
The relationship between physiological stress and wildlife disease: consequences for health and conservation

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Abstract

Wildlife populations are under increasing pressure from a variety of threatening processes, ranging from climate change to habitat loss, that can incite a physiological stress response. The stress response influences immune function, with potential consequences for patterns of infection and transmission of disease among and within wildlife, domesticated animals and humans. This is concerning because stress may exacerbate the impact of disease on species vulnerable to extinction, with consequences for biodiversity conservation globally. Furthermore, stress may shape the role of wildlife in the spread of emerging infectious diseases (EID) such as Hendra virus (HeV) and Ebola virus. However, we still have a limited understanding of the influence of physiological stress on infectious disease in wildlife. We highlight key reasons why an improved understanding of the relationship between stress and wildlife disease could benefit conservation, and animal and public health, and discuss approaches for future investigation. In particular, we recommend that increased attention be given to the influence of
anthropogenic stressors including climate change, habitat loss and management interventions on disease dynamics in wildlife populations.

Additional keyword: physiology.

Introduction

Stress can be broadly defined as a change in the psychological, physiological and/or physical well being of a living organism as a result of exposure to any biological and/or environmental factor that acts as a stressor (challenge to regulatory capacity). Wildlife encounter a range of stressors or threatening processes ranging from habitat loss to climate change, which may activate the hypothalamic–pituitary–adrenal (HPA) axis (stress response) (Madliger and Love 2014). The stress response is not inherently detrimental, but rather, is a complex and essential negative-feedback system involving glucocorticoids among other neuro-endocrine mediators. Thus, the HPA axis regulates the physiological, biochemical and behavioural processes required to maintain allostasis (homeostasis through change; Sapolsky et al. 2000; McEwen 2005). Busch and Hayward (2009) proposed a log-quadratic model for the relationship between glucocorticoids and fitness, which illustrated how the stress response (hereby referred to as ‘stress’) has a critical adaptive advantage up to a point, but when regulatory mechanisms are overcome, allostatic overload occurs and stress incurs fitness costs (McEwen 2005; Busch and Hayward 2009). For example, severe acute and unpredictable or chronic stressors may not allow the HPA axis to reach a recovery phase, resulting in dysfunction of the negative feedback mechanism and subsequent health impairment (Tsigos and Chrousos 1994).

In terms of infectious disease, cost of allostatic overload can include increased infection susceptibility, shedding of infectious agents, severity of clinical signs and poor prognosis (Biondi and Zannino 1997; Agarwal and Marshall 2001). As a result, shifts may occur in the host–parasite equilibrium, the healthy balance between host and parasites that have co-evolved over millennia (Aapanius 1998;
Stress may affect the host–parasite equilibrium via complex interactions with, and direct influence on the immune system (Reichlin 1993; Munck and Náray-Fejes-Tóth 1994; Daynes et al. 1995; Sapolsky et al. 2000). Mediators of the HPA axis, for example, glucocorticoids, can have profound effects on different immunological processes (Sheridan et al. 1994; Aapanius 1998) via receptors on immune cells (Besedovsky and del Rey 1996) and changes in immune gene expression in target tissues (Padgett and Glaser 2003). Stress may also affect host–parasite equilibrium indirectly, for example, by changing characteristics of the protective mucus membranes of the body (Chester 1992) and via behavioural changes that may alter disease transmission pathways (Broom 2003). Studies in laboratory animals (Dhabhar and McEwen 1997), livestock (Salak-Johnson and McGlone 2007), fish (Maule et al. 1989) and humans (Biondi and Zannino 1997) have indicated that stress can affect patterns of infectious disease (Sheridan et al. 1994). Stress has also been suggested as a factor influencing a wide range of diseases in wildlife, including Chlamydia infection in koalas (Brearley et al. 2013), toxoplasmosis in various marsupials (Thompson et al. 2010), chytridimycosis in amphibians (Blaustein et al. 2012; Kindermann et al. 2012; Gabor et al. 2013), avian influenza in migratory birds (Weber and Stilianakis 2007) and white nose syndrome (Cryan et al. 2010) and zoonotic (spread from animals to humans) viruses in bats, including Ebola and Hendra virus (HeV) (Groseth et al. 2007; Plowright et al. 2014). However, associations between stress and disease in wildlife are not commonly empirically tested.

