Received: 30 January 2020 | Revised: 21 February 2020 | Accepted: 24 February 2020

DOI: 10.1111/mec.15397

MOLECULAR ECOLOGY WILEY

NEWS AND VIEWS

Perspective

Two's company, three's a crowd: Exploring how host–parasite–microbiota interactions may influence disease susceptibility and conservation of wildlife

Brian K. Trevelline | Jessica F. Stephenson | Kevin D. Kohl

Department of Biological Sciences, University of Pittsburgh, Pittsburgh, PA, USA

Correspondence
Brian K. Trevelline, Department of Biological Sciences, University of Pittsburgh, Pittsburgh, PA, USA.
Email: brian.trevelline@gmail.com

A large body of research has demonstrated that host-associated microbiota—the archaeal, bacterial, fungal and viral communities residing on and inside organisms—are critical to host health (Cho & Blaser, 2012). Although the vast majority of these studies focus on humans or model organisms in laboratory settings (Pascoe, Hauffe, Marchesi, & Perkins, 2017), they nevertheless provide important conceptual evidence that the disruption of host-associated microbial communities (termed "dysbiosis") among wild animals may reduce host fitness and survival under natural environmental conditions. Among the myriad of environmental factors capable of inducing dysbiosis among wild animals (Trevelline, Fontaine, Hartup, & Kohl, 2019), parasitic infections represent a potentially potent, yet poorly understood, factor influencing microbial community dynamics and animal health. The study by DeCandia *et al.* in this issue of *Molecular Ecology* is a rare example of a host–parasite–microbiota interaction that impacts the health, survival and conservation of a threatened wild animal in its natural habitat. Using culture-independent techniques, DeCandia *et al.* found that the presence of an ectoparasitic mite (*Otodectes cynotis*) in the ear canal of the Santa Catalina Island fox (*Urocyon littoralis catalinae*) was associated with significantly reduced ear canal microbial diversity, with the opportunistic pathogen *Staphylococcus pseudintermedius* dominating the community. These findings suggest that parasite-induced inflammation may contribute to the formation of ceruminous gland tumours in this subspecies of Channel Island fox. As a rare example of a host–parasite–microbiota interaction that may mediate a lethal disease in a population of threatened animals, their study provides an excellent example of how aspects of disease ecology can be integrated into studies of host-associated microbiota to advance conservation science and practice.

KEYWORDS

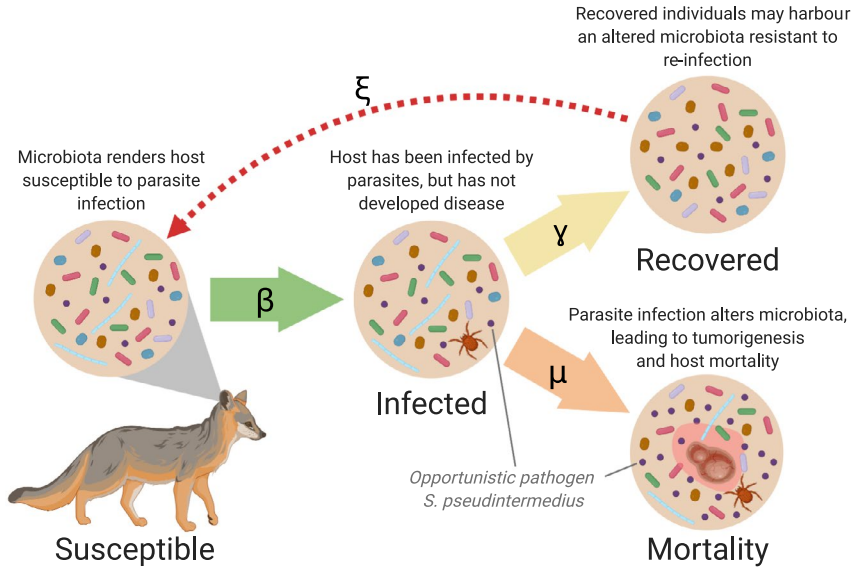
conservation biology, conservation genetics, disease biology, microbial biology, parasitology, species interactions

