Context-dependent symbioses and their potential roles in wildlife diseases

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1. INTRODUCTION

The ‘First Law of Ecology’ could be ‘It depends’ [1]; symbioses, long-term direct relationships between individuals of two or more species, are a case in point. In this review, we use ‘symbiosis’ in its general sense of organisms living in an intimate physical arrangement, interacting in a variety of manners, including mutualism, commensalism and parasitism (including parasites with a wide range of pathogenicities). When possible, we specify which of these categories we refer to, but we cannot always do so because many pairs of species can have multiple relationships that fit in more than one category. This is because the nature (i.e. mutualistic, commensal or parasitic) and outcomes (i.e. the fitness, survival or persistence of participant individuals or populations) of symbiotic relationships often depend strongly on environmental and ecological context [2]. The recognition that context-dependent symbioses are common and important has contributed to the development of evolutionary theory [3], deepened our understanding of many species’ ecologies [4,5], improved our understanding of agricultural biocontrol activity [6] and begun to contribute to human medicine [7–9].

Thus far, however, the role of context-dependent symbioses in wildlife diseases has been relatively neglected, despite preliminary but promising connections among wildlife host disease status, the composition of assemblages of microbial mutualists on hosts and the persistence of populations and species [10,11]. We first review the evidence for context-dependency in symbioses across disciplines and taxa. We then use chytridiomycosis—a pandemic (or panzootic; we prefer the former suffix and use it throughout this review) disease of amphibians—to illustrate the potential that improved understanding of variable symbioses in wildlife disease dynamics may hold for conservation through disease management. The effects of symbiont diversity on disease were recently reviewed elsewhere [12], but we extend this work to include the effects of context-dependent activity of symbionts.

2. CONTEXT-DEPENDENT SYMBIOSES ACROSS DISCIPLINES

(a) Evolution and variable symbioses

Extensive work has been carried out on the evolutionary causes and consequences of context-dependent symbioses. It has been suggested that the combination of a host and its mutualist community, the ‘hologenome’, should be considered the unit of natural selection because of the flexible functions and fitness benefits provided by mutualists [3,13]. This concept, termed the hologenome theory of evolution [14], has been tested in the field and the laboratory. Experiments have shown that the wide array of genotypes presented by microbial mutualists, and their ability to adapt rapidly to novel conditions,
can lead to higher fitness for both the host and its microbial assemblage. Several examples follow. Laboratory exposure of wasps (Trichogramma cordubensis) and their obligate mutualists (bacteria, Wolbachia sp.) to elevated temperatures selected for bacterial genotypes that conferred heat stress resistance to both the bacteria and wasps [15]. Heat-adapted Wolbachia sp. allow Trichogramma spp. to reproduce parthenogenetically, and selection for these bacteria may also occur in natural populations of Trichogramma spp. Wasp species and populations with Wolbachia mutualists occur in warmer areas of Europe than those without Wolbachia [15]. Similarly, in a factorial experiment crossing symbiont and environmental temperature treatments, different bacterial facultative mutualists conferred different levels of resistance to parasitoids on the aphid Acrithosiphon pismum when under heat stress [16]. Field evidence for temperature-related shifts in dominance among three mutualists of A. pismum is equivocal, probably because the costs and benefits of hosting a given symbiont in the wild are influenced by many more factors than just temperature [17]. In 2010, it was reported that the prevalence of mutualist bacteria of the genus Spiroplasma in Drosophila neo-testacea from eastern North America had recently increased, apparently because the bacteria protect D. neo-testacea against the sterilizing effects of a common parasitic nematode [5]. Finally, evidence from reef-building corals shows that host resistance to disease may be increased by changes in the composition of microbial mutualist assemblages [18], although the virulence of bacteria associated with corals can also increase with exposure to abiotic stresses [19].

(b) Context-dependency and symbiogenesis

When the costs and benefits of engaging in symbiosis depend upon environmental or ecological conditions, the stability and likelihood of formation of the symbiosis should vary. Mutualisms, for example, can be thought of as involving two or more organisms that typically invest as little as possible in providing benefits for each other, while maximizing the benefits they derive from the interaction. Ecological (e.g. life stage) or environmental (e.g. temperature) context can change the needs or abilities of the species involved [2], and certain thresholds may need to be met for the ‘goods’ exchanged in mutualisms to be made available. For instance, bacteria often must reach a critical density to initiate physiological functions, a phenomenon known as quorum sensing [20]; so potential mutualisms may not form unless bacteria reach this critical mass often enough in a given environment [21].