Stress has the potential to significantly alter wildlife immune function; however, the extent to which this translates into changes in patterns of infectious disease in wildlife populations remains unclear (Martin 2009; Blaustein et al. 2012). So as to assess this outstanding question, we evaluated the literature on physiological stress and infectious disease. We interrogated the ISI Web of Science (http://www.isiwebofknowledge.com, verified December 2014) by using keywords such as stress, glucocorticoids, wildlife, infection, disease, bacteria, virus, fungi, parasite and pathogen. We selected those studies that examined the influence of stress on infectious diseases in wildlife, using parallel measures of glucocorticoids and infection indices. The reference lists in these sources were also inspected to find further papers.
We concentrated on the relationship between extrinsic stressors and infectious disease in captive and free-ranging vertebrate wildlife including fish, amphibians, reptiles, birds and mammals. Previous reviews have suggested that stress can also affect immunity in other organisms across the evolutionary spectrum (Ottaviani and Franceschi 1996), including invertebrates (Adamo 2012), molluscs (Saarinen and Taskinen 2005; Hooper et al. 2007) and corals (Peters 1984); however, these were considered beyond the scope of the present review that concentrates on stress and disease in vertebrate wildlife. Studies focusing on domesticated fauna in agriculture or aquaculture (Cohen and Kinney 2007) were excluded because they have examined either selectively bred animals that may not react to stressors in the same way as do free-ranging wildlife, or wild-caught animals or those with limited generations in captivity. This is due to vastly different stressor exposure and genetics because the stress response is shaped by both previous exposure (Bejder et al. 2009) and heritable traits (Zhou et al. 2008).

We focussed on glucocorticoids and their metabolites as stress physiology indicators for consistency, and because glucocorticoids provide insights into the mechanisms underpinning the physiological stress response (Cooke et al. 2013). Glucocorticoids have been demonstrated to alter physiological, biochemical and behavioural processes to maintain allostasis during exposure to stressors (Sapolsky et al. 2000; McEwen 2005). They can also be measured in wildlife by using minimally invasive methods (Sheriff et al. 2011) and are widely acknowledged as a practical tool in conservation physiology, wildlife research and management (Cooke et al. 2013; Narayan 2015).

**The importance of increased attention to stress and wildlife disease**

As the frequency and severity of stressors increase globally, the relationship between stress and disease in wildlife populations demands greater attention (Lafferty and Kuris 1999; Aguirre and Tabor 2008; Van Bressem et al. 2009; Blaustein et al. 2012). Infection can influence animal populations via sublethal effects reducing fitness as well as dramatic population-level effects (Scott 1988; Aguirre and Tabor 2008). For example, Owen et al. (2012) found that experimentally elevated plasma
corticosterone can reduce the survival of northern cardinals (*Cardinalis cardinalis*) infected with West Nile virus (Owen *et al.* 2012). Similarly, Pedersen and Greives (2008) demonstrated experimentally that stress, parasitism and malnutrition drive winter population crashes in white-footed mice (*Peromyscus leucopus*). In addition, improving our understanding of the relationship between stress and the incidence, prevalence, intensity, recrudescence and severity of disease in wildlife could benefit biodiversity conservation and One Health (Zinsstag *et al.* 2011). One Health encompasses the collaborative goals of providing optimal health for people, animals (domestic and wild) and the environment, by considering interactions among these three systems (Thompson 2013).

Here, we outline the importance of increased research, monitoring and management of stress and infectious disease in wildlife populations and discuss approaches for future investigation. We draw particular attention to the following three key anthropogenic stressors that human society can practically and directly manage: climate change, habitat disturbance and management interventions.

(1) **Climate change**

Climate change can have a profound effect on disease dynamics in wildlife populations (Hoberg and Brooks 2015). In part, these effects may be mediated by stress because climate change involves a suite of proximate stressors such as thermal extremes and resource limitations (Geyer *et al.* 2011) that elicit a host stress response. For example, chronic stress, such as that associated with resource limitations resulting from prolonged drought, is suspected as a major risk factor for chlamydiosis in koalas, a disease that threatens population survival (Davies *et al.* 2014).