Historically, the connection between host-associated microbiota and disease has focused on pathogenic microbial infections rather than microbial communities as a whole (Dethlefsen, McFall-Ngai, & Relman, 2007). With the advent of culture-independent sequencing techniques has come the realization that host-associated microbiota are complex and dynamic communities that may mediate the establishment and proliferation of colonizing bacterial pathogens, as well as the inflammatory disease they cause through both direct (microbe–microbe) and indirect (immune-mediated) interactions (Kamada, Seo, Chen, & Núñez, 2013). More recently, it has been

recognized that host-associated microbiota may also provide resistance against the establishment of eukaryotic parasites (e.g., protists, helminths and arthropods) through these same direct and indirect mechanisms (e.g., Knutie, Wilkinson, Kohl, & Rohr, 2017; Koch & Schmid-Hempel, 2012; Naik et al., 2012), suggesting that a three-way interaction between hosts, parasites and microbiota may be an important yet understudied aspect of disease resistance and susceptibility among wild animals (DeCandia, Dobson, & vonHoldt, 2018; Dheilly et al., 2019; Lively, de Roode, Duffy, Graham, & Koskella, 2014). The study by DeCandia, Brenner, King, and vonHoldt (2020) in this issue of *Molecular Ecology* helps fill this knowledge gap by providing evidence that host-associated microbial diversity may be a key factor mediating the outcome of a disease, thereby providing a rare example of a host–parasite–microbiota interaction with direct conservation significance. What is unclear, however, is the mechanisms by which host-associated microbial diversity interacts with parasitic and bacterial infections. While this question is not easy to answer, the field of disease ecology provides a useful conceptual framework for investigating these mechanisms within the broader context of wildlife health and conservation.

First, let us consider the potential roles of genetic diversity in this host–parasite–microbiota interaction. Disease ecologists have long recognized the importance of host and parasite genetic diversity in mediating disease susceptibility (e.g., Ganz & Ebert, 2010). We also know that host genotype can shape the composition of host-associated microbiota, with resultant implications for disease susceptibility (Spor, Koren, & Ley, 2011), but how microbial genetic diversity itself influences parasite infections and disease remains largely untested. A major hurdle in determining the role of microbial genetic diversity in the host–parasite–microbiota interaction is disentangling the effects of host genotype from those of the microbiota and the parasite. Importantly, the population of fox hosts in DeCandia et al. (2020) exhibit extremely low genetic diversity (~4% genome-wide heterozygosity; Robinson et al., 2016), suggesting that factors controlling parasite infection and disease are not mediated by host genetics in this system. Moreover, the authors point out that foxes on neighbouring islands are parasitized by ear mites, but do not develop tumours despite exhibiting even lower genetic diversity (Vickers et al., 2015). Overall, these findings suggest that some aspect of microbial genetic diversity could play a role in disease susceptibility in this system. Given that the host-associated microbiome is considered an important component of the host's overall genetic diversity (i.e., the holobiont–hologenome concept; Gordon, Knowlton, Relman, Rohwer, & Youle, 2013) it is possible that microbial genetic diversity on these islands could compensate for the loss of host genetic diversity, perhaps in some cases providing the flexibility necessary for rapid ecological adaptation (Alberdi, Aizpurua, Bohmann, Zepeda-Mendoza, & Gilbert, 2016).

The importance of microbial genetic diversity in disease susceptibility may be related to functional diversity of host-associated microbiota. It is generally understood that functionally diverse ecosystems are resistant to ecological disturbances (e.g., invasions). If



Definitions	Major Questions
β **Infection Rate**	Do microbiota influence host suceptibility to parasite infection? If so, what taxa and/or functions define a susceptible microbial community? Can animals transmit susceptible communities through behavioural interactions?
γ **Recovery Rate**	Do microbiota mediate host recovery? If so, through competition, metabolites, and/or immune function? How do non-lethal parasite infections alter microbial communities?
μ **Mortality Rate**	How long does it take for microbiota to become dysbiotic? What features define a dysbiotic microbiota? How do microbiota influence the rate of disease progression?
ξ **Re-susceptibility Rate**	How stable are the microbial communities of recovered individuals? What taxa and/or functions contribute most to microbial community stability? How long does it take for microbiota to return to a susceptible state?