(c) Ecology and context-dependent symbioses

Both interspecific and organism–environment interactions affect the nature of symbioses. For example, the presence of species in addition to primary symbionts, which could be termed ‘interlopers,’ can drive context-dependency in symbioses. An example is the familiar leaf-cutter ants and their relatives (tribe Atini) from the Neotropics, long known for cultivating obligate fungal mutualists for consumption within their nests [22]. It was thought that non-mutualist microbes are excluded from colonies by worker ants; however, a parasitic fungus (Escovopsis sp.) has been isolated from nests of multiple species of attine ants, and is especially common among the higher leaf-cutters, Atta spp. and Acromyrmex spp. [23]. The fungus can cause rapid and complete destruction of the ants’ fungus garden, and consequently the collapse of the mutualism and the colony [23].

In fact, an entire suite of microorganisms other than the garden fungus is present on ants and in their nests, and contributes to the success or failure of the colony [24]. All 22 species of attine ants studied in one large-scale study were host to actinomycete bacteria, in the genus Pseudonocardia, that produce compounds which selectively inhibit Escovopsis but not garden fungi [25,26]. The anti-Escovopsis function of these Pseudonocardia can itself be inhibited by a black yeast [27]. The yeast decreased in vitro growth of Pseudonocardia, grew better in their presence and was associated with greater losses of garden fungus biomass on infection with Escovopsis. The yeast did not affect antibiotic production by Pseudonocardia, suggesting that its Escovopsis-promoting effects may be owing to competition with the bacteria [27].

Symbiont-assemblage-mediated outcomes were also evident in laboratory experiments with the bacterial symbiont Lactobacillus plantarum from pollcock (Pollachiun sp.) [28]. This bacterium exhibited activity against Vibrio spp. pathogenic to fishes only when it was grown in the presence of Bacillus thuringiensis culture filtrate. Bacillus thuringiensis is a commonly employed biocontrol bacterium in agriculture and forestry and presumably produced a metabolite that induced the expression of anti-Vibrio activity in L. plantarum. Although this precise pairing of symbionts may not occur under natural conditions, similar interactions may occur among microbes in the wild, and these experiments were targeted at development of probiotics for use in aquaculture.

The formation and function of symbiotic mutualisms can be manipulated by the host. In European hoopoes (Upupa epops) and green woodhoopoes (Phoeniculcus purpureus), females exude dark, pungent secretions from their urohygial gland, but only during the short period when they are incubating eggs [29]. These secretions contain antibiotics that inhibit bacterial pathogens. The antibiotics are produced by mutualist Enterococcus bacteria that occur in the secretions [30,31]. Eggs and/or nestlings are presumably protected from infection by these secretions [29,32]. It is not known how the birds regulate the change in secretion type, but non-nesting females and all males produce clear or white secretions, without bacteria, and inactive against pathogens [29].

The effects of temperature on symbioses have been widely investigated, probably at least in part because climate change is looming, and may alter the ecology and conservation status of many species [33]. Also, temperature is a ubiquitous and easily manipulated variable relevant to all organisms. In general, its effects on a given symbiosis depend on the intersection of the thermal responses of the participating species, which are determined in turn by their genetics, physiology and behaviour [34]. For example, the bark beetle Dendroctonus frontalis carries several fungi that can infect and kill pine trees (Pinus spp.), including a species (Ophiostoma minus) that is a parasite of the beetle, and one (Ceratocystis ranaculosis) that is a mutualist [35,36]. In combination, the beetle and its fungi are serious pests of natural forests and pine plantations. Changing the mean temperature of the wood inhabited by the beetle can alter the transmission rates of these fungi from adult beetles to larvae and the amount of pine tree tissue infected [36]. These context-dependent
changes in transmission rates may therefore alter the severity of effects of these pests. *Dendroctonus frontalis* mite assemblages that are also pests of trees also vary with beetle larval incubation temperature [36].