Stress linked to extreme weather events has also been suggested as a contributing factor in mass-mortality events in threatened wildlife species. For example, the normally benign bacteria *Pasteurella hamolytica*, which can be precipitated by stress, has been linked to catastrophic mass-mortality events in the critically endangered saiga antelope (*Saiga tatarica*) following severe winters (Bekenov *et al.* 1998). Recent modelling of data from over 720 animal mass-mortality events in over 2400 populations has indicated that mortality events associated with concurrent stressors and disease have increased in frequency from the 1940s to 2000s (Fey *et al.* 2015). The imperative to investigate the
relationship between stress and disease in wildlife is greater now than ever. Monitoring glucocorticoid parameters and infection indices in wildlife populations over time will allow comparisons to be made as threatening processes progress. In addition, if we can identify which host, pathogen and/or environmental factors (Fig. 1) influence animal responses to major threats such as climate change, we may be better equipped to make conservation decisions (for example, designing selection criteria for managed relocation programs).

(2) Habitat disturbance

Brearley et al. (2013) reviewed the profound impact that habitat loss and fragmentation can have on the prevalence of wildlife disease, and highlighted the role that stress was likely to play as a mediator of this impact. Recent studies have examined the physiological stress response of wildlife to habitat loss and fragmentation (Davies et al. 2013). There have also been studies linking infection patterns in wildlife to habitat loss and fragmentation (Gillespie and Chapman 2006; Hing et al. 2013). However, there appears to be an absence of research that unites physiology and disease diagnoses, measuring glucocorticoid and infection indices in parallel, so as to understand links among habitat loss, stress and infection patterns in wildlife.

Investigating stress and disease in wildlife can also help us identify host factors particular to individuals, populations or species that are resilient (Jessop et al. 2013) in an increasingly urbanised world (Fig. 1). For example, the Australian long nosed bandicoot (Permales nasuta) and southern brown bandicoot (Isoodon obesulus) had faecal glucocorticoid metabolites in the suburbs of Sydney similar to those in National Parks, and metabolites did not co-vary with ectoparasite burden, suggesting that, as generalists able to flourish in a variety of environments, these species may possess traits that make them adaptable to stress and parasite infection in a changing landscape (Dowle et al. 2013). The following question arises: what traits allow some individuals, populations or species to be more resilient to the synergistic effects of stress and infectious disease? Models have been developed in livestock for genetic selection and breeding for robustness based on the stress response (Mormède et al. 2011) and, in the future, wildlife management too may employ similar strategies to build populations that are more resilient to the combined effects of stress and disease.
Climate change and habitat loss are among the key anthropogenic stressors that are significant in terms of the One Health paradigm, which centres on inextricable links among environmental, animal and human health (Daszak et al. 2000; Fig. 2). These links are exemplified in modelling of global emerging infectious disease (EID) data from 1950 to 2008, which indicated a positive association between the number of threatened mammal and bird species and outbreaks of zoonoses in the Asia–Pacific region (Morand et al. 2014). If environmental threats trigger a stress response in wildlife that precipitates infectious disease, there may be consequences for the transmission of zoonotic EID (Fig. 2). This is particularly concerning because Jones et al. (2008) highlighted that over 60% of global EID are zoonoses and wildlife represent the most common source (over 70%). Hence, improving our understanding of how stress affects patterns of disease in wildlife populations will benefit One Health.

Catastrophic contemporary disease outbreaks such as Ebola virus have raised urgent questions about how environmental stressors and interactions among humans, livestock and wildlife influence the role of wildlife in disease emergence and transmission (Fenton et al. 2006; Myers et al. 2013; Plowright et al. 2014). However, the role of wildlife stress in EID epidemiology has yet to be elucidated. Studies have suggested that environmental stressors encountered by wildlife, including climate change and habitat loss, may precipitate zoonotic disease transmission (Hoberg and Brooks 2015). Epidemiological studies have identified trends that suggest that stress-related immunosuppression in flying foxes (pteropid bats; such as that associated with reproduction, poor nutrition, habitat loss, climate change) may have contributed to the emergence of zoonoses, including HeV and Nipah viruses, spread from flying foxes to domestic animals and humans (see the case study ‘physiological stress in bats and HeV control’ later in the paper; Plowright et al. 2008a, 2008b, 2011, 2014).