FIGURE 1 Conceptualization of DeCandia et al. (2020) using SIRS compartmental models of disease. In SIRS (susceptible–infected–recovered–susceptible) models, individuals are assigned to one of three compartments, where each compartment represents a distinct disease phase. The rates at which individuals move from one compartment to another are expressed mathematically (β, γ, μ or ξ), providing a means for tracking changes in disease dynamics within a given population over time. When applied to host–parasite–microbiota interactions, these models may provide a useful framework for identifying key factors influencing disease ecology in wildlife populations. Note that several of the mechanisms and/or open questions identified above are hypothetical and not explicitly discussed by DeCandia et al. (2020)

we consider host-associated microbial communities as traditional ecological communities (Costello, Stagaman, Dethlefsen, Bohannan, & Relman, 2012), we might expect microbial functional diversity to influence host disease susceptibility. The study by DeCandia et al. (2020) clearly demonstrates that reduced microbial diversity and the dominance of *Staphylococcus pseudintermedius* were associated with parasitic infections in Santa Catalina Island foxes. These results echo the findings of the authors' previous work on *Sarcoptes scabiei* mite infections and skin disease among wild canids (DeCandia, Leverett, & vonHoldt, 2019), suggesting that host–parasite–microbiota interactions may be a major determinant of animal health across a variety of taxa and ecological systems. How might microbial functional diversity mediate parasitic infections and disease? Mite infections (and subsequent otitis externa) could result in the loss of bacterial taxa that suppress the growth of *S. pseudintermedius* through competition or the production of antimicrobial metabolites (e.g., Harris et al., 2009). Alternatively, mites may introduce their own symbionts that disrupt an otherwise stable host-associated microbial community. Investigating the potential mechanisms underlying the pattern DeCandia et al. (2020) observe is beyond the scope of the data the authors present in this issue, but the system is clearly ripe to make further key contributions to our understanding of host–parasite–microbiota interactions.

Overall, DeCandia et al. (2020) contribute substantial new insight into our understanding of host–parasite–microbiota interactions as they apply to conservation ecology. Future studies should continue to integrate aspects of disease ecology theory and practice to further elucidate the mechanisms through which the microbiota influences host–parasite interactions, and their consequences. For example, the application of compartmental disease models (e.g., McCallum et al., 2017) to host–parasite–microbiota interactions may provide a useful framework for identifying key factors influencing disease ecology in wildlife populations (Figure 1). These models could be used to monitor fox health and condition, mite infection load, and the host-associated microbiota through time and across islands. Given the paucity of host genetic diversity, this would be an unprecedented test of how diversity in host-associated microbiota contributes to heterogeneity in the interaction between host and parasite. How heterogeneity between hosts in their disease susceptibility may contribute to population-level disease dynamics has become a key focus for both theoretical and empirical disease ecology (VanderWaal & Ezenwa, 2016). The findings of DeCandia et al. (2020) suggest that host-associated microbiota probably contribute to heterogeneity in key parameters known to affect epidemics: the rate at which uninfected hosts become infected, host mortality as a result of infection, and host recovery rate. Given the current unprecedented rates of disease emergence and global travel and shipping, understanding the mechanisms by which microbes introduce this heterogeneity may represent a key advance in our ability to mitigate public health, agricultural and conservation disasters.

ORCID

Brian K. Trevelline https://orcid.org/0000-0002-4514-0467
Jessica F. Stephenson https://orcid.org/0000-0001-8939-5149
Kevin D. Kohl https://orcid.org/0000-0003-1126-2949

REFERENCES

Alberdi, A., Aizpurua, O., Bohmann, K., Zepeda-Mendoza, M. L., & Gilbert, M. T. P. (2016). Do vertebrate gut metagenomes confer rapid ecological adaptation? *Trends in Ecology & Evolution*, *31*(9), 689–699.

Cho, I., & Blaser, M. J. (2012). The human microbiome: At the interface of health and disease. *Nature Reviews Genetics*, *13*(4), 260.

Costello, E. K., Stagaman, K., Dethlefsen, L., Bohannan, B. J., & Relman, D. A. (2012). The application of ecological theory toward an understanding of the human microbiome. *Science*, *336*(6086), 1255–1262.

DeCandia, A. L., Brenner, L. J., King, J. L., & vonHoldt, B. M. (2020). Ear mite infection is associated with altered microbial communities in genetically depauperate Santa Catalina Island foxes (*Urocyon littoralis catalinae*). *Molecular Ecology*, https://doi.org/10.1111/mec.15325

DeCandia, A. L., Dobson, A. P., & vonHoldt, B. M. (2018). Toward an integrative molecular approach to wildlife disease. *Conservation Biology*, *32*(4), 798–807.

DeCandia, A. L., Leverett, K. N., & vonHoldt, B. M. (2019). Of microbes and mange: Consistent changes in the skin microbiome of three canid species infected with *Sarcoptes scabiei* mites. *Parasites and Vectors*, *12*(1), 488.