In plants, the virulence of many bacterial pathogens increases at cooler temperatures [37]. The ultimate cause of this pattern is uncertain, but cooler air may promote formation of liquid films on the surface of host leaves, facilitating bacterial invasion through stomata [37]. The proximate causes of environmentally or ecologically induced pathogenesis by bacteria, though, can be inferred from known mechanisms of bacterial responses to temperature. They include upregulation of heat- or cold-shock protein synthesis [37], reorganization of membrane lipid structure and protein conformation changes [38].

Although not as well studied, environmental variables other than temperature are also likely to influence the ecology of symbioses. For example, coral microbiota are sensitive to pH, dissolved oxygen levels and nutrient flux ([19] and see §3a). Additionally, mutualisms between higher plants and mycorrhizal fungi are usually more crucial to plant fitness when soil nutrient levels are lower [39,40].

Symbioses can also follow seasonal cycles. Koren & Rosenberg [41] identified large, community-level shifts in bacterial assemblages of the coral *Oculina patagonica* in winter and summer, although the most abundant bacteria were always *Vibrio* spp. This relationship held when culture-independent molecular methods were used to analyse the *O. patagonica* microbiota.

(d) Context-dependency of symbioses in agriculture and biological control

Because of the importance of agriculture to society, and the crucial role of mutualist root microbes in nutrient uptake by plants [42], symbioses have been extensively studied in agricultural systems. Biological control schemes in which the control organism is applied to crops or fields can be thought of as induced symbioses, and so are included here.

Formation of crucial crop–microbe mutualisms can depend on environmental conditions. For example, low temperatures can inhibit the formation of rhizobia–legume mutualisms [43]. Nitrogen-fixing *Rizobium* bacteria are ‘welcomed’ to host plant roots by morphological changes triggered by chemical factors released by the bacteria and recognized by the plant [44]. Low soil temperatures, though, can inhibit the synthesis of these compounds in the bacterium *Bradyrhizobium japonicum* [43].

Plant hosts may regulate fungal symbiont gene expression, defying simple classification of an organism as a mutualist, pathogen or commensal. In trials with a variety of common fruits and vegetables, Redman et al. [45] found that fungi of the genus *Colletotrichum* can have effects ranging from mutualistic to pathogenic, depending on which host species they colonize. The authors suggest that labelling a symbiosis more specifically (e.g. as mutualism or parasitism) may be biased heavily by the choice of metrics used; symbionts may benefit hosts in one way (e.g. improved drought tolerance) while imposing costs in other ways (e.g. increased disease susceptibility). This is a key point that probably applies to many symbioses, and should always be considered.

Production of antimicrobial compounds by biocontrol agents can also be strongly affected by environmental and ecological context. The fungus *Letendreaa helminthi-cola*, a mutualist inhabitant of sponges, produces maximum quantities of compounds active against marine fouling organisms only within certain pH, salinity and temperature windows [46]. These maxima are reached outside the windows of salinity and pH that lead to maximum growth of the fungus. Effective use of the fungus in biological control of marine fouling organisms thus requires careful balancing of environmental conditions.

Host plant species, temperature, pH and biocontrol organism strain and culture density can all influence production of antibiotics by agricultural biocontrol bacteria (reviewed by Raaijmakers et al. [6]). *Pseudomonas* spp. bacteria are commonly used in biocontrol, and their effectiveness is subject to environmental context. They form natural mutualisms with many animals and plants, in which the hosts gain bacterial protection from pathogens [10,47]. For example, *Pseudomonas fluorescens* produces antibiotics that can benefit its plant hosts, but expression of the genes for antibiotic production is downregulated at 35°C compared with 30°C [48]. *Pseudomonas* sp. strain F113, isolated from the roots of sugar beets, produces 2,4-diacyethylphloroglucinol, a compound active against soil-born plant pathogens [49]. Rates of production of this metabolite depend on temperature, carbon source and culture surface area-to-volume ratio [49]. However, production rates appear to be constant at all tested values of pH, iron concentration and oxygen concentration [49].

The biological control of animal pests can also be affected by environmental factors. For example, two species of fungi used to control orthopteran pests ranged from highly effective to entirely ineffective depending on environmental temperature [50]. Finally, the responses of biocontrol targets are also likely to vary with the environment, given the variety of defences exhibited by agricultural pathogens [51].

