding of community function and dynamics. ISME J **10**:2557-2568.

Zaneveld, J. R., R. McMinds, and R. Vega Thurber. 2017. Stress and stability: applying the Anna Karenina principle to animal microbiomes. Nature Microbiology **2**:17121.