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Integrating microbiome science and evolutionary medicine into animal health and conservation

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ABSTRACT

Microbiome science has provided groundbreaking insights into human and animal health. Similarly, evolutionary medicine – the incorporation of eco-evolutionary concepts into primarily human medical theory and practice – is increasingly recognised for its novel perspectives on modern diseases. Studies of host–microbe relationships have been expanded beyond humans to include a wide range of animal taxa, adding new facets to our understanding of animal ecology, evolution, behaviour, and health. In this review, we propose that a broader application of evolutionary medicine, combined with microbiome science, can provide valuable and innovative perspectives on animal care and conservation. First, we draw on classic ecological principles, such as alternative stable states, to propose an eco-evolutionary framework for understanding variation in animal microbiomes and their role in animal health and wellbeing. With a focus on mammalian gut microbiomes, we apply this framework to populations of animals under human care, with particular relevance to the many animal species that suffer diseases linked to gut microbial dysfunction (e.g. gut distress and infection, autoimmune disorders, obesity). We discuss diet and microbial landscapes (i.e. the microbes in the animal's external environment), as two factors that are (*i*) proposed to represent evolutionary mismatches for captive animals, (*ii*) linked to gut microbiome structure and function, and (*iii*) potentially best understood from an evolutionary medicine perspective. Keeping within our evolutionary framework, we highlight the potential benefits – and pitfalls – of modern microbial therapies, such as pre- and probiotics, faecal microbiota transplants, and microbial rewilding. We discuss the limited, yet growing, empirical evidence for the use of microbial therapies to modulate animal gut microbiomes beneficially. Interspersed throughout, we propose 12 actionable steps, grounded in evolutionary medicine, that can be applied to practical animal care and management. We encourage that these actionable steps be paired with integration of eco-evolutionary perspectives into our definitions of appropriate animal care standards. The evolutionary perspectives proposed herein may be best appreciated when applied to the broad diversity of species under human care, rather than when solely focused on humans. We urge animal care professionals, veterinarians, nutritionists, scientists, and others to collaborate on these efforts, allowing for simultaneous care of animal patients and the generation of valuable empirical data.

Key words: evolutionary medicine, animal microbiomes, conservation, probiotics, faecal microbiota transplant, microbial rewilding, animal management.

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I. INTRODUCTION

Investigating the microbes inhabiting different areas of animal bodies has provided novel insights into the drivers of animal ecology, evolution, behaviour, and health. These developments have spawned the relatively new and growing field of microbiome science. The term 'microbiome' is most widely used in reference to a community of microorganisms within a defined habitat (Lederberg & McCray, 2001), with expansions of this definition integrating the microbial genomic and metabolic products as well as relevant environments (e.g. microbial ecological niches) (Berg *et al*., 2020). We use the definition proposed by Lederberg & McCray (2001) as it best represents the literature we review and we discuss microbiomes within the context of specific animal ecologies and environmental niches.

Host-associated microbiomes are ubiquitous across the eukaryotic tree of life. In animal hosts, they interact with virtually every aspect of host physiology. Although there is increasing expansion of microbiome research into a wide array of animal systems (Williams *et al*., 2018; Trevelline *et al*., 2019; Jiménez *et al*., 2022), previous research largely has been focused on the relevance of microbiomes to human health and agricultural production (Smith *et al*., 2013; Brugman *et al*., 2018). There have been widespread advancements in understanding human microbiomes over the last two decades, made, in part, through a $1 billion (USD) investment by the US National Institutes of Health. Understanding and manipulating human microbiomes, particularly gut microbiomes, have become regular facets of modern healthcare (Sonnenburg & Fischbach, 2011; Harkins, Kong & Segre, 2020), particularly in the context of evolutionary medicine.

Evolutionary medicine strives to incorporate evolutionary and ecological perspectives into medical theory and practice (Trevathan, 2007; Power *et al*., 2020). A core concept in evolutionary medicine is that extant species, including humans, have adapted over evolutionary time to specific environmental challenges, such that the health, survival, and reproduction of modern individuals is influenced by these evolutionary processes (Gluckman *et al*., 2016). Thus, when an organism's current environment does not match that in which its ancestors evolved, this can result in inappropriate variation in physiological and metabolic responses (Straub, 2012; Trevathan & Rosenberg, 2020) leading, in some cases, to adverse health effects (Power & Schulkin, 2013; Alcock & Masters, 2021). For humans, this mismatch can result from environments that have dramatically shifted away from natural landscapes and towards urban or industrialised settings (Mills *et al*., 2017; Manus, 2018). Such eco-evolutionary disparity is suggested to be at the foundation of many modern illnesses, including allergies (Turke, 2017), obesity (Power & Schulkin, 2013), heart disease (Carrera-Bastos *et al*., 2011; Turaman, 2022), reproductive dysfunction (Charifson & Trumble, 2019), and even psychological disorders (Li, van Vugt & Colarelli, 2018).

The concept that diminished exposures to the environmental conditions in which ancestral organisms evolved can have modern-day health impacts has been termed the 'evolutionary mismatch' paradigm (Low & Gluckman, 2016). Various components of human and non-human animal environments can be mismatched and can be directly or indirectly linked to microbial communities (Fig. 1). For example, the hygiene hypothesis (Fig. 1) posits that, throughout human evolutionary history, host–microbe interactions and exposures have shaped human immune function (Frew, 2019). Minimising these interactions through modern hygiene, sanitation, and urban development is proposed to have resulted in microbial and immune system dysfunction, suggesting a

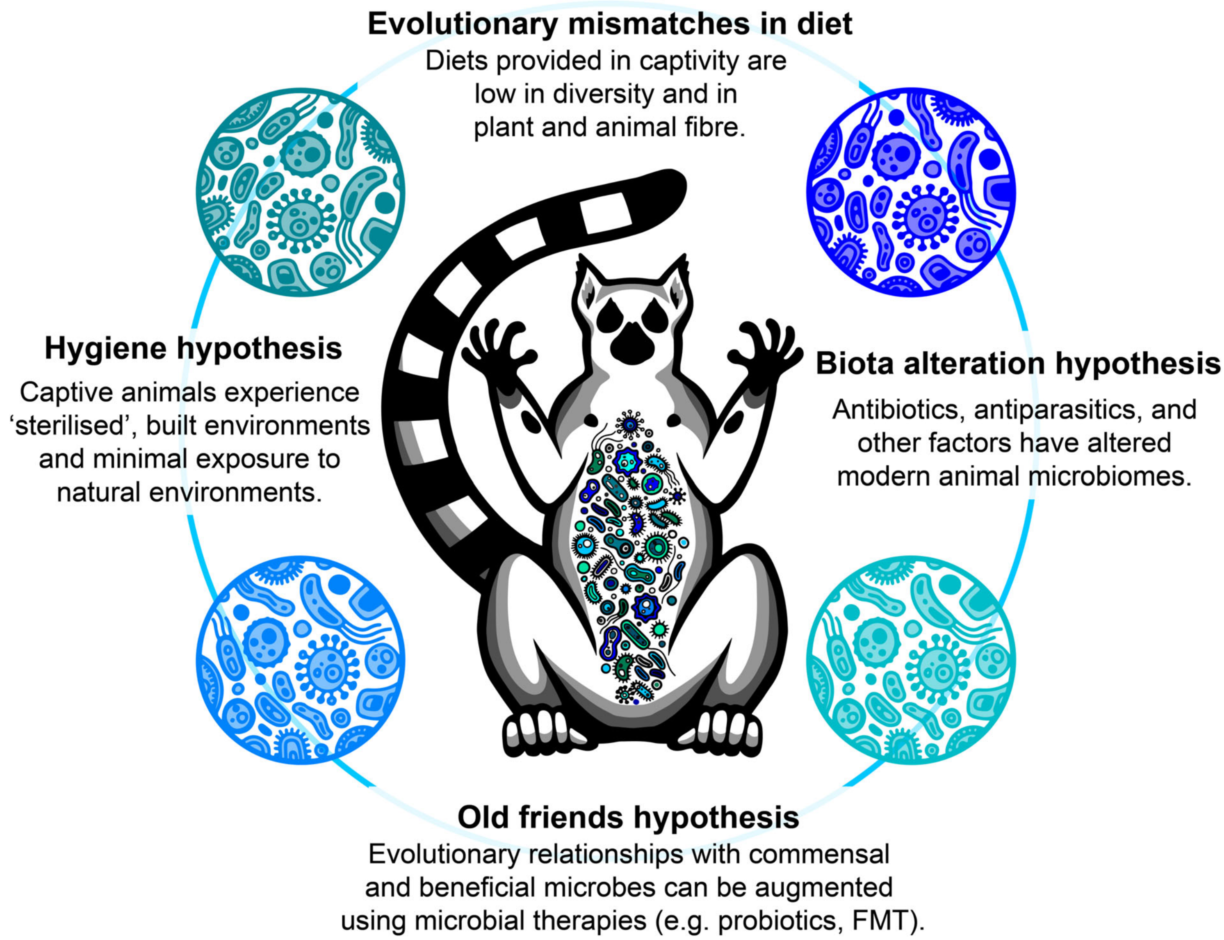

Fig. 1. Examples of evolutionary medicine hypotheses, as applied to animal microbiomes, and implications of modern animal microbiomes in the context of animal care and conservation. FMT, faecal microbiota transplant.

direct link between microbial communities and evolutionary mismatch. Mismatches can be indirectly linked to microbial communities through, for example, the effects of 'westernised' diets (Fig. 1). The high-fat and high-sugar diets of western human populations are thought to represent an evolutionary mismatch that is partly responsible for high rates of obesity and heart disease, as well as gut microbiome dysfunction (Power & Schulkin, 2013; González Olmo, Butler & Barrientos, 2021).