(e) Human medicine and disease

Biomedical scientists and physicians have begun to examine the role of variation in human microbial symbiont assemblages in affecting disease development and progression. Eberl [52] proposed that the immune system does not merely recognize and respond to nonself material, as has been traditionally taught, but maintains an environment favourable to the normal mutualistic and commensal human microbiota, accounting for different activity of given symbionts at different times and in different tissues. If this concept is eventually accepted, then it will be a major shift in the frame of reference in which the operation of the immune system is considered. It is an affirmation of the integrated function of humans and their symbionts (both defensive and nutritional) and of the substantial role of symbiotic homeostasis in preventing disease.

Shifts of specific symbionts from commensal or mutualistic to pathogenic are perhaps the most studied variations in human disease symbioses. *Staphylococcus epidermidis* is a very common member of the human skin microbiota [53], and is thought to usually act as a
mutualist, preventing pathogen colonization both directly by antibiotic production [54] and indirectly by ‘priming’ the immune system to deal with other microbes [53]. It is now recognized as a common and critically important cause of nosocomial infections [55]; the mutualism can become virulent pathogenesis when *S. epidermidis* gains access to internal tissues [53,56]. Similarly, the bacterium *Parachlamydia acanthamoebae* is normally an endosymbiont of the amoeba *Acanthamoeba polyphaga*, which inhabits the human nasal cavity. When it is confined within *A. polyphaga*, it is commensal from the point of view of the human host. However, at warmer temperatures, e.g. when the amoebae are inhaled into the lungs, the bacterium may lyse the *A. polyphaga*, and when large numbers of bacteria are freed, they can cause pneumonia, bronchitis and other respiratory diseases [57,58]. The context-dependent changes that occur in the interactions between humans and *P. acanthamoebae* and *S. epidermidis* when the microbes move between tissues are analogous to changes in other species’ relations when they move between habitats or hosts.

### 3. EMERGING DISEASES OF WILDLIFE

Acknowledgement of the role of context-dependent symbioses has been slower in the literature on wildlife disease and conservation than in the fields discussed earlier. Given the frequent role of mutualists in defence against pathogens [59], and the potential for symbionts to respond rapidly to the environmental changes that are often associated with disease outbreaks and/or population declines [3], we suggest that context-dependent symbioses may be crucial in determining the survival and persistence of many wildlife species. Improved understanding of context-dependent symbioses that affect diseases of conservation importance should be of great use in disease management.

**A single and notable exception to the lack of investigation of the role of symbionts in wildlife diseases is research on the coral diseases that are thought to have driven recent coral reef declines [60]. The long-known obligate mutualism between corals and algae may have predisposed researchers to examine the impact of symbionts when disease concerns emerged for reefs.**

Coral bleaching is the potentially deadly loss of corals’ mutualistic algae and has caused severe degradation of reefs in the Caribbean, Australia and elsewhere [61]. It is known that at least some corals are protected from pathogen attack by antibiotic metabolites produced by mutualistic bacteria [11]. Pathogenesis leading to bleaching may be facilitated by raised water temperature, which can reduce or eliminate the activity of these mutualists [62,63]. Antibiotic activity of bacteria from corals in the genus *Acropora* was reduced at higher temperatures in *vitro*, suggesting that the protection corals receive from pathogens in nature is reduced under similarly warm conditions [11]. Shifts in coral microbiota are also associated with effects other than bleaching. The relative abundances of eukaryotic and bacterial symbionts of the coral *Porites compressa* changed, and their expression of genes associated with disease increased, on exposure to thermal, oxygen, pH and nutrient stressors [19]. In fact, simply moving corals from the wild to aquaria caused significant shifts in their symbiont assemblages, highlighting the mutability of coral microbiota [19].

Changes to symbiotic microbial assemblages are also associated with disease development in other marine invertebrates. In the laboratory, bacterial assemblages of the sponge *Rhopaloeides odorabile* remained stable between 27 and 31°C, but changed dramatically when water temperature was raised to 33°C [64]. The altered high-temperature assemblage was similar to those of bleached corals, whereas the lower temperature assemblage was similar to those characteristic of healthy *R. odorabile* in nature [64].

