AN ABSTRACT OF THE DISSERTATION OF

Rhea Hanselmann for the degree of Doctor of Philosophy in Zoology presented on August 16, 2016

Title: Wildlife Health in Managed Forests: Immunity and Infectious Diseases in Wild Rodents of Oregon.

Abstract approved: _____
Anna E. Jolles

With continual and worldwide human population growth, our impact on the natural environment expands and intensifies every day. We consume natural resources, burn fossil fuels, and release toxic compounds into the air, water, and earth. We build roads that fragment the landscape, construct new settlements, and develop agricultural lands in previously undisturbed areas. And, we introduce non-native species, which compete with and/or prey on native ones. Our actions change the composition of ecosystems by effacing natural environments and decimating plant and animal populations. We have reached a time of unprecedented anthropogenic environmental change. And, while we recognize, and work feverishly to mitigate, countless consequences of our actions, we still lack a profound understanding of just as many of the corollaries of the environmental changes we provoke.

One thing we do know is that human-induced changes in environmental conditions can affect health – from individual organisms, to plant and animal populations, all the way to the level of the ecosystem. Yet, the mechanisms underlying such adverse health outcomes are only partially understood. For instance, we know that alterations in the structure of plant and animal communities, the distribution and demographics of populations, and the abundance of individuals can influence the emergence or re-emergence of infectious diseases. Which species are present in a community, where, when, and in what numbers can all determine the dynamics of pathogens, lead to disease outbreaks, and provide opportunities for spillover into new species. However, given the many environmental-, population-, and organism-level

factors involved, and the complexity by which these variables interact, detecting and predicting the ultimate consequences for the health of animal, including human, populations remains difficult.

Wild animals play important roles in numerous infectious disease cycles, many of which are shared with humans. Considering this and the well-documented effects that human activity can have on wildlife populations, studying the impacts of anthropogenic environmental change on health in wildlife is highly relevant. To understand how human-induced environmental changes affect wildlife health and to make predictions about potential regional or even global consequences for the dynamics of infectious diseases, however, we first need to understand patterns at a local scale.

Here, I describe variation in immune function in captive and wild rodent species native to managed forests in northwestern Oregon, and examine how intensive forest management practices affect these and other physiological processes, and the prevalence of infectious diseases, in a large-scale field experiment. In Chapter 2 of this dissertation, I present baseline data on simple immune parameters in an iconic inhabitant of old-growth forests in the Pacific Northwest, the red tree vole (*Arborimus longicaudus*). I show that both body condition and age are important for immune defenses in this species. Translating these findings to wild populations leads me to predict that degradation of habitat may affect red tree voles not only at the population scale, as is currently the case, but that less obvious consequences for the health of individuals surviving in disturbed or suboptimal habitat are also possible. It is important, therefore, that efforts to conserve this species consider adverse effects of present forest management practices on red tree vole health, as potentially increased disease susceptibility could have detrimental outcomes for this species.

In Chapters 3 and 4, I took advantage of a rare and large-scale experiment to test my predictions regarding the negative consequences of habitat degradation for individual animals in more ubiquitous rodent species known for their resilience to environmental disturbance. I investigated the effects of intensive forest management on stress, health, and immunity (Chapter 3), and on the prevalence of infectious

diseases transmissible to humans (Chapter 4) in deer mice (*Peromyscus maniculatus*), Townsend chipmunks (*Tamias townsendii*), and creeping voles (*Microtus oregoni*) inhabiting managed forest plots in northwestern Oregon. The experimental design employed allowed me to test the effect of regionally representative forest management practices on health and disease outcomes with important implications for public health.

In Chapter 3, I present results which suggest that intensive forest management can have complex, but highly context-dependent effects on the health of wild deer mice. Intensive forest management can shape animals' condition and reproductive activity, increase levels of stress hormone, and stimulate some but depress other immune responses. However, deer mice are only able to respond to the extreme stressor of this disturbance when underlying environmental conditions are favorable. When inhabiting inherently harsh habitat, mice appear unable to cope with additional disturbance imposed by intensive forest management, and only the fittest mice survive.

Finally, in Chapter 4, I identify moderate prevalence of two important and potentially fatal human infections in rodents inhabiting managed forests in northwestern Oregon. In deer mouse populations, Sin Nombre virus was clustered spatially, and prevalence varied between years. But, in the focus of highest infection, the proportion of infected mice, albeit low, appeared to increase with intensity of forest management. For Leptospirosis, I found a similar pattern in creeping voles, but did not observe an association between infection prevalence and forest management in deer mice or chipmunks. I conclude that forest management may drive infectious disease patterns, but that the direction and magnitude of such effects depends on the host-pathogen system.

Taken together, my findings indicate that wild animal health can suffer from declines in habitat quality associated with forest management. For a near-threatened species such as the red tree vole, decreases in the availability of food and nesting habitat have the potential to change susceptibility to infection, which could facilitate disease invasion and further threaten populations. For wild animals that serve as

reservoirs for human infections, especially abundant and apparently resilient species, impaired health can drive the dynamics of pathogens and increase the risk of transmission to humans and other animals. Although many more questions remain, my work contributes to our understanding of the effects of anthropogenic environmental change for wildlife and human health.

Wildlife Health in Managed Forests: Immunity and Infectious Diseases in Wild Rodents of Oregon

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APPROVED:

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Dean of the Graduate School

I understand that my dissertation will become part of the permanent collection of Oregon State University libraries. My signature below authorizes release of my dissertation to any reader upon request.

_____

Rhea Hanselmann, Author

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CONTRIBUTION OF AUTHORS

Rhea Hanselmann conceptualized studies, formulated research hypotheses and objectives, designed and refined methods, acquired financial support, managed, coordinated, and carried out data collection, analyzed, and interpreted results, and wrote the first draft of all manuscripts presented herein.

Megan Cummings collected blood samples from red tree voles, performed all white blood cell counts presented in Chapter 2, drafted parts of and provided comments on earlier drafts of Chapter 2.

Laurie J. Dizney contributed to data collection, interpretation of results, and provided critical review of and commentary on the original and subsequent drafts of the manuscripts presented as Chapters 3 and 4.

Eric Forsman shared subject matter expertise, unpublished data on red tree voles, and the map used in Figure 2.2., and also advised and commented on earlier drafts of the manuscript presented in Chapter 2.

Erin E. Gorsich advised on and assisted with statistical analyses, designed and implemented computer code for analyses, and assisted with interpretation of statistical results for the manuscripts presented as Chapters 3 and 4.

Anna E. Jolles served as primary dissertation adviser, advised on and assisted with concept development and study design, acquired funding, assisted with interpretation of results, and provided critical review of and commentary on the original and subsequent drafts of all manuscripts presented herein (Chapter 2-4).

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DEDICATION

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Chapter 1 – General Introduction

As human populations increase so does our impact on the environment. Through expansion of human settlements and increasing demands for food and resources we convert natural areas to meet our needs, fragmenting, simplifying, and effacing ecosystems, and eventually disturbing them to the point of making habitats unlivable for many species (Pimm et al. 1995; Vitousek et al. 1997; Chapin III et al. 2000; Dirzo et al. 2014). Habitat loss due to human actions has severely impacted numerous wild animals and is responsible for the extinction of some species, while threatening others with the same fate (Dirzo et al. 2014). However, anthropogenic environmental change can also have less obvious consequences for individuals and populations of wildlife that survive in disturbed habitats, consequences that even reach domestic animals and humans, but are more difficult to detect and predict (Acevedo-Whitehouse and Duffus 2009; Brearley et al. 2012).