(3) Wildlife management interventions

An understanding of the relationship between physiological stress and disease in wildlife will help us improve the planning, design, execution and evaluation of wildlife management interventions. It is crucial that we characterise how wildlife respond to research and conservation interventions such as capture and handling (de Villiers et al. 1995; Narayan et al. 2012) and translocation (Kahn et al. 2007) to assess risk, minimise harm and increase the efficacy of these activities. For example, it has
been suggested that the stress of translocation is associated with increased risk of infectious disease in translocated wildlife (Teixeira et al. 2007; Dickens et al. 2010; Sainsbury and Vaughan-Higgins 2012), including recrudescence of latent and normally innocuous pathogens as well as increased vulnerability to diseases at the release site to which the translocated animals may not have been previously exposed (Mihok et al. 1992). However, parallel endocrine and infection investigations have rarely been conducted before, during and after wildlife translocations or, indeed, in instances of wild capture (moving of wild animals into captivity), to investigate the influence of stress and disease in translocation success and the health of translocated and resident populations. A study by Kahn et al. (2007) is a notable exception, finding that translocation of gopher tortoises (Gopherus polyphemus) did not appear to have a significant effect on corticosterone, immune parameters or infection with Mycoplasma agassizii, a common cause of upper respiratory disease in tortoises.

Stress and wildlife disease in management interventions also have relevance to One Health. For example, recent research has suggested that stress and disease in wildlife are highly relevant to the management of bovine tuberculosis (Mycobacterium bovis), which is an economically significant livestock, wildlife and zoonotic disease with ramifications for agriculture and food security (Cross et al. 1998; George et al. 2014). Stress has been linked to increased shedding of M. bovis in badgers (Meles meles) in the United Kingdom (George et al. 2014). These findings have direct relevance for M. bovis and badger management. They suggest that stressful interventions such as culling may contribute to increased shedding by wildlife hosts (Carter et al. 2007). Greater attention to stress and wildlife disease will help design effective wildlife policy and management plans with potential benefits to One Health, welfare, biosecurity, agriculture and associated financial consequences.

**Approaches to understand the relationship between stress and disease in wildlife**

There are many different ways stress and disease can be investigated in wildlife; however, here we discuss the merits and challenges of an approach using glucocorticoids and infection indices measured
in parallel. This approach has rarely been applied in wildlife, but has been recommended as a means to investigate the impact of anthropogenic activities on wild animals (Muehlenbein 2009). Combining glucocorticoid and infection indices with assessments of host reproductive history (Narayan et al. 2012) and survivorship (de Villiers et al. 1995) has also been proposed as an approach to investigate the fitness costs of stress.

Glucocorticoid indices are advantageous for investigating stress and disease in wildlife because they provide a mechanistic understanding of the underlying physiological processes mediating the stress response and are being increasingly used in wildlife research (Cooke et al. 2013). We now have at our disposal minimally invasive and non-invasive tools to investigate stress and disease in wildlife (Sheriff et al. 2011; Hunt et al. 2013; Narayan 2013). Using validated enzyme immunoassays and radioimmunoassays, glucocorticoids can be measured in the peripheral circulation (Palme et al. 2005). Alternatively, glucocorticoid metabolite concentration can be measured in faeces (Palme 2005), urine (McMichael et al. 2014), feathers (Bortolotti et al. 2008), saliva (Majchrzak et al. 2014), exhaled breath (Hunt et al. 2013) and water (Gabor et al. 2013). Research on glucocorticoid receptors may also prove useful to evaluate stress and disease in wildlife, although these methods remain invasive (Liebl and Martin 2013).

Parallel glucocorticoid and infection parameters have been measured in few studies; however, these studies have included species ranging from the seahorse (Anderson et al. 2011) to amphibians (Kindermann et al. 2012; Gabor et al. 2013), birds (Lindström et al. 2005; Kitaysky et al. 2010), lizards (Oppliger et al. 1998) and non-human primates (Chapman et al. 2006; Clough et al. 2010), indicating the potential of this method to be used in different taxa. This approach has been applied in a small number of stress and disease studies conducted on endangered species in challenging field conditions (Aguirre et al. 1995; Chapman et al. 2006). For example, plasma corticosterone positively correlated with fibropapilloma virus, an emerging disease threatening endangered green turtle (Chelonia mydas; Aguirre et al. 1995). Stress and infection indices were also found to correlate in endangered red colobus monkeys (Piliocolobus badius) where a positive correlation was observed among poor nutrition, parasitism and faecal glucocorticoid metabolites (Chapman et al. 2006).
There are numerous challenges, both theoretical and practical, to investigating stress and disease in wildlife by using glucocorticoids and infection parameters in parallel, particularly methodological limitations and pitfalls in the interpretation of results. First, researchers must keep in mind that the relationship between stress and infection is likely to vary depending on a variety of stressor, host, environment and pathogen factors (Fig. 1). Second, caution must be exercised when interpreting the results of glucocorticoid assays (Lane 2006; Dantzer et al. 2014). For example, high glucocorticoid values are not necessarily detrimental and low values beneficial, particularly if chronic stress leads to dysfunction of the HPA axis, rendering an animal unable to mount an appropriate stress response (Busch and Hayward 2009; Narayan and Hero 2014). Caution must also be exercised when interpreting changes in glucocorticoids solely as physiological responses to stressors because variations in glucocorticoids can occur normally, for example, with diurnal rhythms, exercise, pain, season and reproduction (Lane 2006).