Dethlefsen, L., McFall-Ngai, M., & Relman, D. A. (2007). An ecological and evolutionary perspective on human–microbe mutualism and disease. *Nature*, *449*(7164), 811.

Dheilly, N. M., Martínez Martínez, J,, Rosario, K., Brindley, P. J., Fichorova, R. N., Kaye, J. Z., … Thompson, L. R. (2019). Parasite microbiome project: Grand challenges. *PLOS Pathogens*, *15*(10), e1008028

Ganz, H. H., & Ebert, D. (2010). Benefits of host genetic diversity for resistance to infection depend on parasite diversity. *Ecology*, *91*(5), 1263–1268.

Gordon, J., Knowlton, N., Relman, D. A., Rohwer, F., & Youle, M. (2013). Superorganisms and holobionts. *Microbe*, *8*(4), 152–153.

Harris, R. N., Brucker, R. M., Walke, J. B., Becker, M. H., Schwantes, C. R., Flaherty, D. C., … Minbiole, K. P. C. (2009). Skin microbes on frogs prevent morbidity and mortality caused by a lethal skin fungus. *The ISME Journal*, *3*(7), 818.

Kamada, N., Seo, S.-U., Chen, G. Y., & Núñez, G. (2013). Role of the gut microbiota in immunity and inflammatory disease. *Nature Reviews Immunology*, *13*(5), 321.

Knutie, S. A., Wilkinson, C. L., Kohl, K. D., & Rohr, J. R. (2017). Early-life disruption of amphibian microbiota decreases later-life resistance to parasites. *Nat Comm*, *8*, 86.

Koch, H., & Schmid-Hempel, P. (2012). Gut microbiota instead of host genotype drive the specificity in the interaction of a natural host–parasite system. *Ecology Letters*, *15*(10), 1095–1103.

Lively, C. M., de Roode, J. C., Duffy, M. A., Graham, A. L., & Koskella, B. (2014). Interesting open questions in disease ecology and evolution. *The American Naturalist*, *184*(S1), S1–S8.

McCallum, H., Fenton, A., Hudson, P. J., Lee, B., Levick, B., Norman, R., … Lello, J. (2017). Breaking beta: Deconstructing the parasite transmission function. *Philosophical Transactions of the Royal Society B: Biological Sciences*, *372*(1719), 20160084.

Naik, S., Bouladoux, N., Wilhelm, C., Molloy, M. J., Salcedo, R., Kastenmuller, W., … Conlan, S. (2012). Compartmentalized control of skin immunity by resident commensals. *Science*, *337*(6098), 1115–1119.

Pascoe, E. L., Hauffe, H. C., Marchesi, J. R., & Perkins, S. E. (2017). Network analysis of gut microbiota literature: An overview of the

research landscape in non-human animal studies. *The ISME Journal*, *11*(12), 2644–2651.

Robinson, J. A., Ortega-Del Vecchyo, D., Fan, Z., Kim, B. Y., vonHoldt, B. M., Marsden, C. D., … Wayne, R. K. (2016). Genomic flatlining in the endangered island fox. *Current Biology*, *26*(9), 1183–1189.

Spor, A., Koren, O., & Ley, R. (2011). Unravelling the effects of the environment and host genotype on the gut microbiome. *Nature Reviews Microbiology*, *9*(4), 279.

Trevelline, B. K., Fontaine, S. S., Hartup, B. K., & Kohl, K. D. (2019). Conservation biology needs a microbial renaissance: A call for the consideration of host-associated microbiota in wildlife management practices. *Proceedings of the Royal Society of London B: Biological Sciences*, *286*(1895), 20182448.

VanderWaal, K. L., & Ezenwa, V. O. (2016). Heterogeneity in pathogen transmission: Mechanisms and methodology. *Functional Ecology*, *30*(10), 1606–1622.

Vickers, T. W., Clifford, D. L., Garcelon, D. K., King, J. L., Duncan, C. L., Gaffney, P. M., & Boyce, W. M. (2015). Pathology and epidemiology of ceruminous gland tumors among endangered Santa Catalina Island foxes (*Urocyon littoralis catalinae*) in the Channel Islands, USA. *PLoS ONE*, *10*(11), e0143211.

How to cite this article: Trevelline BK, Stephenson JF, Kohl KD. Two's company, three's a crowd: Exploring how host–parasite–microbiota interactions may influence disease susceptibility and conservation of wildlife. *Mol Ecol*. 2020;00:1–4. https://doi.org/10.1111/mec.15397