By diminishing habitat quality and changing community assembly, environmental disturbance can alter the species composition, abundance, and population structure of an ecosystem (Sullivan and Boateng 1996; Dirzo et al. 2014). Changes in wildlife populations at the landscape-level can influence disease risk and result in dilution or amplification of infectious disease prevalence (Keesing et al. 2010; Salkeld et al. 2013; Civitello et al. 2015). For instance, low mammal community diversity has been shown to increase the likelihood of ticks feeding on white footed mice (*Peromyscus leucopus*). Since mice are highly competent reservoir hosts for *Borrelia burgdorferi*, the causative agent of human Lyme disease, ticks are more likely to become infected with the bacterium and transmit the disease to other animals, including humans. Therefore, low species diversity in Lyme endemic ecosystems can increase the risk for humans and other animals of acquiring disease (Ostfeld and Keesing 2000). Similar observations have been made for other pathogens, including West Nile virus (WNV) on the East Coast (Ezenwa et al. 2006) and Sin Nombre virus in the Pacific Northwest (Dizney and Ruedas 2009) of the United States. But, depending on the pathogen, the particular host species present in a system, and their community-wide inter- and intra-specific interactions, increasing species diversity can

also amplify disease prevalence (Clay et al. 2009a; Salkeld et al. 2013).

Besides altering the composition, abundance, and/or diversity of species in an ecosystem, anthropogenic environmental change can also adversely affect physiological processes that allow animals to respond to changes in their environment (Acevedo-Whitehouse and Duffus 2009; Stephen 2014). For example, having to cope with poor habitat quality can stress wild animals, either directly via human presence or intermittent activities that disrupt normal behaviors, or indirectly via changes in the availability of food sources, opportunities for shelter, or encountering mates (reviewed in Acevedo-Whitehouse and Duffus 2009; French et al. 2010). Stress, can lead to redistribution of energy reserves and alter immune function (Dhabhar et al. 1995; Dhabhar 1998, 2008; Braude et al. 1999). Suppression of protective immune mechanisms, or upregulation of inflammatory defenses can change an individual's susceptibility to disease and influence disease transmission at the population scale (Patz et al. 2000; Daszak et al. 2001; Bartolomucci 2007; Bradley and Altizer 2007; Aguirre and Tabor 2008; Acevedo-Whitehouse and Duffus 2009).

Non-specific diseases, which might include those with multiple potential hosts such as zoonoses (diseases transmitted from animals to humans), have been predicted to increase with environmental disturbance. However, the direction of relationships between environmental stressors and disease transmission have also been shown to be extremely variable and difficult to anticipate (Lafferty and Holt 2003; Brearley et al. 2012). Despite the obvious significance of these processes, both for the conservation of wildlife species threatened by habitat loss as well as for human and domestic animal health, the underlying physiological mechanisms, especially in wildlife systems, are only partially understood (Acevedo-Whitehouse and Duffus 2009). This lack of knowledge, and the complexity and unpredictability of the interactions between human-induced environmental change, wildlife health, and disease, underline the need to investigate the physiology and immune defenses in wildlife inhabiting disturbed environments. Furthermore, focusing on wildlife species that have the potential for being important disease hosts and describing the ecology of relevant infections in altered ecosystems is essential for understanding the potential

consequences of anthropogenic environmental change for animal and human health (Daszak et al. 2000; Patz et al. 2000).

The goal of my dissertation research was to examine how regionally relevant anthropogenic environmental change influences health and disease in wild rodents inhabiting managed forest ecosystems in northwestern Oregon. In my first data chapter (Chapter 2), I investigated animal-level factors that shape immune function in red tree voles (*Arborimus longicaudus*). Red tree voles are an iconic, near-threatened species endemic to old growth forests in northwestern California and western Oregon (Forsman and Swingle 2005). Especially in northwestern Oregon, red tree vole populations have been severely affected by habitat loss secondary to conversion of old growth forests to intensively managed young and minimally diverse stands (Forsman et al. In press). In recent years, much research has been focused on documenting red tree vole populations, examining their role in the forest ecosystem, and understanding how habitat loss affects this species (reviewed in Forsman et al. In press). And, results from this body of work have shaped considerations for the preservation of declining old growth habitat and informed forest management policy (United States Fish and Wildlife Service 2011).

However, beyond merely documenting presence/absence of red tree voles, recognizing potential effects of changing habitat quality on animals' physiology contributes data important for the conservation of this species. Taking advantage of a rare opportunity to work with red tree voles in captivity, I measured basic immune parameters in animals across a wide range of ages, and examined how age, sex, and condition shapes the number and distribution of white blood cells and the ability of plasma to kill bacteria *in vitro*. I found that fatter, and potentially older animals appeared to shift their immune responses towards immediately deployable innate defenses. For a short-lived species such as the tree vole, innate immunity is critical for preventing infection, maximizing fitness, and ensuring survival (Lee 2006; Previtali et al. 2012). The data collected from these captive animals shed light onto how this species might respond to habitat quality diminished by intensive forest management in the wild, and pave the way for future work on red tree vole health. Impaired health,

altered susceptibility to infection, and subsequent invasion of disease could present additional threats not previously considered in conservation efforts for this species.

The results of my work on red tree voles allowed me to understand the importance of animal-level factors in shaping immune function in rodents and informed data analyses on health and immune measures researched in my subsequent chapters. In Chapters 3 and 4, I investigated the effect of intensive forest management on health and disease in three rodent species pervasive in forests of northwestern Oregon. For this work, I made use of a unique experimental set-up located in the Oregon coastal mountain range consisting of replicated, large forest plots managed at different levels of intensity representative of current industrial practices.

Intensive forest management (IFM) is a regionally widespread and severe type of anthropogenic environmental disturbance. In northwestern Oregon, most of the old-growth forest habitat has been converted to intensively managed stands dominated by fast growing Douglas fir (*Pseudotsuga menziesii*) trees (Swanson and Franklin 1992). Management practices in this region include clearcutting and substantive application of herbicide mixtures to prevent early successional growth of broadleaf vegetation (Tatum 2004; Wagner et al. 2004). The impact of IFM on wildlife populations and species distribution has been researched extensively. For instance, intensive herbicide application was shown to decrease songbird diversity and abundance on clearcut and intensively sprayed plots relative to clearcut unsprayed plots (Betts et al. 2013). Studies examining the effects of clearcutting and herbicide application on small mammal communities, however, show conflicting results. Abundance of some species of rodents decreased on clearcut herbicide-treated plots (Santillo et al. 1989), but rodent diversity and abundance remained unchanged in response to clearcutting and spraying in other systems (Sullivan et al. 1997; Cole et al. 1998).

For highly mobile species, such as birds, disturbance caused by logging activity can result in animals emigrating to less disturbed areas (Betts et al. 2013). And, once forest structure has been restored and resources have regenerated, these same species may return to their original habitats with little measurable long-term impact on their populations. Also, the chemicals applied to clearcuts appear not be

directly toxic for most animals (Giesy et al. 2000; McComb et al. 2008) and are thought to have no direct effects on individuals or populations of wild animals (Tatum 2004; Wagner et al. 2004). However, the poor habitat quality that results from clearcutting and intensive herbicide use is likely to adversely impact the health of minimally mobile wildlife species with small home ranges that persist in managed forest ecosystems. Yet, information on the impact of intensive forest management strategies on wildlife health remains scant (Voutilainen et al. 2012).

Rodents are highly adaptable to changes in their environment, often persist in disturbed habitats, and frequently demonstrate high site fidelity (Maser et al. 1981; Maser 1998; Wood et al. 2010). Rodents are also important pathogen carriers and play a part in many infectious disease cycles (Mills and Childs 1998; Meerburg et al. 2009). These characteristics, along with their ubiquitous distribution in our research sites and the relative logistical ease with which they are sampled, made them excellent model organisms in which to study the impacts of intensive forest management on wildlife health and infectious disease prevalence (Sánchez-Chardi et al. 2007; Meerburg et al. 2009).