The evolutionary mismatch paradigm can be extended to non-human animals. Captive animals living in non-natural environments are often prone to diseases and disorders that are rare or absent in their counterparts living in natural habitats (Dallas & Warne, 2022). Although the mechanisms of these diseases are multi-faceted, it is now known that microbiomes can and often do play a role in animal health patterns (Peixoto, Harkins & Nelson, 2021). Moreover, animal microbial communities can be manipulated in ways that can improve host–microbe symbiosis and potentially alleviate the consequences of evolutionary mismatch to improve animal health (Niederwerder, 2018; Jin Song *et al*., 2019; Thacher *et al*., 2023).

With increasing threats to global wildlife populations, greater numbers of animal species will require conservation efforts to reduce biodiversity loss (Ceballos, Ehrlich & Dirzo, 2017). Currently, over 8,600 species of animals are managed in *ex-situ* populations at facilities accredited under the Association of Zoos and Aquariums. Of these species, ~1,000 are considered threatened or endangered, with the *ex-situ* populations serving as captive assurance populations or stewards for their species (Association of Zoos & Aquariums, 2022). These numbers are undoubtedly greater when considering animals held at unaccredited facilities or in the pet trade. Although one ultimate goal of maintaining *ex-situ* conservation populations can be animal reintroduction into natural habitats, the success of such endeavours has been limited. Various studies show that conservation-oriented translocations and reintroductions of endangered species have average success rates of only 11–53% (Jule, Leaver & Lea, 2008). In a review of carnivoran reintroductions, captive-born carnivorans were more likely to die of disease than were their counterparts born *in-situ* (Jule *et al*., 2008). Living under human care in *ex-situ* managed populations (e.g. in zoos or wildlife centres), as opposed to in natural habitats, has far-reaching impacts on animal behaviour, health and physiology, including changes to host microbiomes (McKenzie *et al.*, 2017). These factors can contribute to health issues that arise while animals are housed in *ex-situ* facilities and can create barriers for conservation efforts such as reintroductions.

In this review, we suggest that evolutionary medicine – the incorporation of evolutionary and ecological perspectives into assessments of animal health – combined with microbiome science, can be productively applied to animal care, management, and conservation. In particular, we highlight that the comparative study of the gut microbiomes across animals inhabiting natural habitats (*in-situ* populations) and in those housed under human care (*ex-situ* populations) can have broad applicability to animal management and conservation. We consider the extensive literature on gut microbiomes, but also provide some evidence for relevant patterns in non-gut communities. We focus on vertebrate animals, particularly mammals, as they best represent the existing literature, as well as a significant portion of animals under human care. Although beyond the scope of this review, we recognise the role of non-gut microbial communities (e.g. skin, oral, and reproductive microbiomes) in shaping animal health and reproduction, as well as microbial interactions in non-mammal hosts (Williams *et al.*, 2018; Comizzoli *et al.*, 2021).

We first propose a novel framework for combining evolutionary medicine and microbiome science, with the goal of improving animal care, management, and conservation. Within the context of this framework, we (*i*) briefly summarise recent findings regarding differences between the gut microbiomes of *in-situ* and *ex-situ* animals, (*ii*) discuss potential mechanisms underlying these differences, with a focus on diet and microbial landscapes (i.e. the combined microbial communities of animals and their environments), and (*iii*) highlight the potential benefits – and pitfalls – of modern microbial therapies, such as pre- and probiotics, faecal microbiota transplants, and microbial rewilding *via* environmental exposure.

We suggest 12 actionable steps, numbered sequentially and summarised in Table 1, that can be taken to actively incorporate evolutionary perspectives and hypotheses into animal care and conservation (Fig. 1). These 12 steps are congruent with the idea that microbiomes should be considered as integral components of animal health, such that they should be examined in tandem with physiological factors when considering how an animal's health and wellbeing are influenced by a given situation. Just as an animal's physiological health is a product of its evolutionary and proximate history, so too is its microbiome. Diseases known to affect specific species in captivity may have a previously unknown microbial component, the study of which could contribute to successful treatment. For example, in captive black rhinoceroses (*Diceros bicornis*), iron overload disorder has been a longstanding problem for susceptible species (Olias *et al.*, 2012). In a comparison of the gut microbiomes of taxonomically disparate rhinoceros species that are either susceptible or not susceptible to this disorder, susceptible species had the most similar distal gut microbiome structures, suggesting that susceptibility is somehow linked to microbiome

Table 1. Suggested actionable steps for incorporating evolutionary medicine and microbiome science into animal care and conservation.

Diet and feeding ecology	1.	Expand diets beyond basic categorisations and incorporate diverse and variable foods that mimic native diets.
	2.	Re-evaluate animal care regulations to include ecological and evolutionary perspectives on animal behaviour and health.
	3.	Combine microbiome studies with management efforts to minimise dietary mismatches, informing both the practical and scientific components of animal care.
Microbial landscapes	4.	Promote future study of microbial transmission between hosts in both *in-situ* and *ex-situ* populations of animals.
	5.	Consider coprophagy as a potential adaptive behaviour, as opposed to being a signal solely of physiological or psychological distress.
	6.	Minimise the sterilisation of animal dietary items and environments.
Prebiotics	7.	Identify and emphasise the components of evolutionarily appropriate diets that promote relevant beneficial microbes.
Probiotics	8.	Consider combining commercial probiotics with prebiotics to promote the incorporation of beneficial microbes and reinforce beneficial native communities.
Faecal microbiota transplants (FMTs)	9.	Apply FMTs, not as a last resort, but as a microbially informed, prophylactic or therapeutic treatment that can be used in a wide variety of health-relevant scenarios.
	10.	Bank faeces from susceptible individuals or species during healthy states, allowing for pre-screening and readily accessible transplant material.
	11.	Integrate microbiome science and veterinary knowledge to determine best practices for the use of FMT in animal care.
Microbial rewilding *via* environmental exposure	12.	Provide early and long-term access to naturalistic environments and diverse, external microbial communities (*via* e.g. outdoor spaces, free-ranging) to enable microbial rewilding and improve host–microbe symbiosis.

composition (Roth *et al.*, 2019). Treatments for such conditions can be tailored to integrate both the physiological and microbial components of animal health. We use these types of perspectives and examples to highlight the importance of combining evolutionary frameworks and microbiome science to improve animal care and conservation.

II. EVOLUTIONARY FRAMEWORK FOR ANIMAL MICROBIOMES

Our framework for considering animal microbiomes and their role in host health and wellbeing incorporates concepts from evolutionary medicine as well as ecology (Fig. 2). Notably, the theory of alternative stable states (May, 1977), which predicts that ecosystems can exist under multiple sets of 'states', informs our conceptualization of how animal microbiomes may fluctuate over short and long timescales. We refer to 'alternative adaptive states' as representations of microbial communities that may differ from previous communities in structure or function, but that have reached an alternative stable state, and are adaptive for the host. We use this framework to suggest actionable steps, particularly for *ex-situ* animal populations.

The microbiomes of most animals exist in an evolved adaptive state that reflects conditions experienced by the host over proximate and evolutionary time (Fig. 2) (Koskella & Bergelson, 2020; Voolstra & Ziegler, 2020). The structure and function of these microbial communities should be in step with the requirements of the host and be influenced by the external environment. These communities often show a degree of plasticity and natural fluctuation, enabling the community to withstand and/or recover from minor