It has been proposed that although environmentally induced shifts in the microbiota may lead to disease, the ability of the microbiota to respond rapidly to changed environmental conditions may also have positive effects [3]. As a precursor to the more general holism of evolution theory (see §2a.), Reshef et al. [18] suggested that the diverse assemblages of microbial mutualists inhabiting corals enable rapid responses to disease or environmental changes. According to this coral probiotic hypothesis, the ability of some corals to develop disease resistance, despite not having an antibody-mediated immune response, is conferred by shifting mutualist communities that match prevailing conditions and provide temporally variable immunity-like services [18].

The potential to manipulate the microbial communities of corals for disease management in ways similar to the biocontrol schemes used in agriculture has been tested. A range of options, including inoculation of hatchery-reared corals with beneficial bacteria or pathogen-targeting bacteriophages, followed by transplantation to reef sites, were reviewed by Teplitski & Ritchie [65]. In one case, phages cultured directly from natural reef material and applied to coral prevented infection by the bacterial bleaching agent *Vibrio coralliilyticus* for at least two months [66], establishing the potential for a medium- to long-term protective effect. Similar deliberate alteration of symbionts and their activities, either by directly adding beneficial mutualists or indirectly by altering context, could be helpful in management of other wildlife diseases.

**Context-dependent symbioses and other wildlife diseases**

Although more is known about how variation in symbiont activity affects disease in corals than for any other group of wildlife, a better understanding of context-dependency in coral–microbe relationships is required [65]. The same, if not greater, need and potential exists for research on context-dependent symbioses and their relationships to diseases of other wildlife. For example, bats in the northeastern United States have recently suffered catastrophic declines caused by a condition termed white-nose syndrome (WNS) [67]. The fungus *Geomyces destructans* is associated with the deaths of greater than 500,000 bats in the affected area, but is present, apparently as a commensal, in some European bats [68]. Modelling of bat die-offs and physiology, together with *G. destructans*’ relatively cool thermal optimum, suggest that providing artificially warmed roosting sites for hibernating bats could ameliorate the effects of WNS by
reducing *G. destructans*’ virulence or prevalence [67,69]. Preliminary studies of bats’ bacterial symbionts have also begun, seeking anti-*Geomyces* bacteria and looking for changes to the microbiota of diseased animals [70].

There is substantial evidence that context-dependent symbioses are important in evolution, ecology, agriculture and human disease. They are also clearly important in coral disease. Evidence is beginning to accumulate that they are important in another wildlife disease crisis, chytridiomycosis, a pandemic infectious disease of amphibians caused by the fungal pathogen *Batrachochytrium dendrobatidis* (*Bd*) [71]. It is clear that there is substantial context-dependency in the relationship between amphibians and the pathogen [72–74]; however, we will focus on amphibian–bacterial mutualisms that are likely to be useful in management. Our recommendations for research on symbiosis and chytridiomycosis are intended to promote work that contributes to management of disease outbreaks and to act as a catalyst for future studies of context-dependent symbioses in other wildlife diseases with conservation or public health importance.

(c) Amphibian declines, disease management and context-dependent symbioses

*Bd* has been found on six continents, infecting 350-plus amphibian species [75], and is responsible for declines, extirpations and extinctions in over 200 species [76]. The effects of chytridiomycosis differ widely among species and populations, and are often clearly associated with environmental temperature [10,77,78]. Recent work [79] has demonstrated that the growth of *Bd in vitro* can be strongly moderated by antimicrobial metabolites secreted by a wide range of bacteria that are resident on amphibian skin. Bacteria can also affect the course and outcome of chytridiomycosis caused by experimental inoculations of amphibians with *Bd* [80,81], and the prevalence of potentially mutualistic bacteria may affect the ability of populations of some amphibians to persist when *Bd* first appears [10,82].

The prevalence and intensity of *Bd* infection tend to be greater, and the severity of *Bd*-caused amphibian declines has been worst, at high elevations and in cooler seasons, particularly in the tropics where the majority of extirpations have occurred [77,78,83]. To date, the fungus’s relatively cool *in vitro* optimal temperature window, centred on 17–25°C, has been regarded as the cause for this cool-weather pattern of declines [84,85]. However, chytridiomycosis has also had severe impacts in habitats that are cooler than the fungus’s optimal thermal window, possibly owing to reduced immune defences [86] or increased fecundity of *Bd* at cool temperatures [87]. The pervasiveness of context-dependence in mutualisms and other symbioses leads us to suggest another possible explanation; bacteria that produce metabolites active against *Bd* [10,79,81] may have reduced activity in cool environments, which may allow the virulence of *Bd* to persist below its *in vitro* thermal optimum.