For my research on intensive forest management, I was interested in exploring two main relationships: 1) the association between IFM and rodent health, and 2) the link between IFM and infectious disease prevalence. To this end, I trapped wild deer mice (*Peromyscus maniculatus*), Townsend chipmunks (*Tamias townsendii*), and creeping voles (*Microtus oregoni*) on forest plots managed at three levels of intensity and located in two forestry districts differing in their underlying environmental conditions. In Chapter 3, I focused on stress, health, and immunity of wild deer mice. I found a detectable, but context-dependent effect of the level of disturbance on deer mouse health. Animals inhabiting plots located in an area of relatively mild weather conditions were able to respond to the stressors associated with poor habitat quality secondary to forest management. In contrast, mice already contending with harsher environmental conditions appeared unable to mount physiological responses to the additional disturbance of forest management. These results suggest that, when human disturbance is the only major stressor, wild animals may be able to adapt to or cope

with changes to their habitat. But, when human activity represents one of many stressors, which is likely to be the norm for animals living in the wild, the consequences for health and, potentially disease susceptibility, could be dire.

In light of rapidly changing environmental and climatic conditions worldwide, it is essential to understand the behavior of infectious and especially zoonotic pathogens in natural systems, and to examine the influence of local environmental disturbance on disease patterns (Gubler et al. 2001). Knowing the prevalence and dynamics of disease in wildlife populations across a range of habitats can inform predictions about how pathogens may react to ongoing environmental change on a regional and even global scale with the ultimate aim of assessing the risk for wildlife and human health.

In Chapter 4, I examined whether disease prevalence was related to the level of forest management. For this work, I focused on three important and potentially fatal zoonotic pathogens known to be carried by rodents (Mills and Childs 1998; Meerburg et al. 2009), but not previously described in the forests of northwestern Oregon. Specifically, I estimated the prevalence of Sin Nombre virus (SNV) in deer mice, determined the prevalence of Leptospirosis in the three focal rodent species, and tested opportunistically collected rodent fleas for *Yersinia pestis*, the causative agent of Plague.

Sin Nombre virus, is a directly-transmitted pathogen relatively specific to its primary deer mouse host mouse that can cause life-threatening disease in humans (Childs et al. 1994). *Leptospira interrogans* causes one of the most widespread zoonoses in the world. This generalist bacterium is harbored by numerous wild and domestic animal hosts, all of which can play a role in transmitting infection directly or via contaminated soil and water among host animals and to humans (Evangelista and Coburn 2010). Finally, *Yersinia pestis* is a deadly generalist bacterium that can be transmitted directly between hosts, but most commonly causes disease when infected flea vectors bite susceptible species, including humans (Perry and Fetherston 1997; Wimsatt and Biggins 2009).

Although plague has been described in parts of Oregon, I found no evidence of

the bacterium in any of the fleas tested. I did, however, identify a distinct spatially and temporally defined focus of SNV infection in deer mice. And, within this focus, I observed disease prevalence to increase with forest management intensity, albeit not significantly. Leptospirosis was present in all three rodent species, but only in creeping voles was infection positively associated with forest management. These results appear to indicate that forest management may drive disease patterns, but that the direction and magnitude of effects depend on the host-pathogen system. The finding of two important zoonoses not previously described in rodents in my study area is also relevant for public health. Forest workers, hunters, and outdoor recreationists frequent the managed forests of northwestern Oregon, and the public must be made aware of the potential risk of disease to them and, for Leptospirosis, to their pets.

In conclusion, I examined the link between environmental change and wild animal health, and show that human activity can have important consequences for health and disease. I report on animal-level variation in immunity in a near-threatened species of rodent and discuss the potential implications of my findings for the conservation of this species in the wild. I then demonstrate a context-dependent effect of a severe type of intensive forest management on multiple measures of wildlife health, and also describe how disease prevalence in wild rodents may be shaped by disturbance. My results suggest that, when making wildlife and land management decisions and drafting policy, it is important to consider how habitat quality can shape intrinsic, animal-level factors, which, in turn, can influence immune defenses and alter susceptibility to disease. Of course, several additional questions arise from this work. The most urgent step is to examine how animal health measures affected by forest management translate to infection risk in the individual, and to determine whether animal health drives disease patterns observed at the population scale. Nonetheless, the findings of my research contribute a piece to the puzzle that is understanding the effects of anthropogenic environmental change on wildlife health and the implications for infectious disease dynamics.

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Chapter 2 – Condition and age may drive immunity in red tree voles. Is fatter and older better?

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ABSTRACT

The red tree vole (*Arborimus longicaudus*) is an iconic inhabitant of coniferous forests in western Oregon and northwestern California. There is concern that the species may be declining as a result of the systematic conversion of old forest to intensively managed young forest throughout large parts of its range. Despite these fears, the effects of environmental disturbance on the health of red tree voles has not been documented. Consequences for immunity are of particular interest since impaired immune defenses can increase susceptibility to infections and influence both population and disease dynamics. We used 46 captive red tree voles to gain a basic understanding of this species' immune system. We examined innate and adaptive constitutive immunity using total and differential white blood cell counts, and quantified innate induced immune function using a spectrophotometric plasma bacterial killing assay. We analyzed associations between immune parameters and body condition, age, and sex. Fatter animals had more innate white blood cells (neutrophils and eosinophils), but fewer adaptive lymphocytes. Innate immune function was also slightly stronger in older animals, while lymphocyte proportions decreased with age. Thus, fatter, and possibly older, animals may shift immune investment towards innate defenses, preparing them for fast, non-specific responses to infection. We hypothesize that loss of habitat may decrease body condition and longevity in wild red tree voles. Thin and young individuals may be less able to devote sparse resources to innate immune defenses, but neglecting this investment could make them more vulnerable to infections. These findings underline the importance of preserving preferred red tree vole forest habitat, and pave the way for studies examining health and infection risks of wild red tree voles in habitats of differing quality.

INTRODUCTION

The red tree vole (*Arborimus longicaudus*, subfamily Microtinae) is a highly specialized inhabitant of mature and old-growth conifer forests in western Oregon and northwestern California (Forsman et al. In press, 2004a; Marks-Fife 2016; Figure 1).

A. longicaudus is a solitary, arboreal, and nocturnal rodent that exhibits unique dietary and habitat adaptations and has been described as "one of the most specialized arboreal mammals in the world" (Maser 1998). Red tree voles are one of few documented animals using conifer needles as a principal food source (Forsman et al. In press; Benson and Borell 1931; Zahler 1996). By stripping away the unpalatable, terpenoid-rich resin ducts, red tree voles are able to consume needles of Douglas fir (*Pseudotsuga menziesii*), grand fir (*Abies grandis*), Sitka spruce (*Picea sitchensis*), and western hemlock *(Tsuga heterophylla*; (Taylor 1915; Walker 1930; Benson and Borell 1931; Kelsey et al. 2009). Discarded resin ducts are used in the construction of large, chambered nests in the forest canopy (Taylor 1915; Maser 1966).

Red tree voles play an important role in old-growth forest ecosystems. Their nests provide habitat for numerous other wildlife species, including other small mammals, and several species of amphibians and invertebrates (Brown 1965; Swingle 2005; Forsman and Swingle 2007). Furthermore, red tree voles are one of the most common prey items consumed by the threatened northern spotted owl (*Strix occidentalis caurina*) – another iconic specialist endemic to old forests in western Oregon and northwest California (Maser 1965; Forsman et al. 2004a; b).