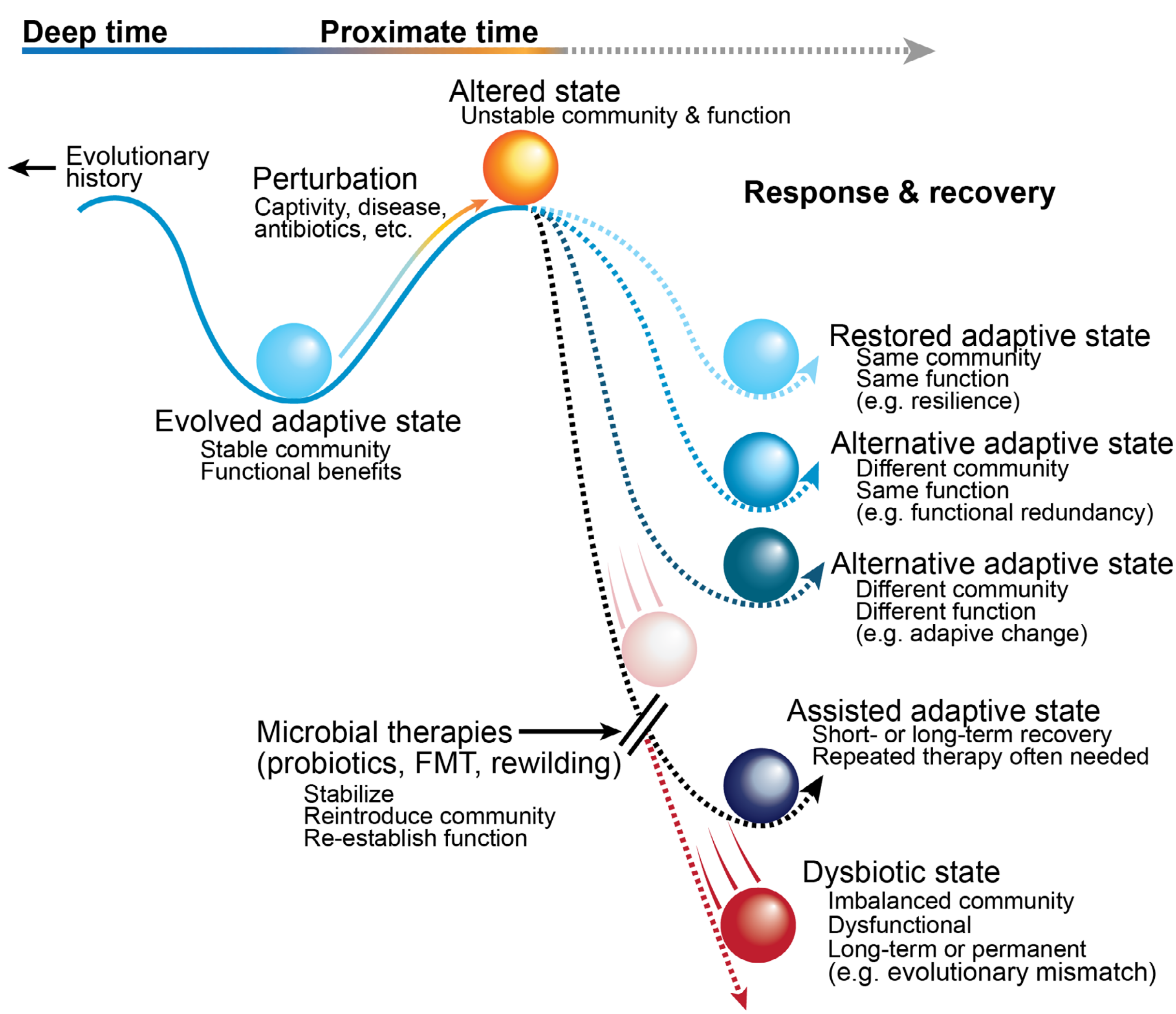

Fig. 2. Illustrating the evolutionary framework for understanding potential responses of animal-associated microbiomes (spheres) to perturbations, including captivity and events experienced in captivity (e.g. antibiotic treatment). Over both evolutionary and proximate timescales, the communities experience stable/adaptive states (valleys) as well as unstable states (peaks). FMT, faecal microbiota transplant.

disruptions. However, perturbations (e.g. disease, acute environmental disruption, or captivity) can occur such that the microbial community is shifted into an altered, unstable state (Fig. 2). This shift can be precipitated both by direct effects on the microbiome (e.g. changes in diet and incoming nutrients or microbial extermination *via* antibiotics) and by effects on the host that indirectly influence the microbiome (e.g. increased physiological challenges or immune dysfunction). Over time, as the host assimilates or recovers, the microbial community may be resilient and be restored, or it can be shifted into an alternative adaptive state. This alternative state can have a different community structure from the original, evolved state, with certain microbial taxa being differentially affected while others remain stable. Many microbial communities show functional redundancy, whereby different microbes can perform similar or identical functions. Thus, it is possible for the community structure to vary but the overall functional potential to remain the same. Alternatively, both the community structure and functional potential could change but still promote host–microbe symbiosis, reflecting an adaptive change in response to new microbial or host requirements.

Although often achieved without assistance, microbiome recovery can be promoted by considering microbial influences when an animal experiences a perturbation. In some cases, however, the microbial community cannot appropriately respond to the perturbation and remains unstable, becoming imbalanced and 'mismatched'. The latter outcome can reflect the perturbation severity, the host's genetic or physiological vulnerability, and/or the specific microbial dynamics. Severe perturbations may also differentially affect microbial members of the same community and/or have specific influences on different communities within the same host (e.g. at different body sites). The imbalance can cause discordance between microbes and hosts, often leading to negative health outcomes, as exemplified by evolutionary mismatches. In these cases, microbial therapies provide avenues to stabilise the community and shift it to an assisted adaptive state. These therapies can be single events, which may be most effective in assisting recovery following a discrete, disruptive influence (e.g. antibiotic treatment or acute infection). Microbial therapies can also be applied as reoccurring treatments to help prevent or mitigate microbial imbalance (dysbiosis) in cases where the cause of the imbalance is long-term, unavoidable, or unknown.

The capacity of the microbial community to recover to an alternative adaptive state *versus* fall into dysbiosis depends on the host's ecological and evolutionary history, as well as the host–microbe relationship: the same perturbation will not equally impact all individuals or species. For example, the microbiome of an animal that has evolved to subsist on high-fibre leaves will respond differently to decreased fibre intake than will the microbiome of an animal that has a more generalised diet. Similarly, species that have undergone population bottlenecks, and subsequently have low genetic diversity and lower immune tolerance, may be particularly vulnerable to long-term microbial imbalance. Although this framework has broad applicability, understanding the process in specific animals requires an evolutionary perspective that includes study of *in-situ* and *ex-situ* animal populations.

III. MICROBIOME VARIATION BETWEEN *IN-SITU* AND *EX-SITU* CONSPECIFICS

Captivity presents animals with a complex suite of variables and parameters that differ from those found in their *in-situ* habitats. The challenges presented to animals under human care can differ greatly from those under which the animal evolved and can directly influence physiology and metabolism, including *via* direct and indirect effects on microbiom.

Despite widespread notions that captivity has universally negative impacts on animal microbiomes, its influence is complex and varies across host taxa. Importantly, comparisons of microbial communities across *in-situ* and *ex-situ* conditions should consider multiple aspects of the microbiome, including diversity, overall community composition, and, when possible, community function. In multiple primate species, captivity has been shown to have a 'humanising' effect on gut microbiomes, such that they appear to converge on a composition that resembles the microbiomes of 'westernised' humans (Clayton *et al*., 2016). Nonetheless, recent evidence suggests that such homogenisation is far from universal. *In-situ* animals do not necessarily have more diverse gut microbial communities than do their *ex-situ* counterparts and captivity does not have a universally similar effect on the overall structure of animal gut microbiomes. Moreover, given the different environments and potentially different physiological requirements between *in-situ* and *ex-situ* animals, the microbiome of *in-situ* animals would likely not be appropriate for *ex-situ* conditions. For instance, in a study of multiple *in-situ* and *ex-situ* ring-tailed lemur (*Lemur catta*) populations, the most 'perturbed' animals – those kept as illegal pets – had gut microbial diversity and richness that rivalled that of lemurs living in pristine natural forests, yet the microbial community composition was distinct between *in-situ* and *ex-situ* populations (Bornbusch *et al*., 2022b). In a study of black rhinoceros gut microbiomes, community composition and microbial function differed significantly between *in-situ* and *ex-situ* populations whereas the diversity of gut microbes was similar across populations (Gibson *et al*., 2019). In comparative studies of *in-situ* and *ex-situ* individuals representing 41 mammalian species (gut microbiomes; McKenzie *et al*., 2017) and 18 amphibian species (skin microbiomes; Kueneman *et al*., 2022), the effect of captivity on microbial diversity and composition varied across host taxa and according to host traits such as feeding strategy, physiology, and habitat. Differences in microbial structure and function between *in-situ* and *ex-situ* animals could be adaptive. Combined, these results indicate that the influence of captivity on animal microbiomes varies across different aspects of the microbiome (e.g. microbial richness, composition, and function) as well as across different environmental settings, all while being dependent on the host's ecology and evolutionary history.

Of the numerous variables that differ within and between natural and captive environments, we highlight two particular factors – diet and microbial landscapes – that are demonstrably linked to microbiome structure and function and have health implications that could be best understood from an evolutionary medicine perspective. For each of these factors, we report on the evidence for an evolutionary mismatch and then discuss how microbiome science, combined with eco-evolutionary perspectives of animal health, could be used to understand better and, ultimately, to alleviate the negative effects of mismatch.

(1) Diet and feeding ecology

Dietary differences provide a well-supported mechanism underlying variation in gut microbial communities between *in-situ* and *ex-situ* animals (Ley *et al.*, 2008; Dallas & Warne, 2022). For most species occurring in *ex-situ* populations, providing exact matches to natural diets is generally unfeasible, owing to financial constraints and limited or no access to native dietary items. Our discussion of diets as evolutionary mismatches should be considered within the bounds of practicality. In particular, we will focus on how diets provided to animals under human care often differ in a wide range of nutritional and other parameters from the diets of their counterparts living in natural habitats, and how these differences may impact animal health and well-being. Lastly, we suggest three actionable steps (1–3 in Table 1) to incorporate evolutionary perspectives of diet into animal care and management.