Another challenge in the interpretation of stress and wildlife disease studies is that infection itself can act as a stressor, elevating glucocorticoids as part of the host’s efforts to mobilise energy and redistribute resources towards fighting infection while also preventing collateral damage to the body (Sapolsky et al. 2000; Dunn 2007; Laver et al. 2012). For example, wild-captured rodents experimentally exposed to fleas had higher faecal glucocorticoid metabolite concentrations than did controls (St Juliana et al. 2014), and male fence lizards (Sceloporus occidentalis) naturally infected with Plasmodium mexicanum mounted a greater corticosterone response to capture and handling than did uninfected lizards (Dunlap and Schall 1995). The bi-directional relationship between stress and infection poses a challenge to establishing causality in observation studies. Experimental approaches can be used to investigate causality and the multi-dimensional nature of the stress–disease relationship, including experimental stressors (Oppliger et al. 1998), experimental infections (Warne et al. 2011; Kindermann et al. 2012; Marino et al. 2014) and parasite treatment experiments (Goldstein et al. 2005; Raouf et al. 2006; Pedersen and Greives 2008; Monello et al. 2010). However, experimental approaches have numerous logistical and ethical challenges, particularly when working with small populations of free-ranging endangered species. Captive populations may serve as useful
surrogates for experimental studies of stress and wildlife disease, provided that limitations are acknowledged, such as potential behavioural and physiological differences between captive and wild counterparts, and the stressors that may be alleviated or imposed by captivity itself (Narayan et al. 2012).

There are also considerations when measuring infection indices in wildlife. For example, faecal egg counts for parasite oocysts and viral titres can naturally vary with demographic, temporal and spatial variables, and potentially co-vary with the same factors that influence the stress response (Plowright et al. 2014). Limitations of diagnostic tests (such as detection threshold, sensitivity and specificity) must also be considered, particularly if tests are being adapted for use in wildlife species for the first time. Continuous testing and validation of sampling methods, assay protocols and experimental designs will be necessary to build robust research programs that can reliably and efficiently evaluate the relationship between stress and disease in wildlife species.

**Case study: physiological stress in bats and Hendra virus (HeV) control**

Improving our understanding of the relationship between physiological stress and disease dynamics in bat populations may be a key strategy to help characterise the epidemiology of HeV, predict outbreaks and protect animal and human health (Plowright et al. 2008b, 2014; McMichael et al. 2014). HeV, a RNA virus of the family *Paramyxoviridae* and genus *Henipavirus*, was identified as an emerging zoonotic disease in Australia in 1994 (Field et al. 2007). *Pteropus* species of fruit bats, including vulnerable species such as grey-headed flying fox (*Pteropus poliocephalus*), have been identified as the asymptomatic natural reservoir hosts (Young et al. 2000). Horses develop highly fatal respiratory or neurological disease after oronasal exposure to HeV virions in bat secretions including urine (Westbury 2000; Marsh et al. 2011). Following direct contact with sick horses, veterinary and stable staff have contracted severe meningoencephalitis, which, in four cases, proved fatal (Playford et al. 2010). Eastern-coast states of Australia continue to report sporadic equine cases (New South Wales Department of Primary Industries 2015).
The epidemiology of HeV remains incompletely understood, particularly the host and environment factors driving spill-over events (Hyatt et al. 2004; Smith et al. 2011). Changes in flying fox ecology associated with anthropogenic stressors including climate change, habitat fragmentation and urbanisation, have been proposed as drivers of HeV disease dynamics (Bradley and Altizer 2007; Plowright et al. 2011; Dietrich et al. 2015). These ultimate stressors are associated with proximate stressors such as nutritional stress, which are, in turn, overlaid on challenges such as the demands of reproduction (Plowright Field et al. 2008). Although experimental evidence is not available at this time, a leading hypothesis is that physiological stress alters bat immune function and increases the rate of virion shedding (Plowright et al. 2008a, 2008b). Hence, physiological stress may be one of the important factors influencing HeV emergence and outbreaks.