The red tree vole's specialized habitat requirements, restricted geographic range, and limited ability to disperse through unsuitable habitat render it particularly vulnerable to disturbance (Howell 1926; Carey 1989; Swingle 2005). Over a century of logging has removed much of the old forest habitat on which this species depends and appears to have led to declines in red tree vole populations throughout their geographic range. Particularly affected are populations in northwestern Oregon where most forests are privately- or state-owned and managed. (Forsman et al. In press; Forsman and Swingle 2005; Dunk and Hawley 2009; Figure 2). Currently, red tree voles are listed as near threatened by the International Union for Conservation of Nature (Linzey and NatureServe (Scheuering, E. and Hammerson, G.) 2008), and numerous populations appear on the U.S. Fish and Wildlife Service's 2011 Federal List of Candidate Species for consideration under the Endangered Species Act. The primary threat thought to be affecting red tree voles is the loss of old forest habitat due

to timber harvest and wildfires (Forsman and Swingle 2005). However, there is also concern that the recent range expansion of the barred owl (*Strix varia*) could result in increased predation pressure on tree voles (J. K. Swingle and E. D. Forsman 2015, pers. comm.).

While evidence suggests a negative impact of disturbance and gradual habitat loss on red tree voles at the population scale (Forsman et al. In press; Aubry et al. 1991; Martin and McComb 2002), it is equally likely that the health of individuals is compromised (Deem et al. 2001). Yet, the consequences of habitat loss for the health and immunity of individual red tree voles have not been examined. If the deleterious effects of disturbance extend to the immune system, exposure to infectious organisms – even if minimally virulent under ideal conditions – could have potentially detrimental consequences for red tree vole populations. Considering that habitat loss may lead to increased competition, animal-animal contact, and thereby facilitate parasite exposure, having a functional immune system is of particular importance (Smith et al. 2009).

Anthropogenic environmental disturbance, such as logging, can depress wildlife populations (e.g. (Carey 2000) and compromise the health of individual animals (Acevedo-Whitehouse and Duffus 2009). Loss and fragmentation of habitat can prevent dispersal, intensify intra- and inter-species competition, and reduce overall resource availability (Diffendorfer et al. 1995; Fischer and Lindenmayer 2007). Increased time spent foraging and competing for essential nutrients or habitat uses energy that could otherwise be invested in reproduction (Frid and Dill 2002). While obvious indicators of fitness, such as growth and reproductive output may be affected, the ability to respond to infections by mounting an immune response can also suffer from resource restriction (Demas and Nelson 1998a; Klasing 1998; Martin et al. 2008; Kusumoto 2009).

The vertebrate immune system defends against infectious insults and is generally divided into innate and adaptive arms. Innate defenses include molecular (e.g. complement protein) and cellular (e.g. neutrophils) mechanisms that act rapidly against a multitude of infectious organisms. In contrast, adaptive immunity (e.g.

lymphocytes) is slower to develop, but provides highly specific, long-term protection (e.g. antibodies) that is especially useful against repeated exposure to the same organisms (Kennedy 2010). Studies examining immune investment of animals along a life history continuum posit that short-lived, fast-paced species such as microtine rodents are likely to preferentially allocate resources to general, immediately available innate defenses, as opposed to relying on the slower protection conferred by the adaptive immune system (Sheldon and Verhulst 1996; Lochmiller and Deerenberg 2000; Previtali et al. 2012). Red tree voles reach reproductive maturity within a few months, have a short gestation period (≈ 28 days), produce multiple litters per season, have low annual survival rates in the wild, and, in captivity, rarely live past 2 years (Clifton 1960; Hamilton 1962; Swingle et al. 2010). Based on these life history characteristics, we expect immune investment in red tree voles to focus on innate mechanisms.

The ability to develop and maintain immune defenses is also influenced by extrinsic, environmental factors that result in stress or diminished nutritional condition (Demas and Nelson 1998a; Klasing 1998; Lochmiller and Deerenberg 2000; Kusumoto 2009). Animals facing a stressor such as poor habitat quality, heightened competition, or increased predation rates may compensate, for instance by changing their foraging behavior (Dill 1983; Kie et al. 1991; Alanärä et al. 2001) or by suppressing or delaying breeding (Ylönen and Ronkainen 1994; Eccard and Ylönen 2001; Haapakoski et al. 2012). However, prolonged exposure to a stressor, or exposure to multiple stressors may exceed the animal's ability to cope, resulting in a negative energy balance (Marcogliese and Pietrock 2011; Côté et al. 2016). The combined effect of multiple environmental stressors is an especially important consideration for a vulnerable species such as the red tree vole that is already contending with the repercussions of anthropogenic changes to its environment (Huff et al. 1992; Swingle et al. 2010). As a result, when exposed to an infectious disease, red tree voles in disturbed habitats may not be in a position to mount a protective immune response. Parasites and pathogens that do not pose a problem for the animals

under more ideal conditions may thus have significant effects on host health and fitness.

Knowledge of red tree vole immunology is nonexistent. Consequently, we have no way of predicting the implications of potential parasite exposure, emergence, or invasion on this species. Here, we take a first step towards filling this knowledge gap by examining basic immune measures in a well-characterized captive population of red tree voles. As a second step, we investigate covariation in immunity with body condition, age, and sex.

METHODS

Study population and sample collection.—Study animals were drawn from captive red tree voles housed at Oregon State University's Research Animal Isolation Laboratory. These animals were part of a study examining dental ontogeny in red tree voles (Marks-Fife 2016). All animals were housed and reared in a temperature- and light-controlled environment simulating natural conditions. Freshly harvested Douglas fir branches were supplied daily. Tree voles were humanely euthanized at pre-determined dates spanning a nine-month period at ages between 60 and 480 days.

Prior to euthanasia, subjects were anesthetized to a deep surgical plane using isoflurane delivered in 100% oxygen (Tec 3 vaporizer, Vaporizer Sales & Service). Animals were exsanguinated via cardiac puncture with a 25-gauge needle and 1-ml syringe coated with sodium heparin, and whole blood samples were collected into lithium heparin-coated microtubes (Becton Dickinson, Product # 365958).

All animal procedures followed American Society of Mammalogists guidelines (Sikes 2016) and were approved by the Institutional Animal Care and Use Committee at Oregon State University (Animal Care and Use Protocol # 4406).

White blood cell counts.—To examine constitutive innate and adaptive immunity, we performed manual total and differential white blood cell counts using standard hematological methods (Pilny 2008). At the time of sample collection, blood smears were prepared using one drop of whole blood obtained directly from the syringe. Smears were allowed to air dry and were stored at room temperature until

staining with a commercially available Romanofsky stain (Diff-Quik™, Dade Behring, Product # B4132-1A). Differential counts were performed by counting 100 white blood cells in the monolayer of the blood smear using a compound microscope at 1000X magnification (oil immersion) and determining the percentage of each of five cell types, including predominantly innate (neutrophils, monocytes, eosinophils and basophils) and adaptive (lymphocytes) circulating immune cells.

The total number of circulating white blood cells per microliter of whole blood was estimated using a commercially available acetate red blood cell lysis buffer with gentian violet white blood cell stain (Leuko-TIC®, Bioanalytic, Product # 004013-0007), which we adapted for use with small blood volumes. Briefly, 5 µl of whole blood was transferred to 95 µl of Leuko-TIC® buffer solution, the 1:20 mixture was inverted and allowed to sit at room temperature for a minimum of 30 seconds. Both chambers of a Neubauer counting chamber (Hausser Scientific, Product # 3500) were filled with 10 µl of the diluted blood sample and, for each chamber, all cells in the 9 large squares were counted using 100X magnification. Total white blood cell counts per microliter of whole blood were computed by multiplying the average number of cells in the two chambers by the dilution factor (20), and dividing by the product of the number of squares counted (9) and each square's volume (0.1 µl; Voigt and Swist 2011). Finally, for each of the five cell types identified on the blood smear, absolute counts per microliter of blood were estimated by multiplying the percent cell count by the total white blood cell count.