Categorisations of animal feeding strategies – e.g. herbivory, carnivory, and omnivory – are a cornerstone of foraging ecology. They arise from placing animals in discrete bins based on their most commonly or abundantly consumed food items. Widely applied across virtually all animal groups, including insects (Sweet, 1979), fish (Hyatt, 1979), birds (Kissling, Sekercioglu & Jetz, 2012), and mammals (Laws, 1981), these longstanding labels provide the foundation for crafting the diets of animals under human care. For example, in captivity, frugivores have long received diets rich in cultivated fruits (Plowman, 2015; Schwitzer, Polowinsky & Solman, 2009), whereas carnivores are often provided with commercially processed meats (Pearson, Knight & Melfi, 2005).

It has now become apparent that these categorisations may be oversimplified. Animals *in-situ* can vary their diets markedly across seasons (Smith, 1974; Worman & Chapman, 2005), life-history phases (Knoff, Hohn & Macko, 2008; Pereira *et al.*, 2015), and biogeographical locations (Díaz-Ruiz *et al.*, 2013; Barnagaud *et al.*, 2019), providing dietary diversity that often crosses, or at least blurs, the classification boundaries. By contrast, diets provided to animals under human care usually have limited diversity and are relatively homogenised over time (Dallas & Warne, 2022). Moreover, the standard interpretation of dietary classifications and associated food items rarely reflect the nutritional value of native dietary items. For example, fruits can vary drastically in nutrient content across ripening (Gautier *et al.*, 2008; Houle, Conklin-Brittain & Wrangham, 2014) and between native and cultivated varieties (Schwitzer *et al.*, 2009). Fruits consumed by animals in their natural habitats are often high in complex plant fibres, containing significant concentrations of plant secondary compounds and low concentrations of simple sugars (Milton, 1999). By contrast, fruits that are cultivated for human consumption and provided to animals under human care are often high in sugar, low in fibre, and have had most of the secondary compounds selectively bred out of them (Schwitzer *et al.*, 2009). Similarly, *in-situ* carnivorans will consume their prey's hair, skin, bones, and offal, which are rich in animal fibres, nutrients, and minerals (Kohl, Coogan & Raubenheimer, 2015; Machovsky-Capuska *et al.*, 2016), whereas captive carnivorans are often fed processed muscle meats that lack these dietary constituents (Depauw *et al.*, 2013). Although classifications of dietary strategies will likely remain necessary for simplicity and continuity in general discussion, a suggested actionable step (1) is to reconsider the use of rigid, dietary categorisations when formulating diets and, instead, incorporate diverse and variable food items that mimic natural diets or satisfy key nutritional needs.

(*a*) *Diet as an evolutionary mismatch*

Scientists and animal nutritionists have proposed that there can be evolutionary mismatches between the diets provided in captivity and those that a species evolved to consume (Power, 2012; Schulte-Hostedde *et al.*, 2015). While animal care professionals strive to provide the most nutritionally appropriate diets within financial and sourcing constraints, these mismatches have contributed to the prevalence of various diseases and disorders (e.g. diabetes, obesity, gastroenteritis) in *ex-situ* animal populations (Goodchild & Schwitzer, 2008; Henson *et al.*, 2017; Cabana, Jasmi & Maguire, 2018). Paralleling evolutionary perspectives on human diets (Gluckman *et al.*, 2016), some have equated these mismatches to the effects of high-sugar, low-fibre, 'westernised' diets in humans (Power & Schulkin, 2013; Logan & Jacka, 2014), which can similarly increase these disease risks. Beyond compositional differences in the foods of *ex-situ* and *in-situ* animals, consistent food availability and calorie intake in captive animals does not reflect the fluctuations seen in nature. An *ex-situ* animal's environment, in this case promoting easy access to high-calorie foods, resembles the modern human's environment (Power, 2012).

In *ex-situ* animals, the lack of variation in food quality or availability can promote behavioural and physiological irregularities. One example of these negative consequences derives from the lack of natural hibernation in captive animals (McCain, Ramsay & Kirk, 2013; Geiser, 2020; Blanco *et al.*, 2021). Decreased physiological and metabolic activity is an adaptive condition for many animals living in seasonal environments, and often depends on the environmental cues of differential food availability and nutrient intake (Humphries, Thomas & Kramer, 2003; Pigeon, Stenhouse & Côté, 2016). In fat-tailed dwarf lemurs (*Cheirogaleus medius*), an obligate hibernating primate, seasonal torpor is common in captivity, but sustained hibernation is rare to non-existent (Blanco *et al.*, 2021). When researchers mimic hibernation-promoting conditions (e.g. by providing high-sugar fruits for fattening or food restriction, cold temperatures, or altered photoperiods), captive lemurs show patterns of fat deposition, torpor, and lipid metabolism that more closely resemble those of *in-situ* hibernating conspecifics (Blanco *et al.*, 2022). It may seem counterintuitive that food restriction could be beneficial; yet it is a key component of successful hibernation, without which naturally hibernating animals may experience physiological and metabolic dysfunction in captivity. Despite being evolutionarily appropriate, substantial food restrictions are difficult to enact under captive management due to animal care regulations. While the premise of these regulations – the ethical care and use of animals – is indispensable, we suggest an actionable step (2) of re-evaluating certain restrictions to better incorporate evolutionary perspectives and to accommodate natural adaptations.

(*b*) *Microbiomes and dietary mismatches*

Because host diet is a major driver of gut microbiome structure and function, dietary mismatches can have tangible consequences for an animal's microbiome and, ultimately, its health. For non-human animals, the effects of these mismatches on microbiomes and resulting health outcomes vary according to feeding ecologies. In particular, most animals that consume largely plant-based diets rely heavily on microbial fermentation of complex plant fibres to provide bioavailable energy, nutrients, vitamins, and minerals. In these animals, mismatched diets that are low in complex plant fibre can significantly alter the gut microbiome, which may substantially increase host morbidity and mortality. In five species of non-human primates, the gut microbiomes of folivorous species were more heavily impacted by captivity than were those of non-folivorous species (Frankel *et al.*, 2019). In red wolves (*Canis rufus*), captive individuals fed kibble diets harboured disparate microbiomes compared to those fed meat-based diets, and both groups differed significantly from *in-situ* individuals (Bragg *et al.*, 2020). Many dietary generalists suffer from obesity and diabetes in captivity (Bray & Edwards, 2001; Schwitzer & Kaumanns, 2001; Bauer *et al.*, 2011), which have been linked to dietary mismatches. By contrast, certain herbivorous ruminants are among the few animals to reportedly show little to no difference in microbiomes between *in-situ* and *ex-situ* individuals (McKenzie *et al.*, 2017). By studying the microbiomes of *ex-situ* and *in-situ* animals, while considering their respective diets, we can better understand the links and potential mismatches between diet and animal health (e.g. Keady *et al.*, 2023). For future research and management, we suggest an actionable step (3) to pair microbiome studies with management efforts to minimise dietary mismatches, thus combining and informing both the scientific and practical components of animal care.

Overall, it is undeniable that the diets fed to animals under human care are an important component of maintaining health and wellbeing. An evolutionary perspective that incorporates diverse animal feeding ecologies and adaptations is a crucial first step for formulating appropriate diets. Understanding the impacts of different diets on animal microbiomes provides a valuable window into understanding how evolutionary medicine can be applied to animal health.

(2) **Microbial landscapes**

Animals evolved and continue to exist in a 'bacterial world' where microbes are ubiquitous both in animal hosts and in their environment (McFall-Ngai *et al.*, 2013). The external microbial communities include those found in air, water, soil, other animals (conspecifics and heterospecifics), man-made substrates, and food items (Fig. 3) (Mony *et al.*, 2020). These myriad external communities form what we refer to as 'microbial landscapes' – unique combinations of microbial consortia that interact and vary over time and across environments. The potential for animal hosts to pick up and incorporate external microbes from their microbial landscape plays an important role in the assemblage of microbiomes across an animal's lifetime (Adair & Douglas, 2017; Selway *et al.*, 2020). In animals under human care, the microbial landscape can differ drastically from that experienced by conspecifics living in more natural habitats (Bornbusch *et al.*, 2022*a*; Dallas & Warne, 2022). In this section, we discuss how the acquisition of external microbes can shape animal microbiomes, from early-life vertical transmission (e.g. *via* parturition or nursing) to acquisition from environmental sources, such as soils or dietary items. We discuss how these processes differ between *in-situ* and *ex-situ* animals and we suggest three actionable steps (4–6 in Table 1) by which microbial landscapes can potentially be harnessed or incorporated to improve the health of captive animals.