The time- and resource-intensive nature and variable success rates of methods for controlling the impacts of chytridiomycosis suggested to date [88–93] mean that there is currently no broadly effective curative or preventative treatment available for wild amphibian populations [80,94]. Substantial excitement has been generated by the potential for probiotic augmentation of the natural cutaneous microbiota of amphibians; i.e. increasing the abundance of antifungal bacteria to enhance their protective anti-*Bd* effects, which could improve the success of epidemic prevention and amphibian reintroductions [10,79–81]. This process has been called ‘bioaugmentation’ [81].

No published work to date has assessed how environmental or ecological context might alter the anti-*Bd* activity or protective effects of bacteria that inhabit amphibian skin. Temperature, pH, the presence or absence of *Bd* and other microbes, and amphibian antimicrobial peptide secretions [95] all may affect the defences amphibians naturally gain from their resident bacteria, as well as the degree of success of bioaugmentation.

It appears likely that bioaugmentation has great potential for mitigation of amphibian declines owing to chytridiomycosis, but selection of appropriate candidate bacteria for bioaugmentation from among the range of bacteria present on amphibians should be informed by evaluations of the effectiveness of candidate bacteria under environmental conditions similar to those encountered in nature. In general, bacteria alter the expression of genes that produce antifungal compounds depending on their interactions with other microbes and on the environment [38,47]. Some bacteria that are good candidates for bioaugmentation could be overlooked, and poor candidates could be misidentified as effective against *Bd*, if context-dependency is not assessed when examining potential anti-*Bd* mutualists. It is likely that some bacteria’s activity against *Bd* may be greater in nature than in the standard laboratory conditions in which most screening work has been carried out. Context-dependent changes in anti-*Bd* activity could also reduce or completely negate the protective activity of bacteria screened *in vitro* when they are augmented *in situ*.

Unmanaged amphibian populations could also be affected by context-dependency in the activity of anti-*Bd* bacteria. We suggested earlier that context-dependent changes in the activity of mutualistic bacteria against *Bd* could explain the relatively high virulence sometimes exhibited by chytridiomycosis at temperatures well below those optimal for *Bd* growth. Additionally, frogs have reappeared at some upland sites from which they were initially extirpated [96]. It is not presently known whether this reflects growth from relictual *in situ* populations or recolonization. In either case, changes in what might be termed the amphibian hologenome could be responsible; individuals with the most robustly antifungal bacteria might be the most successful recolonizers from persisting lowland populations, and selection *in situ* could raise the prevalence of antifungal bacteria if reappearances are caused by the growth of relictual populations.

The lack of information on context-dependence of the activity of anti-*Bd* bacteria is largely owing to the young state of amphibian–microbe research, but is also symptomatic of how microbes have been studied in the past. Others have noted that traditional microbiological and microbial ecology studies have involved *in vitro* study of bacteria and fungi far-removed from their native environments, often eliminating all relevant context [97,98]. The same isolationist approach seems, in part, responsible for the general lack of focus on context-dependent symbioses in wildlife disease and conservation.
4. CONCLUSIONS

Links between host disease status, symbiont activity, and environmental and ecological context are important in evolution, ecology, agriculture and medicine, and may be of conservation consequence for many wildlife diseases. We have focused on three of the most high-profile wildlife diseases and syndromes (chytridiomycosis, WNS and coral bleaching). Context-dependent symbioses in these and other wildlife diseases are likely to have implications for their management, for public health and for more basic research agendas. Increasing understanding of the role of context-dependent symbioses in wildlife disease may proceed most efficiently when researchers engage in multidisciplinary collaboration. Researchers who specialize in wildlife disease and conservation ecology may consider working with specialists in microbial ecology and the study of symbioses. Those in the agricultural, medical, evolutionary and ecological specialties that have already dealt extensively with context-dependent symbioses may be of particular assistance.

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