Plasma bactericidal ability.—As a measure of induced innate immune function, we quantified the bactericidal ability of plasma against a non-pathogenic, gentamicin-resistant Dh5a strain of *E. coli* using a spectrophotometric bacterial killing assay (BKA) adapted from French and Nueman-Lee (2012), which we optimized for red tree voles. In this assay, the inhibition of bacterial growth after reacting bacteria with plasma is compared to uninhibited bacterial growth in control wells, and is used to compute a proportional bacterial killing ability for each sample.

To conduct the BKA, whole blood samples were centrifuged at 2000 x g (VWR, Product # 93000-196) for 20 minutes to separate plasma from the red blood

cell and platelet pellet. Plasma was transferred to freezer vials (Corning®, Product # 430487) and stored at -80 °C until use. At the time of assay, samples were thawed at room temperature and all reagents were pre-warmed to 37 °C. Using a 96-well round bottom plate (Becton Dickinson, Product #351177), 25 µl of plasma was diluted with 25 µl sterile Phosphate Buffered Saline (PBS) in duplicate (2 wells/animal). A known number of colony forming units of *E. coli* (150–200 CFU) suspended in 30 µl of PBS was added to all wells except negative control wells. Positive control wells contained 50 µl PBS and *E. coli*, and negative control wells contained PBS only (80 µl). The plate was incubated on a MaxQ™ 4450 shaking incubator (37 °C at 175 rpm; Thermo Scientific, Model # 4333) for 30 minutes allowing time for the plasma to react with bacteria. Finally, 100 µl of sterile Tryptic Soy Broth (Hardy Diagnostics, Product # C7141) prepared with gentamicin (VWR, Product # 97062-974) at 1:1000 to prevent growth of bacterial contaminants was added to all wells, and background absorption was measured at 300 nm wavelength using an Epoch Microplate Spectrophotometer (Bio-Tek®). The plate was incubated at 37 °C and 175 rpm, and absorbance was re-measured at 24 hours. After subtracting the baseline (0-h) absorbance from the 24-h reading, bactericidal ability was calculated as follows: (mean positive control absorbance - mean sample absorbance)/mean positive control absorbance. This formula yielded the proportional decrease in bacterial growth (i.e. bacterial killing) produced by plasma compared to uninhibited growth in control wells (French and Neuman-Lee 2012).

Statistical analyses.—Study population demographics, including sex, age at sacrifice (days), mean body mass (g), and mean body length (snout to base of tail; mm) were summarized using descriptive statistics. For each animal, the residual of mass regressed against body length was used as a measure of body condition (Schulte-Hostedde et al. 2005). To examine covariation between sex, age, and growth, we first explored the effects of sex and age on mass, length, and condition using simple linear regression models. Further, to ensure that our study population was representative of wild red tree vole populations, we used a simple linear model to compare mass-length

residuals from our study animals to unpublished data available from wild-caught individuals (data provided by E. D. Forsman and J. K. Swingle February 2015).

We were interested in knowing if immune parameters differed between male and female voles, were affected by age, or changed with body condition. To this end, we constructed separate multiple linear regression models with total and absolute white blood cell counts, proportions (percent cell type divided by 100) of the five white blood cell types, and plasma BKA as response variables, and examined sex, age, and body condition as explanatory variables for each of these immune parameters. Total and absolute white blood cell numbers were log-transformed to meet normality and constant variance assumptions (Ives 2015). When examining absolute cell counts, we controlled for differences in the total number of white blood cells between animals by including total cell count in all models. Finally, for cell type proportions and BKA, we used a logit transformation appropriate for this type of non-Bernoulli proportion data (Warton and Hui 2011). We then examined the effect of removing each variable on model quality using Akaike's information criterion adjusted for small sample sizes (AICc). We reconstructed increasingly simpler models eliminating terms identified based on lower model AICc until removal of additional terms did not lower the information criterion any further. The model with the lowest AICc was chosen as the final model. The only exception to this was for eosinophil counts where the second-best model was chosen in order to retain total white blood cell counts in the model. All statistical analyses were performed using R versions 3.0.1. and 3.2.3. (R Development Core Team 2013, 2015).

RESULTS

Description of study population and dataset.—We used data from 46 red tree voles (21 males and 25 females) sacrificed between October 2013 and July 2014 (Table 2.1). Body mass and length increased linearly with age, but neither differed between male and female voles (Supporting Information S2.1a). Body condition (mass-length residual) was not affected by age or sex (Supporting Information S2.1a),

and did not differ between our captive study population and data obtained from 260 adult, wild-caught red tree voles (Supporting Information S2.1b).

White blood cell counts were performed for all 46 animals. Plasma samples of sufficient volume for measuring bactericidal ability were available for 32 individuals (16 males and 16 females). The final model for total white blood cells was the null model and we found neither condition nor age or sex to be associated with the total number of white blood cells (Supporting Information S2.2). The direction of effect of condition, age, and sex on each immune measure is summarized in Table 2.2.

Body condition influences white blood cell distribution.—On average, lymphocytes made up over 75% of circulating white blood cells and were the most abundant cell type observed in all of the 46 red tree voles in our population (Table 2.3). However, the proportion of lymphocytes decreased linearly as body condition increased, while controlling for age (logit(PropLym) vs. Condition: $\beta = -0.186$, $t_{2,43} = -3.99$, $P = 0.0003$; Figure 3a). In contrast, the proportion of neutrophils and of eosinophils increased with increasing body condition (logit(PropNeu) vs. Condition: $\beta = 0.237$, $t_{1,44} = 3.60$, $P = 0.0008$; logit(PropEos) vs. Cond: $\beta = 0.173$, $t_{1,44} = 3.05$, $P = 0.004$; Figure 3a). While fatter animals did not appear to generate more white blood cells overall, instead, the absolute number of circulating neutrophils and eosinophils increased significantly, while absolute lymphocyte numbers decreased with body condition leading to the shift in cell proportions observed (log(Neu) vs. Condition: $\beta = 0.183$, $t_{3,42} = 3.08$, $P = 0.004$; log(Eos) vs. Condition: $\beta = 0.571$, $t_{2,43} = 3.06$, $P = 0.004$; log(Lym) vs. Condition: $\beta = -0.033$, $t_{3,42} = -3.11$, $P = 0.003$; Figure 3b). Monocyte numbers also trended upwards as condition increased, but this effect was not significant at $\alpha = 0.05$ (log(Mon) vs. Age: $\beta = 0.117$, $t_{2,43} = 1.93$, $P = 0.059$). No other effects of body condition on white blood cell counts or proportions were noted. And, since condition was not retained in the final model for BKA, we did not observe an association between condition and the ability of red tree vole plasma to inhibit bacterial growth (Supporting Information S2.2).

Age has weak effects on immunity.—The total number of white blood cells did not change with age. But, both the proportion and absolute number of lymphocytes

decreased slightly with increasing age, when condition was also accounted for (logit(PropLym) vs. Age: β = -0.002, $t_{1,43}$ = -2.71, P = 0.010; log(Lym) vs. Age: β = -0.0004, $t_{1,43}$ = -2.59, P = 0.013; Figure 4). In contrast, although not significant at α = 0.05, both the proportion of monocytes and bactericidal ability showed an upward trend, increasing with age (logit(PropMon) vs. Age: β = 0.0016, $t_{2,30}$ = 1.88, P = 0.067; logit(BKA) vs. Age: β = 0.0013, $t_{2,30}$ = 1.76, P = 0.089; Figure 4). We did not observe any other relationships between age and immune parameters.

Sex.—We did not find any differences between males and females in any of the immune measures examined and sex was not retained in any of the final models (Supporting Information S2.2).

DISCUSSION

Substantial evidence links anthropogenic environmental disturbance to declines in wildlife populations (Gibbons et al. 2000; Atkinson et al. 2008), but the animal-level mechanisms underlying these population-wide patterns are less commonly explored. This gap is especially apparent for species such as the red tree vole that have unusual behaviors (e.g. arboreality), unique dietary requirements, and a restricted geographic distribution. These characteristics make red tree voles not only vulnerable to disturbance events, but also logistically difficult to study. In light of such practical challenges, studies of captive animals can open windows into basic physiological mechanisms.