(*a*) *Microbial transmission between hosts*

Broadly, microbial transmission can be described as vertical (i.e. generational transmission from parents to offspring) or horizontal/environmental (i.e. acquisition from non-parental sources). One of the most widely studied examples of vertical transmission is the transfer of microbes during mammalian birth (Ferretti *et al.*, 2018; Korpela *et al.*, 2018). The contribution of maternal microbes to infant microbiota colonisation – from pregnancy and parturition through lactation – is a vital component of infant development (Mueller *et al.*, 2015; Comizzoli *et al.*, 2021). Additionally, the horizontal transmission of microbes between social partners and community members can result in group 'signatures' that are hypothesised to play a role in social behaviour and communication (Archie & Tung, 2015; Grieneisen *et al.*, 2017; Leclaire *et al.*, 2017; Greene *et al.*, 2019). In certain organisms, host–host microbial

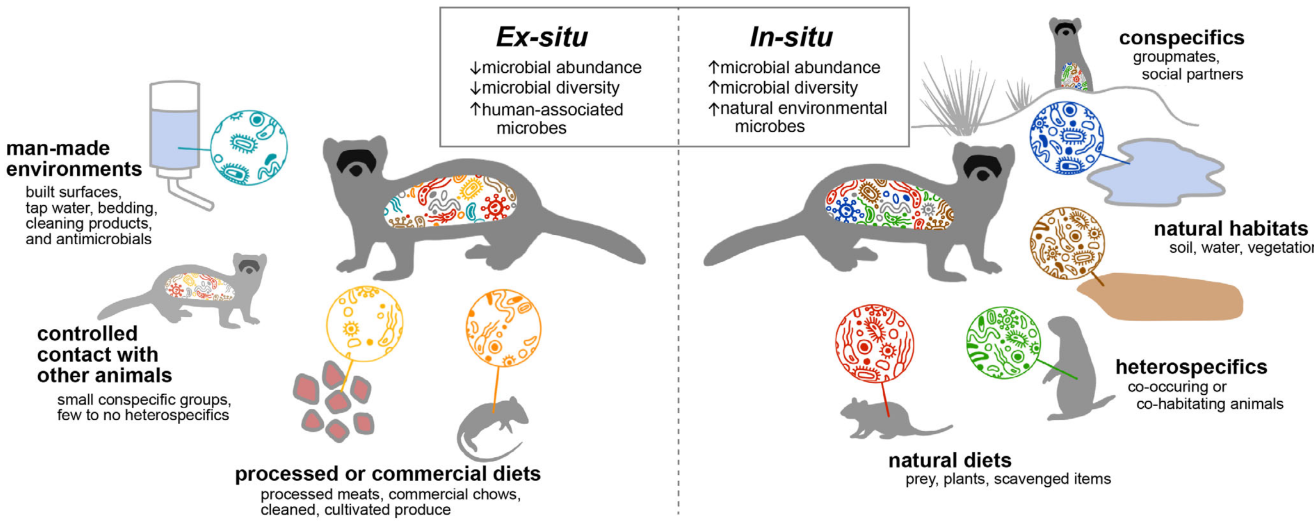

Fig. 3. Variation in microbial landscapes between *in-situ* and *ex-situ* conspecifics. We use a black-footed ferret (*Mustela nigripes*), an endangered carnivoran, as an example to portray varying exposures to environmental microbiomes between *in-situ* and *ex-situ* conditions.

transmissions have even been proposed as one of many adaptive factors in the evolution of group-living (Troyer, 1984; Montiel-Castro *et al.*, 2013). Troyer (1984) put forth the hypothesis that, in some herbivore species, the fermentative microbes required for herbivores to extract nutrients from their plant-based diets are horizontally acquired through close social contact with conspecifics. This social transmission, along with other evolutionary, ecological, and behavioural traits, is suggested to provide an adaptive advantage to multi-generational social groups that facilitate this microbial transmission.

Another form of host–host microbial transmission is coprophagy, the consumption of faeces. Non-autologous coprophagy, eating the faeces of another animal, is particularly prevalent during neonatal development, when young ingest their parents' faeces. In ptarmigans (*Lagopus muta*), coprophagy of maternal faeces by chicks within the first week of life was speculated to assist with early gut colonisation and nutrition, particularly because, immediately after hatching, chicks consume the same diets as their mothers (Kobayashi *et al.*, 2019). In mammalian neonates of many species, coprophagy is commonly seen leading up to weaning, again indicating the need to obtain microbes necessary for processing an adult diet (Osawa, Blanshard & Ocallaghan, 1993; Weir, 2014; Quercia *et al.*, 2019; Kambe *et al.*, 2020). In adulthood, coprophagy is most often associated with re-digestion and increased nutritional gains (Sakaguchi, 2003), but there also may be impacts on the microbiome. In a study of captive voles (*Lasiopodomys brandtii*), the prevention of coprophagy resulted in body mass loss, decreased memory capacity, and altered gut microbiome structure (Bo *et al.*, 2020). The researchers were able to reverse some of these effects *via* supplementation with microbial metabolites (short-chain fatty acids), indicating important links between coprophagy, microbial function, and host physiology.

The opportunity for microbial transmission between hosts, whether *via* social contact or coprophagy, differs between *ex-situ* and *in-situ* animal populations. The formation of social groups in captivity is based on animal welfare, but is also dictated by space limitations and behavioural considerations (Price & Stoinski, 2007). As a result, animals under human care are often housed in groups that differ, compositionally, from those seen in *in-situ* counterparts. In *ex-situ* animals, coprophagy is widely viewed as a detrimental behaviour that indicates a deficit or disease and is often actively discouraged. While these management strategies may decrease disease transmission *via* pathogenic microbes, they may simultaneously minimise sharing of beneficial microbes. The influence of reducing microbial transmission pathways in captivity has yet to be examined. We suggest two actionable steps: (4) promote future study of host–host microbial transmission in both *in-situ* and *ex-situ* populations of animals and (5) consider coprophagy as a potential adaptive behaviour, not just a signal of physiological or psychological distress. These steps will enable a more holistic perspective on how social dynamics and host–host transmission may shape animal microbiomes and health.

(*b*) *Exposure to and acquisition of environmental microbes*

Although microbial transmission between animals has long received scientific attention, the interactions between host-associated and environmental consortia, outside of epidemiological contexts, is a relatively new area of study. Although the exact mechanisms by which external microbes can be incorporated into host-associated communities remain unclear, the process is likely mediated by the host's immune function, physiology, and the dynamics between the external and native host microbes. The immune system has been proposed to act as an 'ecological filter,' dictating which incoming microbes are filtered out *versus* retained within a host community (Stagaman *et al.*, 2017). Stomach acids are known to determine, in part, which microbes survive to travel to and/or colonise the lower gut tract (Beasley *et al.*, 2015). The density, resource availability, and competitive dynamics in the native microbiome may determine the survival of external microbes, similar to the concept of resisting pathogens *via* competitive exclusion (Hardin, 1960; Segura Munoz *et al.*, 2022).

There is growing evidence that the assembly and maintenance of animal-associated microbiomes includes acquisition of select environmental microbes. Piglets that were exposed to topsoil microbiomes during lactation showed faster maturation of their gut microbiomes and greater capability of digesting adult diets compared to piglets that lacked such exposure (Vo *et al.*, 2017). Amphibian hosts filter environmental microbes such that dominant environmental microbes are excluded, yet specific low-abundance microbes that have anti-fungal function capacities are incorporated into skin microbiome communities (Walke *et al.*, 2014; Muletz *et al.*, 2012). Likewise, pikas (*Ochotona* spp.) seem to acquire low-abundance microbes from their environment, specifically those that are enriched in genes for carbohydrate degradation (Li *et al.*, 2016).

Evidence suggests that the relationships between diet and gut microbiota may, in part, stem from the ingestion and retention of food-associated microbes (Smith *et al.*, 2015). When characterising the gut microbiomes of two vulture species (*Coragyps atratus*, *Cathartes aura*), researchers found a conserved, yet low-diversity, community that was dominated by the microbes (Clostridia and Fusobacteria) found in the guts of the scavenged mammalian carcasses (Roggenbuck *et al.*, 2014). These specific microbes are also known to be bird pathogens, leading the authors to speculate that vultures have co-opted the pathogenic microbes to assist with protein degradation and have adapted by becoming tolerant of the pathogenic toxins (Roggenbuck *et al.*, 2014; Zepeda Mendoza *et al.*, 2018). In a study of five species of captive non-human primates housed at the same facility and fed nearly identical diets, researchers found species-specific signals of dietary microbes in the monkeys' gut microbiomes (Bornbusch *et al.*, 2023). This finding suggested that, despite uniform intake of microbes associated with the identical diets, there was an unknown, host-specific mechanism that dictated which of the incoming dietary microbes persisted in the monkeys' gut microbiomes. At many animal facilities, dietary items are washed, bleached, or processed to remove potential pathogens. Although the impact of cleaning or processing diets on animal microbiomes is currently unknown, we expect that it would significantly minimise the presence of microbes on those dietary components, with relevant consequences for diet–host microbial interactions.

Many animals also practice forms of geophagy (i.e. earth-eating), which is suggested to have adaptive purposes related to nutrient and microbial supplementation (Johns & Duquette, 1991; Borruso *et al.*, 2021). In indri (*Indri indri*), a folivorous lemurid, geophagy was linked to detoxification of plant secondary compounds and to the presence of fungal microbes present in the lemurs' guts (Borruso *et al.*, 2021). Many of the fungi found in both soil and lemur guts were saprotrophic, capable of breaking down decaying or fermenting plant matter. The authors posited that indri have incorporated these environmental fungi into their gut microbiomes to assist with the breakdown of their plant-based diet.