Currently McMichael et al. (2014) are conducting parallel investigations into glucocorticoid metabolites and HeV dynamics. This valuable information on the relationship between physiological stress in bats and HeV will inform policy and management of flying fox populations. The potential effects of stress to flying foxes on HeV spill-over has been discussed at a policy and legislative level in Australia and, on these grounds, highly disruptive methods employed overseas for ‘bat control’, such as culling (Florens 2012), are now banned in some Australian jurisdictions (Degeling and Kerridge 2013). However, stressful management interventions for ‘problem’ flying fox populations continue to be applied in Australia. For example, aversive stimuli such as noise cannons are used sporadically to drive bats away from urban centres where people complain about noise, smell and damage to gardens (Degeling and Kerridge 2013). Information about significant stressors associated with HeV virion shedding would inform cost–benefit evaluation of disruptive management approaches and would be a valuable resource on which to formulate public health advice.

Hendra virus provides a contemporary example of how the relationship between physiological stress and disease dynamics can inform responsible, evidence-based One Health and wildlife-conservation policy and management. More broadly, the above case study may have implications for other emerging viral diseases for which bats act as reservoir hosts, including Ebola (Calisher et al. 2006; Plowright et al. 2008b, 2014; Smith and Wang 2013).
Conclusions

Despite suggestions that stress plays an important role in disease dynamics, this remains a neglected area in wildlife research. Rhyan and Spraker (2010) described how mounting stressors may profoundly change disease-transmission cycles using the analogy of ‘adding bags of sand to a rowboat until it sinks’. Understanding the dynamics of stress and disease in wildlife will help us keep healthy biological systems ‘afloat’ by identifying novel management targets and assisting priority setting and policy decisions.

Wider application of stress physiology and diagnostic tools to characterise links between stress and disease in wildlife will benefit One Health and biodiversity conservation. Greater collaboration between human and animal health experts, conservation researchers, comparative physiologists and disease ecologists will enable further progress in understanding the stress–disease synergism to prevent the loss of iconic species and reduce the risk of contemporary and emerging infectious diseases.

We propose a defined approach using parallel glucocorticoid parameters and infection indices to investigate stress and disease in wildlife. This approach can be applied to examine the influence of physiological stress associated with key anthropogenic stressors, including climate change, habitat disturbance and management interventions, on disease dynamics. It is time to fully incorporate stress and wildlife disease in the overall management of environmental, animal and human health.

Acknowledgements

This work was supported by the Australian Academy of Science Margaret Middleton Foundation, Holsworth Wildlife Research Endowment, Foundation for National Parks and Wildlife, Murdoch University School of Veterinary and Life Sciences and Australian Society for Parasitology. S. G. was supported by an Australian Research Council DECRA (DE120101470). S. H. was supported by an Australian Postgraduate Award with a Murdoch University Strategic Top-up Scholarship. The authors
thank the Murdoch University Design Studio for assistance with figures and the reviewers for their feedback.

References


Fig. 1. Factors that may influence the response of wildlife to stress and disease. Stress, host, parasite and environment factors may influence the response of wildlife to stress and disease.
**Fig. 2.** Stress and disease in One Health. Conceptual flow diagram of how the physiological relationship between stress and disease may shape the role of wildlife in the transmission of emerging infectious disease. (1) Stress to wildlife can influence infection dynamics and wildlife may also be a source of stress. (2) The environment can be a source of stress and stress can also influence the hosts’ interaction with the environment. (3) Pathogens can act as a stress and stress can also affect infection dynamics. (4) Environmental factors may influence the stress and disease response of wildlife and wildlife may also contribute to environmental change. (5) Pathogens may be shed into the environment and environmental factors can facilitate persistence of pathogens. (6) Humans can be a source of environmental stress and environmental factors can also influence human infection dynamics. (7) Pathogens may affect the whole wildlife host stress response and stress may exacerbate infection. (8) Some pathogens can infect humans, domestic hosts and wildlife. (9) Interactions among humans, domestic hosts and wildlife can facilitate disease transmission. (10) Humans and domestic animals may be a source of stress for wildlife but may also be susceptible to many of the same stressors. The heavier dashed lines and related bolded text represent priority interactions and/or influences.