We took advantage of an existing captive population of red tree voles to examine the immune system – a physiological mechanism susceptible to environmental stressors and crucial for survival in the face of ubiquitous exposure to infectious organisms. Importantly, we observed links between immunity, body condition, and age. Our results suggest that body condition is an important driver of immunity in red tree voles. We observed a strong relationship between an animal's condition and the distribution of innate and adaptive white blood cells. Larger proportions of neutrophils and eosinophils were observed in 'fatter' animals, at the

cost of lymphocytes – the predominant circulating white blood cell type in this species.

Neutrophils are short-lived, non-specific, and fast-acting (minutes) effector cells of the innate immune system that combat invading microorganisms, specifically bacteria, fungi, and protozoa by directly engulfing them or by releasing proteins to break down organisms extracellularly. Eosinophils also play an integral role in the innate immune system. They too are relatively short-lived and fast-acting (hours) granulocytes, but are primarily responsible for fighting multicellular parasites such as helminths. Lymphocytes function primarily in the adaptive arm of the immune system. Lymphocytes recognize and destroy infected cells via cell- and antibody-mediated mechanisms. Although very specific and effective, the process of antigen recognition and development of immunological memory is relatively slow (weeks to months; (Kennedy 2010).

Increased proportions of neutrophils and eosinophils in red tree voles with higher body condition may indicate that, under favorable conditions when energetic resources are available, animals increase their investment in innate immune cells. Having elevated innate immunity can improve an individual's ability to respond rapidly to a wide range of infectious organisms. As a relatively short-lived species, red tree voles are unlikely to encounter the same pathogen multiple times during a lifetime. Therefore, for red tree voles and other short-lived animals with fast-paced life histories, having well-developed, innate defenses that are broadly protective and immediately deployable may carry a higher benefit than investing excess resources into the development and maintenance of adaptive immune defenses (Promislow and Harvey 1990; Lee 2006; Previtali et al. 2012).

Given that the body condition estimates from our study population were comparable to existing data from wild animals, we posit that the patterns we observed may parallel those seen in wild red tree voles. The potential negative impacts of habitat loss and fragmentation on animal health, especially on condition and immunity, could play a role in mediating ongoing red tree vole population declines in the wild.

While life history parameters such as size, longevity, age at sexual maturity, and reproductive output can shape the vertebrate immune system (Lee 2006; Ardia et al. 2011), stressors associated with environmental or seasonal changes can also disrupt or weaken immune defenses (Acevedo-Whitehouse and Duffus 2009). Specifically, a negative relationship between nutritional resource restriction and immunity has been demonstrated in multiple species in both wild and captive settings, and includes work in numerous small mammal systems (Demas and Nelson 1998b; Klasing 1998; Lochmiller and Deerenberg 2000; Brzęk and Konarzewski 2007; Houston et al. 2007; Kusumoto 2009). Several of these studies illustrate the additive impacts that multiple stressors, such as resource restriction combined with seasonal temperature fluctuations can have on the immune system (Demas and Nelson 1998b; Kusumoto 2009). These findings have direct relevance for red tree voles. For red tree voles in the wild, additive stressors on immune function may include increased time and energy spent locating suitable nesting trees in disturbed habitat and subsequently defending this habitat against competitors; decreased frequency or duration of foraging trips due to heightened risk of predation; or enhanced exposure to infectious diseases. All of these stressors, combined with recurring events such as breeding, harsh winter temperatures, or seasonal desiccation of conifer needles, their primary food and water source, can decrease the ability of red tree voles to store energy and thereby have the potential to weaken their immune system.

In addition to extrinsic stressors associated with loss of habitat, the possible effect of a low-energy diet of conifer needles on the immune system is another consideration specific to red tree voles. Metabolizable energy, protein, and lipids are essential for the development and maintenance of the immune system, and especially for mounting an immune response during infection (Scrimshaw 1977, 1991; Singh et al. 2013). At the same time, decreased activity and food intake are typical consequences of infection (Scrimshaw 1977, 1991; Lochmiller and Deerenberg 2000). Although red tree voles are adapted to their low-calorie diet, infectious disease could affect this species disproportionately, since sickness may interfere with harvesting and consuming the large quantities of needles required on a daily basis (Howell 1926;

Clifton 1960; Forsman et al. 2009). Therefore, dietary specialization may pose an additional challenge to red tree vole condition and immunity, and may present one more variable that increases this species' vulnerability to the cascading effects of disturbance.

In our captive study population, age appeared to influence immune patterns in red tree voles. Older animals had progressively fewer lymphocytes, while their plasma showed a stronger ability to kill bacteria *in vitro*. As mammals age, thymus involution and reduced production and release from the bone marrow decrease the number of circulating lymphocytes (Linton and Dorshkind 2004; Weng 2006; Pilny 2008). Considering the relatively short life expectancy of red tree voles (1-2 years) and the comparably long time span covered by this study (480 days), it is not surprising that we were able to observe a similar pattern of immunosenescence in our population. Opposing the decline in adaptive immunity, we also found some evidence that innate immune function may improve as red tree voles grow older. Upregulation of innate immune responses, especially of inflammatory mediators, with age has been reported in humans and laboratory animals, and may be the reason for the upward trend in bactericidal ability we observed in older red tree voles (Gomez et al. 2005).

Our finding that fatter and older animals preferentially invest in innate immune defenses has important implications for the conservation of red tree voles in the wild. When faced with poor habitat quality, animals likely struggle to maintain their nutritional condition and may have decreased survival, possibly yielding a 'thinner' and younger population. These surviving individuals may be unable to invest in innate immune defenses such as neutrophils, eosinophils, or plasma-mediated antibacterial strategies. Lacking these fast-acting defenses can make them more vulnerable to the effects of infectious diseases, which is especially concerning considering the amplified animal-animal contact and resulting exposure to infections that can occur as suitable habitat dwindles (e.g. Deem et al. 2001; Smith et al. 2009). With habitat having declined and red tree vole populations being increasingly isolated in the fragmented northwestern forest landscape (Forsman et al. In press; United States Fish and Wildlife Service 2011), it is imperative that we increase our understanding of the biology of

this unique native mammal. This includes studying its health and the disease threats it faces in the wild.

Our results provide a foundation for future work on red tree vole health. To bridge the gap between these initial findings in captive animals and red tree vole conservation in the wild, animal health and infections need to be examined in free-ranging red tree vole populations. Taken together, this information will allow us to better understand the true health threats faced by red tree voles in the wild.

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TABLES

Table 2.1.—Demographic parameters for 46 captive red tree voles (*Arborimus longicaudus*) sacrificed at Oregon State University between October 2013 and July 2014: sex, age, mean body mass, and mean body length (snout to base of tail) at time of sacrifice. (*SD* = standard deviation)

	Sample size	Age (Days)	Mass (g) (Mean ± *SD*)	Length (mm) (Mean ± *SD*)
Female (n = 25)				
	3	60	24.3 ± 1.16	86.7 ± 4.04
	1	120	27.0	89.0
	3	180	27.3 ± 0.58	102.0 ± 4.00
	4	240	25.8 ± 2.06	99.3 ± 2.36
	3	300	28.0 ± 3.46	101.3 ± 6.35
	3	360	26.3 ± 1.16	97.7 ± 2.52
	3	420	29.0 ± 3.61	99.3 ± 1.16
	5	480	28.2 ± 1.92	101.0 ± 8.12
Male (n = 21)				
	1	60	25.0	90.0
	4	120	25.3 ± 1.71	95.8 ± 1.71
	3	180	25.7 ± 0.58	96.7 ± 6.51
	2	240	26.0 ± 1.41	92.5 ± 0.71
	3	300	26.0 ± 2.65	92.3 ± 4.51
	3	360	27.3 ± 2.08	100.3 ± 4.93
	4	420	26.0 ± 2.83	98.3 ± 6.24
	1	480	28.0	104.0

Table 2.2.—Summary of results from multiple linear regressions examining associations between immune parameters and condition, age, and sex in captive red tree voles (*Arborimus longicaudus*). (Filled arrows indicate significance at $\alpha < 0.05$. Empty arrows indicate significance at $\alpha < 0.1$.)