(*c*) *Microbial landscapes as evolutionary mismatches*

From the perspective of evolutionary medicine, the concepts of microbial landscapes and environmental acquisition have ties to longstanding hypotheses on human health, including the hygiene and old friends hypotheses (Rook, 2010; Bloomfield *et al.*, 2016; Frew, 2019) (Fig. 1). These hypotheses suggest that exposure to and symbiosis with microbes over human evolutionary history have shaped health responses in modern populations. More recently, the biota alteration or biome depletion hypothesis, an updated interpretation of these two classic hypotheses, posits that the industrialisation of human society led to a depletion of human commensal and symbiotic microbiota and reduced exposure to diverse environmental microorganisms (Villeneuve *et al.*, 2018). This reduction in microbial exposure has been associated with increased inflammatory and autoimmune disorders (e.g. allergies, inflammatory bowel disease) found in modern human populations (Bilbo *et al.*, 2011; Villeneuve *et al.*, 2018). There is evidence that, in humans, exposure to natural, microbially rich environments at an early age is critical for immune development, disease resistance, and host–microbe–physiology integration (Mills *et al.*, 2017). Continual exposure to the minimal or altered microbial communities of 'built environments' has been linked to increased disease risk (Parajuli *et al.*, 2018; Nicolaidis, 2019; Ahn & Hayes, 2021). Globally, populations living in more developed and urbanised regions have higher rates of autoimmune disorders compared to populations living in less developed or rural areas (Zuo *et al.*, 2018; Flies *et al.*, 2019).

Paralleling this industrialisation of human environments, captive animals often live in settings that have reduced and/or altered microbial landscapes (Bornbusch *et al.*, 2022*a*; Dallas & Warne, 2022). Husbandry practices and veterinary care introduce cleaning products and antibiotics to the microbial landscapes of captive animals (Hartmann *et al.*, 2016; Maamar, Hu & Hartmann, 2020), further differentiating these landscapes from those experienced by *in-situ* animals (Thompson *et al.*, 2017). Recent studies in captive ring-tailed lemurs showed that increased exposure to naturalistic environments (e.g. natural habitats or outdoor, forested enclosures) promoted greater covariation between the lemurs' microbiome and the surrounding soil microbes (Bornbusch *et al.*, 2022*a*,*b*). Even within lemurs at a single facility, greater access to natural, forested habitats correlated with a greater contribution of soil microbes to the lemurs' gut microbiomes (Bornbusch *et al*., 2022*b*). Increasing evidence indicates that varying exposure to external microbes drives the rate of microbial transmission between sources. Environmental acquisition may play a greater role in structuring or augmenting the microbiota of animals living in microbe-rich *in-situ* environments compared to animals living in *ex-situ* environments that have altered or minimised microbial presence. In addition to the inherent psychological and behavioural value of providing naturalistic environments to wildlife under human care, we see increasing evidence that exposure to rich, natural microbial landscapes has the potential to augment host-associated microbiomes. Within the standards of proper care, we suggest that actionable step (6) is to minimise the sterilisation of animal dietary items and environments. This proposal is further discussed below in Section IV.4.

Explanatory frameworks for microbiome assembly have emerged from clinical studies that aim to control for as many variables as possible and reduce external, microbial contamination. For example, coprophagy, which is common in rodents, is now thought to have been an unexamined influence in early studies of rodent microbiomes (Moore & Stanley, 2016; Hugenholtz & de Vos, 2018). The behaviour is now minimised or eliminated altogether in laboratory rodents, despite its natural role in shaping rodent microbiomes (Hirakawa, 2001). On the extreme end of the spectrum, germ-free or gnotobiotic animals housed in sterile environments are used to study mechanistic details of how microbiomes influence host physiology (Wostmann, 2020). Although these studies have immense value, particularly for clinical research, the simplification of microbial landscapes likely limits detection of biologically relevant interactions between host-associated and external microbiota.

In summation, animal evolution occurred in tandem with shifting microbial landscapes. Numerous components of biology and health are shaped by how animals are exposed to and interact with these external microbial communities. The alteration or minimization of these interactions, as we see in urban human societies and captive animal environments, can disrupt the associated evolutionary adaptations, leading to dysbiosis and negative health outcomes. Host-associated microbiomes are not the only important microbial communities that should be considered when aiming to improve animal care and conservation.

IV. MICROBIAL THERAPIES AND REWILDING AS TOOLS TO OVERCOME EVOLUTIONARY MISMATCH

Treating and manipulating host-associated microbiomes is an expanding, beneficial component of human and animal medicine (Barko *et al*., 2018; Niederwerder, 2018; Lam, Alexander & Turnbaugh, 2019). However, in the past, manipulations were largely limited to reducing or even eliminating certain microbial members. For example, modern hygiene and sanitation, important to preventing disease, have greatly reduced exposure to many sources of external microbes, thus leading to the aforementioned hygiene hypothesis (Fig. 1). Another recent example of microbial manipulation is the use of antibiotics to combat bacterial infections. Although antibiotics have been instrumental in the progress of modern medicine, we are now recognising the negative consequences of widespread antibiotic use, such as the significant alteration of global microbial communities and the explosion of antibiotic resistance (Laxminarayan *et al*., 2013; Patel *et al*., 2020; Brown *et al*., 2022). In response, there is increasing interest in enhancing or reinforcing host-associated microbiomes as opposed to eliminating them (Ouwehand *et al*., 2016; D'Accolti *et al*., 2022; Gul & Alsayeqh, 2022).

Here, we describe microbial therapies as those that (*i*) enhance microbial communities *via* non-microbial supplements, or (*ii*) provide supplemental microbial communities. These therapies traditionally include prebiotics and probiotics, along with faecal microbiota transplants (FMTs). We expand on this definition to include exposure to environments that include elements similar to *in-situ* conditions as a means to promote 'microbial rewilding' (i.e. the augmentation of host-associated microbiomes to overcome potential evolutionary mismatches).

Within our evolutionary framework, the microbial therapies discussed below represent tools to manipulate microbiome response and recovery beneficially (as seen in Fig. 2). In addition, we suggest six actionable steps (7–12 in Table 1) to integrate microbial therapies into animal care and conservation.

(1) Prebiotics

Diet can be manipulated in a microbially informed way to improve host–microbe symbiosis. Prebiotics are nutrients or other dietary constituents that facilitate the abundance or function of beneficial microbes, usually by providing resources for microbial metabolism (Bindels *et al*., 2015; Cunningham *et al*., 2021). Whereas dietary supplements have long been considered from the perspective of benefitting host nutrition and physiology, many of these supplements are now known also to be prebiotics, extending their benefits to include microbial effects (Slavin, 2013; Nogueira *et al*., 2019). Prebiotics can reduce pathogenic infections by promoting the growth and maintenance of beneficial microbes that outcompete incoming or dormant pathogens (i.e. competitive exclusion; Callaway *et al*., 2008). They can further promote the production of valuable metabolites for the host (e.g. fermentation products and bioavailable nutrients; Verbeke *et al*., 2015).

In addition to specific nutritional supplements, whole dietary items can act as prebiotics. In the gut microbiomes of frugivorous ruffed lemurs (*Varecia* spp.), supplementation with daily romaine lettuce increased the abundance of fibre-degrading and health-promoting microbes (Greene *et al*., 2020). Similarly, in a study of five species of non-human primates, replacement of sugar-rich fruits with nutritionally appropriate vegetables – representing a significant decrease in sugar intake – resulted in increased abundances of cellulolytic bacteria, including some known to decrease gut inflammation (Bornbusch *et al.*, 2023). In carnivorans, whole prey can provide dietary components, such as animal fibre, that promote microbial fermentation (Depauw, 2013). Specific food items from an animal's native diet also may be used as prebiotics for *ex-situ* populations. When researchers brought wild woodrats (*Neotoma albigula*) into captivity, individuals fed commercial rodent chow only retained 62% of their native gut microbiome over time. By contrast, individuals fed a specific native food (*Opuntia* cactus) showed 90% retention of 'wild' native microbes (Martínez-Mota *et al.*, 2020). These dietary supplementations with readily available, prebiotic food items provide an accessible avenue to augment animal microbiomes.

Much like overall diets can and should be tailored to an animal's feeding ecology and evolutionary history, prebiotics should be equally targeted. A common example is complex plant fibre, a dietary component that, when fermented by certain gut microbes, provides important short-chain fatty acids that maintain gut health in animal hosts (Baxter *et al.*, 2019; Jha *et al.*, 2019). In the folivorous Coquerel's sifaka (*Propithecus coquereli*), supplementation with a diversity of wild plant species *versus* with a single species significantly influenced microbiome diversity and composition: diverse browse, which better approximates a native diet, promoted greater microbial diversity, enrichment of fibre-degrading microbes, and greater concentrations of colonic short-chain fatty acids (Greene *et al.*, 2018). For carnivorans, animal fibre, rather than plant fibre, may play a similar role in shaping gut microbiota and metabolites. A study of *in-vitro* microbial fermentation using cheetah (*Acinonyx jubatus*) faecal inoculum showed that the fermentation of prey skin, hair, cartilage, and bone were significant sources of short-chain fatty acid production (Depauw, 2013). In other hosts, insect meal may act as a prebiotic due to chitin promoting the growth of microbes such as *Bifidobacterium* (Lopez-Santamarina *et al.*, 2020; Lange & Nakamura, 2021), which has reported health benefits (Kurmann & Rašić, 1991; Rodriguez & Martiny, 2020). Yet, in animals that lack chitin-degrading microbes, insect supplementation may have little to no impact. We suggest that an actionable step (7) is to identify and augment the prebiotic components of animal diets that promote beneficial microbes. Comparing nutritional values between the diets of *in-situ* and *ex-situ* conspecifics would provide an avenue towards mitigating the dietary mismatches faced by many captive animals.