Immune measure	Condition	Age	Sex	log(twbc)
Total white blood cells	-	-	-	n/a
Lymphocytes	⬇	⬇	-	⬆
Monocytes	⇧	-	-	⬆
Neutrophils	⬆	-	-	⬆
Eosinophils	⬆	-	-	-
Proportion lymphocytes	⬇	⬇	-	n/a
Proportion monocytes	-	⇧	-	n/a
Proportion neutrophils	⬆	-	-	n/a
Proportion eosinophils	⬆	-	-	n/a
Bacterial killing ability	-	⇧	-	n/a

Table 2.3.—Distribution of white blood cells in 46 captive red tree voles (*Arborimus longicaudus*) sacrificed at Oregon State University between October 2013 and July 2014: total (cells/µl) and differential (%) counts determined from samples collected at time of sacrifice. (*SD* = standard deviation)

		Mean ± *SD*	Median	Range
White blood cells/µl		4,816 ± 2,147	4,376	1,867–10,460
Distribution (%)	Lymphocytes	77 ± 11	80	44–96
	Monocytes	8 ± 6	6	2–27
	Neutrophils	13 ± 9	12	1–45
	Eosinophils	2 ± 2	1	0–8
	Basophils	1 ± 0.3	0	0–2

FIGURES

Figure 2.1.—Study species. Adult (above) and juvenile red tree voles (*Arborimus longicaudus*) from the captive study population at Oregon State University pictured among Douglas fir (*Pseudotsuga menziesii*) branches. This species feeds almost exclusively on conifer needles. (Photo reproduced with permission, copyright Michael Durham Photography, Portland, Oregon.)

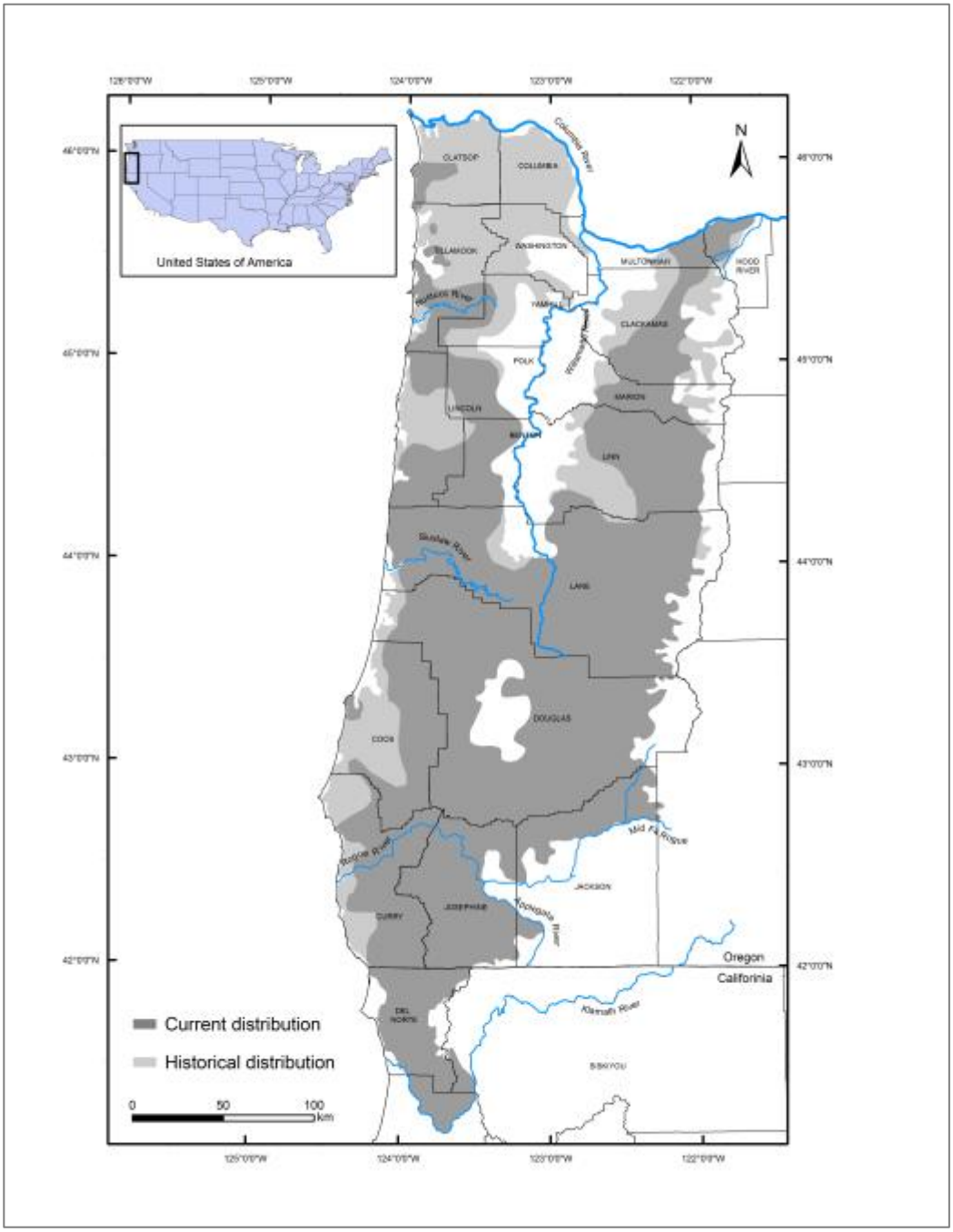
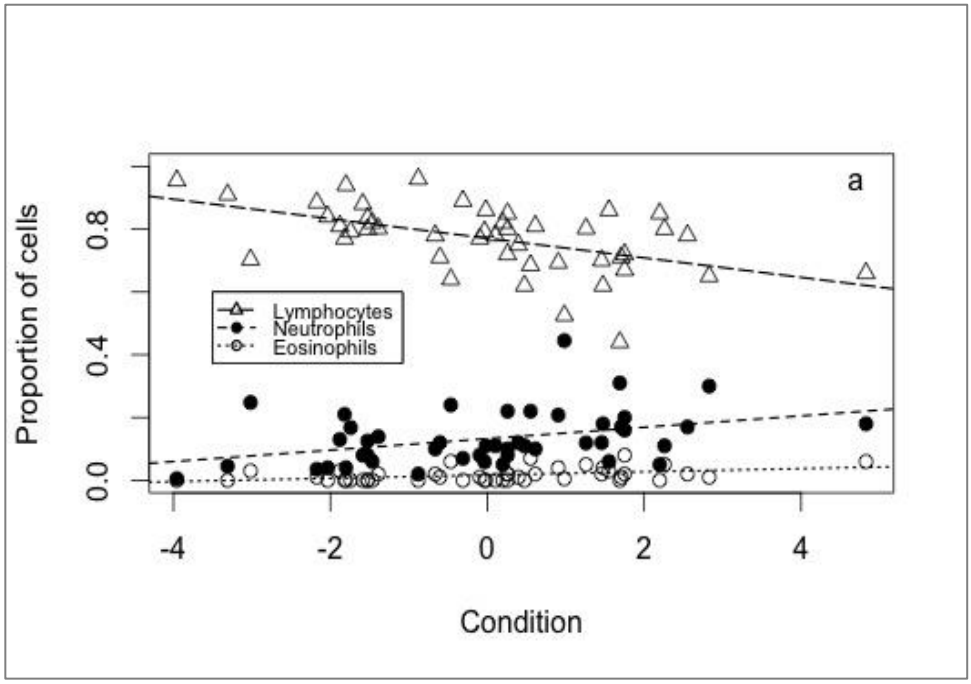
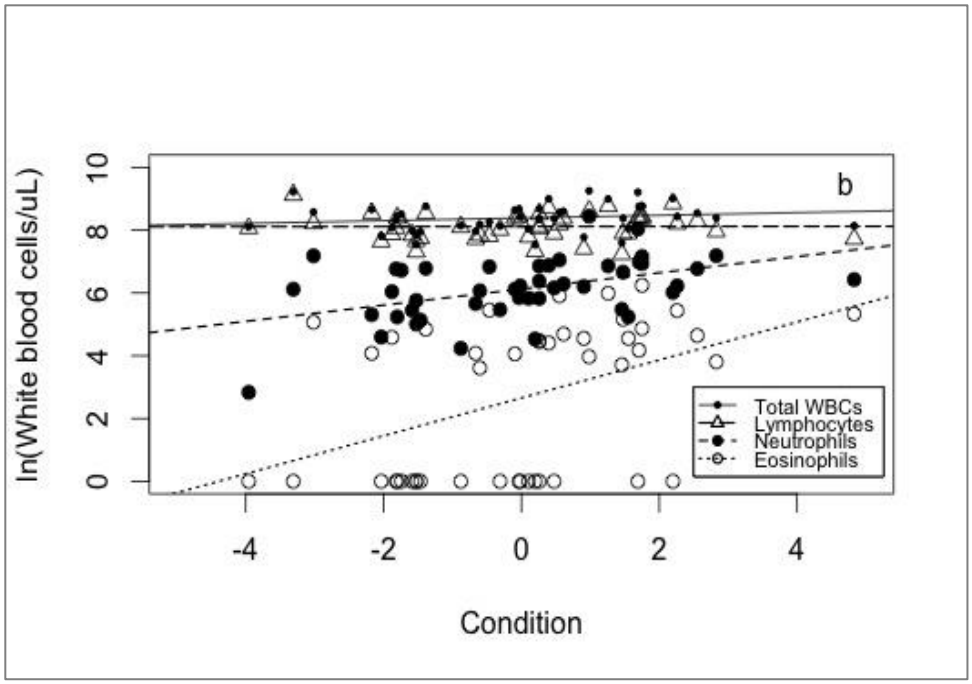