(2) Probiotics

Probiotic therapy introduces live microorganisms that are thought to have therapeutic potential and is the most widely used of microbial therapies. In 2022, commercial probiotics had an estimated $60 billion (USD) global market value, with an annual growth rate of up to 10%. The introduced microbes can produce metabolites, such as short-chain fatty acids, that improve gut function and digestion (Kerry *et al.*, 2018) and can further stimulate physiological defences by interacting with white blood cells that are important for immune system function (Madsen, 2006). They can also outcompete harmful microbes *via* competitive exclusion (Callaway *et al.*, 2008), occupying niches in the gut that would otherwise be susceptible to invasion by pathogens.

Initially, identifying probiotic potential relied on the assumption that microbial strains abundant in the guts of healthy individuals (Veiga *et al.*, 2020) could also benefit less healthy individuals (Suez *et al.*, 2019). These single-strain candidates, such as members of the *Bifidobacterium* and *Lactobacillus* genera, comprise most of the commercial probiotics marketed today (Gareau, Sherman & Walker, 2010), including those for non-human animals. Even in humans, however, the efficacy of commercial and prescription probiotics is poorly understood (Culligan, Hill & Sleator, 2009; Lerner, Shoenfeld & Matthias, 2019; Washburn, Sandberg & Stofer, 2022). For example, the effects of traditional probiotics vary widely across individuals depending on age, diet, lifestyle, genetics, and other factors, even when intended for treatment of the same disease (Suez *et al.*, 2019). In a meta-analysis of clinical uses of commercial probiotics to treat acute diarrhoea, probiotics were found to reduce the risk of acute diarrhoea in children by 35–75% (Sazawal *et al.*, 2006). Yet in adults, it lowered the risk of acute diarrhoea by as little as 7% (Sazawal *et al.*, 2006). The same meta-analysis showed no difference in the efficacy of single-strain probiotics *versus* combinations of multiple, single-strain treatments. In a study of humans and mice receiving microbial therapies following antibiotic treatment, the administration of an 11-species probiotic mixture facilitated colonisation by the probiotic microbes, but it simultaneously hindered recolonisation by native gut microbiomes and delayed the recovery of mucosal function (Suez *et al.*, 2018).

For non-humans, most existing data on probiotic use come from livestock, aquatic animals, and companion animals, with inconsistent treatment efficacy. In ruminant livestock, early attempts at probiotic treatments were performed using *Lactobacilli* strains, which are common probiotic microbes used in humans; however, the over-proliferation of *Lactobacilli* and resulting lactic acid production caused ruminal acidosis, a disease of the rumen that can be fatal in severe cases (Chaucheyras-Durand & Durand, 2010). Since then, probiotic formulations specifically targeted to cows, sheep, and goats – and not relying on probiotic data generated in other animal species – have been associated with increased growth, disease resistance, and milk production (Chaucheyras-Durand & Durand, 2010; Xu *et al.*, 2017). Likewise, supplementing chicken feed with specific probiotic strains has been associated with increased egg production and quality, as well as improved gut health in the hens (Khan *et al.*, 2007; Peralta-Sánchez *et al.*, 2019). The promise of probiotics as a replacement for routine use of antibiotics in livestock production has extended to aquatic animals; targeted probiotics have been used in commercial fish and shrimp farming successfully to combat pathogenic infections (El-Saadony *et al*., 2021; Knipe *et al*., 2021). Lastly, in companion animals, the administration of probiotics containing *Enterococcus faecium* or *Bifidobacterium* sp., plus a nutrient medium to support the microbes, significantly decreased acute diarrhoea in adult dogs being brought into a shelter or suffering from gastrointestinal infection (Rose *et al*., 2017; Kelley *et al*., 2009). Nevertheless, the beneficial effects of probiotics were often limited to the period of treatment, suggesting that the microbes were not successfully colonising the gut. Jugan *et al*. (2017) concluded that, at that time, no specific commercial probiotic was associated with enough evidence of effectiveness to be widely recommended for use in small-animal veterinary medicine.

For zoo and exotic animals, empirical and clinical data on probiotic use are almost non-existent. When surveying accredited US zoos on the use of probiotics, over 25 different products were reported, with little standardisation of administration within the same target species (personal communication with member institutions of the Association of Zoos and Aquariums Nutritional Advisory Group). A targeted, evidence-based approach is needed to identify probiotic microbes that are tailored to the host species (Garcias-Bonet *et al*., 2023). This targeted approach is already a growing facet of human medicine: precision probiotics are based on the premise that more individualised treatment of health disorders increases the chance of success (Veiga *et al*., 2020).

Rather than administering a suite of single-strain microbes that have been selected based on their abundance in healthy, often heterospecific individuals, an evolutionary framework would suggest considering a species' co-evolutionary history with microbes. Considering species-specific microbiomes will be crucial for identifying candidate probiotics. Although it may be tempting to 'mine' the microbiomes of *in-situ* animals for potential probiotic microbes to use in *ex-situ* populations, that approach may prove risky. The differences in microbial communities, host physiology, and immune responses between *in-situ* and *ex-situ* animals would likely represent barriers for successful transplantation or colonisation of 'wild' microbes in *ex-situ* animal microbiomes. Moreover, the identity of probiotic candidates is of less importance than their function and dynamics when introduced to the target microbial community (e.g. the microbiomes of *ex-situ* animals). Thus, under our proposed framework, we suggest that the microbiomes of healthy, *ex-situ* animals, which have presumably adapted to *ex-situ* conditions, may represent the most suitable community in which to identify precision probiotic candidates for use in other *ex-situ* conspecifics. Moreover, precision probiotics have been paired with targeted prebiotics that promote the growth and maintenance of the beneficial bacteria in the probiotic formulation. This combination of relevant microbes and their preferred substrates, known as a 'synbiotic', is a novel and promising approach (Swanson *et al*., 2020). When probiotics are necessary, actionable step (8) is to combine probiotics with prebiotics that are known to bolster the animal's native microbes. This dual approach could promote the incorporation of potentially beneficial probiotic microbes, as well as reinforce the existing microbial community.

(3) Faecal microbiota transplants (FMTs)

Another promising microbial therapy, grounded in ecological and evolutionary frameworks, treats the host with an entire microbial community and its by-products. Communities of microbes interact as complex ecosystems such that species removal or translocation into a new environment can dramatically alter microbial behaviour, function, and even survival. If the entire community of organisms is moved as a unit, however, it may better recreate its functional capacity in its new environment. This approach to microbial therapies suggests that the greatest efficacy stems from the collective action of entire communities of microbes, not just from one or two strains (Walter, Maldonado-Gómez & Martínez, 2018).

The prime example of this type of therapy is FMTs. FMTs involve transplanting a microbial community, typically sourced from the faeces of a healthy conspecific, into a recipient's gut. In humans, FMTs are most commonly known for their effectiveness in treating *Clostridioides difficile* infections (Bakken *et al*., 2011; Mattila *et al*., 2012), and are now being tested as treatment for everything from gut infections and liver disease to cancer and psychiatric disorders (Bakken *et al*., 2011; Chen *et al*., 2019). There are stool banks devoted to providing healthy, donor stool for FMTs (OpenBiome, https://www.openbiome.org/).

Although FMTs are now widely studied and accepted in human medicine, empirical research on FMTs outside of clinical settings is sparse. Moreover, in cases of FMT use in non-human animals, FMTs are often administered as a 'last resort' after other treatments have failed. Nevertheless, FMTs have a long history of use in non-human animals, generating significant anecdotal evidence of their benefit. For instance, European farmers have been transplanting rumen material, a process initially called 'transfaunation', for hundreds of years, using it to restore normal rumen function in unhealthy livestock (Brag & Hansen, 1994; Borody *et al*., 2004). In companion animals, FMTs have only recently been incorporated into veterinary practice, with empirical evidence limited to a handful of case studies (Chaitman *et al*., 2016; Niederwerder, 2018). In domestic dogs, FMT application is most commonly incorporated into treatment for parvovirus and chronic enteropathy, with some evidence of success (Pereira *et al*., 2018; Schmitz, 2022).

In various exotic animals, FMT has been valuable in treating acute or chronic diarrhoea, which can be especially lethal to neonates. For instance, in kangaroo (*Osphranter* sp.) joeys, the use of FMTs has been reported to reverse diarrhoea in nearly every case (Milliken, 2019). For giraffe (*Giraffa camelopardali*) calves requiring hand-rearing and intensive care, FMTs combined with milk replacer contributed to the resolution of diarrhoea in the majority of individuals (Dixon *et al*., 2021). In Coquerel's sifakas infected with *Cryptosporidium* and treated with antibiotics, FMT administration aided in the successful recovery of normal gut flora in most cases (McKenney *et al.*, 2017). Likewise, ring-tailed lemurs that received an FMT following antibiotic treatment showed more rapid recovery of gut microbiome communities compared with animals that received antibiotics alone (Bornbusch *et al.*, 2021). In a two-toed sloth (*Choloepus didactylus*) experiencing abnormally frequent and loose stools, administering multiple FMTs of donor faeces from a co-housed conspecific shifted the recipient's microbiome and alleviated the abnormal defecation (Thacher *et al.*, 2023). Similarly, in captive common marmosets (*Callithrix jacchus*), FMTs eliminated *C. difficile* infection in the gut tract (Yamazaki *et al.*, 2017).

Beyond their efficacy in treating diseases, FMTs appear to convey more general health benefits, sufficient even to extend lifespan. For instance, in the African turquoise killifish (*Nothobranchius furzeri*), FMTs from young fish to middle-aged ones delayed the onset of age-related behavioural declines and increased longevity relative to control fish (Smith *et al.*, 2017). Even *in-situ* animals may sometimes benefit from FMT when their populations suffer dramatic environmental shifts. In a recent study, scientists were able to expand the dietary flexibility of koalas (*Phascolarctos cinereus*) by providing FMT from individuals feeding on different types of eucalyptus (Blyton *et al.*, 2019). This flexibility may allow koalas rescued from wildfires to be moved more successfully to new eucalyptus forests.

FMTs have further shown some success in replicating microbial function between interspecific donor and recipient animals. An FMT of faeces from warthogs (*Phacochoerus africanus*) to domestic piglets resulted in modification of the gut microbiome and protection against African Swine Fever, a virus that is fatal to domestic pigs but largely asymptomatic in warthogs (Zhang *et al.*, 2020). Mice that received a transplant from hibernating (*versus* active) bears showed greater fat metabolism – a finding that replicated the natural difference in metabolism between hibernating and active bears (Sommer *et al.*, 2016).

Although more empirical data are needed, existing studies, combined with extensive anecdotal evidence, provide strong support for FMTs as valuable therapeutics in a wide range of animals. We thus suggest that actionable step (9) is to consider FMTs, not as a last resort, but as a microbially informed therapeutic or prophylactic treatment, that can be used singly or in combination with non-microbial therapies in a wide range of animals facing a variety of health-related issues.

Unlike commercial probiotics, for which preparation requires the isolation, purification, and propagation of specific microbial strains – and, in some cases, adherence to regulatory standards – FMTs are simple, cost-effective, and often better tailored to the intended recipient. Faecal matter from healthy conspecifics is often readily available at relatively minimal cost. Moreover, banking faecal samples obtained from animals while they are healthy – particularly for individuals or species that are prone to disease – provides opportunities for future autologous FMTs whenever the need arises. Samples can be pre-screened for known parasites and pathogens prior to banking, ensuring safe and immediate use in the future. Methods for FMT preparation and administration can be simple. Faeces can be incorporated into a slurry or encapsulated into pill form, both of which can be administered *via* standard diet or during veterinary examinations. In clinical cases, more stringent protocols, similar to those that have been published for humans (OpenBiome, https://www.openbiome.org/) can be readily applied. Even when microbial therapies cannot be administered after a perturbation, such as following reintroduction, they can be considered as a prophylaxis to prepare the host and its microbiome for the transition.

Just as FMT can provide beneficial microbes, so too can it pass on intestinal pathogens and parasites. Although rare, cases of FMTs transferring antibiotic-resistant or toxin-producing pathogens to the recipient have been documented in humans (Khanna & Kraft, 2021; Zellmer *et al.*, 2021). To ensure the safety of clinical FMTs in humans, protocols have been put in place to screen donor faeces for pathogens, parasites, toxins, and antibiotic resistance genes, as well as the overall functional potential of the microbes (Hanssen, de Vos, & Nieuwdorp, 2021). Creating standards for safe and effective FMT in animal care is an even greater challenge because of (*i*) the mismatch between the diversity of animals under human care and the limited species represented in FMT studies, and (*ii*) the spectrum of potential pathogens these animals may harbour (Niederwerder, 2018). We thus suggest two additional actionable steps for FMTs: (10) For individuals or species that are particularly prone to gut infection or distress, banking and pre-screening faeces during healthy states should be adopted to provide a readily accessible resource for future FMTs; and (11) microbiome science should be integrated with veterinary knowledge to determine best practices for uses of FMT in animal care and conservation. This is an interdisciplinary task that may seem daunting but is poised to offer novel and beneficial treatment avenues for many *ex-situ* animals.

(4) Microbial rewilding *via* environmental exposure

Broadly, 'rewilding' refers to the restoration of perturbed ecosystems to their natural state, commonly *via* the reintroduction or conservation of native 'keystone' inhabitants (Perino *et al.*, 2019). The concept has notably been applied to macro-habitat restoration, including the reintroduction of large herbivores (van Klink *et al.*, 2020; Lorimer, 2017). The same rewilding hypothesis can be applied to micro-level ecosystems such as animal gut microbiomes. Notably, there is the potential to facilitate the acquisition of environmental microbes – *via* exposure to natural, diverse microbial landscapes – so as to guide microbial structure and function. Recently, this premise has been applied to the human gut microbiome through the Microbiome Rewilding Hypothesis, which posits that the restoration of 'green' habitats and promotion of diverse environmental microbiomes in urban settings can improve human gut microbiomes and health (Mills *et al.*, 2017; Robinson, Mills & Breed, 2018). Given that captive animals likewise experience minimised or altered microbial exposures and built environments, they may benefit from the same premise.

This more novel form of microbial therapy, using environmental exposures, is particularly understudied. Nevertheless, the Microbiome Rewilding Hypothesis has direct applicability to captive animals. In laboratory mice, rewilding *via* exposure to outdoor enclosures influenced immune cell frequencies and increased colonisation by symbiotic, intestinal fungi and bacteria, some of which were causally linked to increased circulation of immune-boosting white blood cells (Lin *et al*., 2020; Yeung *et al*., 2020). In captive-born harlequin frogs (*Atelopus varius*), a 'soft-release' to outdoor mesocosms resulted in rapid changes to the structure and anti-fungal properties of the skin microbiomes, more similar to communities seen in *in-situ* frogs (Kueneman *et al*., 2022). In another study, researchers tested for microbial rewilding in a population of ring-tailed lemurs that were born *in-situ*, then captured and initially held as illegal pets in unnatural settings, and subsequently relocated to a rescue centre in Madagascar where they lived in naturalistic environments (Bornbusch *et al*., 2022*a*). Access and exposure to naturalistic settings, including outdoor forested enclosures, rewilded these lemurs' gut microbiomes by shifting microbial composition to resemble the microbiomes of *in-situ* lemurs, decreasing the frequency of antibiotic resistance genes, and increasing covariation with environmental microbes (Bornbusch *et al*., 2022*a*). We suggest that actionable step (12) is to provide early and long-term access to naturalistic environments (*via* e.g. outdoor spaces, free-ranging) or foods (e.g. natural unbleached dietary items, such as browse or carcasses) that contain diverse, external microbial communities. Such access may simultaneously improve the health of captive animals and better prepare them for reintroductions.

V. CONCLUSIONS

(1) We present a framework for understanding and potentially manipulating animal gut microbiomes through the lens of evolutionary medicine. Within this framework, we provide evidence for the relevance of evolutionary medicine beyond human health, incorporating eco-evolutionary concepts into the care and conservation of *ex-situ* animal populations.

(2) The vast array of animal species under human care presents a complex challenge for veterinarians, nutritionists, animal care professionals, and scientists alike. Although we have focused this review on mammals, for which there is robust evidence, our proposed framework is widely applicable to vertebrates and even invertebrates across the tree of life. Consideration of both the evolutionary and proximate history of animal species, and the associated interactions with their microbiomes, can improve how we understand their current state and can inform future treatment and care protocols.

(3) We highlight that evolutionary mismatches in diet and microbial landscapes, and their associated impacts on animal microbiomes, may underpin widespread health issues in *ex-situ* populations. We suggest that the effects of these mismatches depend on the capacity of the host species and their microbiomes to adapt to conditions under human care. This vulnerability is directly linked to the species' ecology and evolution. While the microbiomes of many species may adapt without assistance, the microbial communities of certain individuals and species may require intervention to maintain host–microbe symbiosis.

(4) For most applications and in most animal species, empirical evidence on the effectiveness – and perils – of microbial therapies is limited. We acknowledge that there is potential to introduce harm and to waste resources when evidence and standards are lacking. Nevertheless, prebiotics, probiotics, FMTs, and microbial rewilding all have immense potential to address some of the most intractable problems in animal health and conservation. In particular, we suggest that microbial therapies can be used to alleviate the consequences of evolutionary mismatches. We encourage the generation of additional empirical data on the use and efficacy of microbial therapies in non-domesticated animals; without additional data, microbial therapies may never reach their full potential for animal care and conservation.

(5) We provide 12 actionable steps (Table 1) through which the concepts of evolutionary medicine can be incorporated into practical animal care and conservation. Importantly, promoting and performing interdisciplinary research that integrates microbiome science into veterinary medicine and conservation biology can have transformative benefits for all associated fields. We urge animal care professionals, veterinarians, nutritionists, scientists, and others to collaborate on these efforts, allowing for simultaneous care of animal patients and the generation of valuable empirical data.

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In memoriam of Dr Jay Schulkin, a dedicated and endlessly curious scholar whose contributions to the study of Evolutionary Medicine helped shape the foundations of the

field and its future directions. Jay was a tireless mentor who openly shared his excitement for science and knowledge. His kindness and enthusiasm sparked inspiration in everyone with whom he worked. Jay's commitment to this review was a driving force behind its conceptualization and completion. We honour Jay's life and career by dedicating this review to him and by continuing his legacy of excellent science and mentorship. He will be greatly missed. To those who knew him: focus, finish, what's next!

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