Figure 2.2.—Map showing the estimated historical (~1914) and observed current (1983–2006) distribution of red tree voles in northwestern California and western Oregon (Forsman et al. In press). The specific habitat requirements, which restrict this species to medium elevation mountains, result in red tree voles competing for increasingly sparse habitat largely managed for timber production.


a
Proportion of cells
0.0
0.4
0.8
Lymphocytes
Neutrophils
Eosinophils
-4
-2
0
2
4
Condition

a)


b
ln(White blood cells/uL)
0
2
4
6
8
10
Total WBCs
Lymphocytes
Neutrophils
Eosinophils
-4
-2
0
2
4
Condition

b)

Figure 2.3.—Association between body condition and white blood cells in 46 captive red tree voles (*Arborimus longicaudus*) sacrificed between October 2013 and July 2014. The proportions of lymphocytes, neutrophils, and eosinophils changed with body condition (a). While the total number of white blood cells stayed constant, the number of lymphocytes decreased, but the neutrophil and eosinophil counts increased in fatter animals (b). These results may indicate increased investment in innate immune defenses when resources are available.

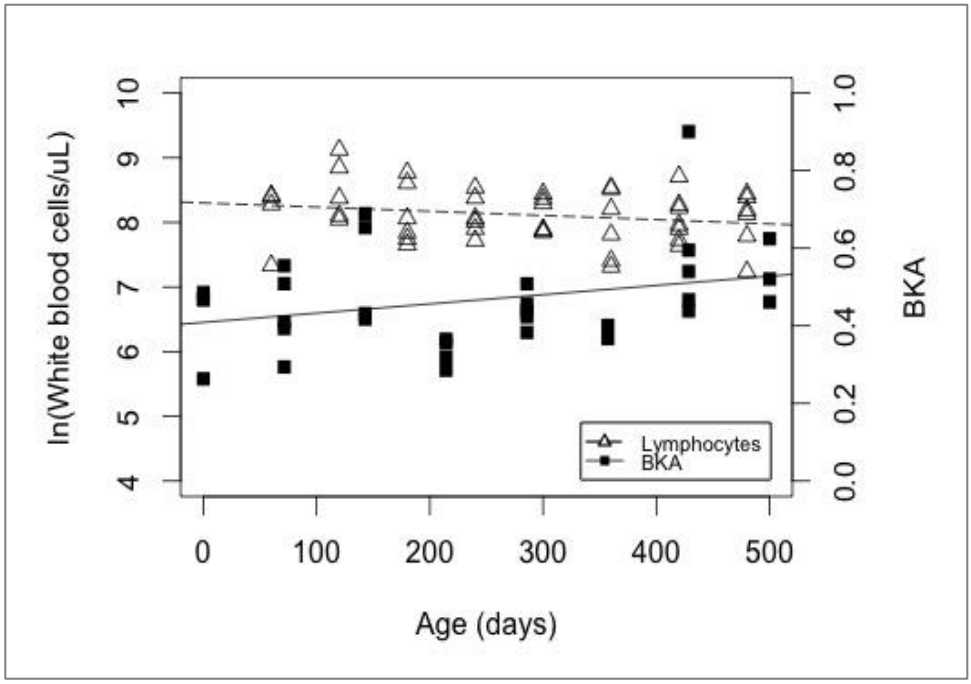


Figure 2.4.—Association between age and immune measures in 46 captive red tree voles (*Arborimus longicaudus*) sacrificed between October 2013 and July 2014. The number of lymphocytes decreased, while plasma bactericidal ability increased with age in red tree voles. This may be evidence for a shift away from adaptive cellular and towards innate molecular immunity with age. However, improved innate immune function in older animals may also be the result of immune upregulation in response to increasing frequency of parasite exposure. (For presentation purposes, lymphocyte counts were transformed using a natural logarithm in this figure.)

Chapter 3 – Context-dependent Effects of Intensive Forest Management on Stress, Health, and Immunity in Wild Deer Mice (*Peromyscus maniculatus*)

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ABSTRACT

Wildlife health is the normal functioning of physiological processes that allow animals to respond to challenges they face in their environment. Anthropogenic environmental change can impact the health of wild animals by altering these processes with both immediate and long-term consequences at the individual- and population-scales. Effects of anthropogenic environmental change on wildlife health can be direct or indirect and, frequently, are context-dependent, making them difficult to predict and detect. To examine how a severe type of anthropogenic environmental disturbance affects wildlife health, we sampled deer mice (*Peromyscus maniculatus*) inhabiting managed forests across three experimentally manipulated levels of management intensity at two locations that differed in their underlying environmental conditions. Using mixed effects models, we assessed the relationship of forest management and location on measures of stress, health, and immunity: hair corticosterone, condition, female reproductive activity, scarring, total and differential white blood cell counts, bactericidal ability of whole blood, and phytohemagglutinin skin swelling. We identified three categories of association: 1) underlying environmental context (i.e. location); 2) forest management level; and 3) an effect of forest management that was dependent on location. We found mice to be in better condition and have stronger bactericidal ability under more favorable environmental conditions. But, we also observed mice in most intensively managed plots to be in better condition than animals on control plots at both locations, and recorded the highest proportion of pregnant or lactating mice on the harshest sites. Finally, we found that forest management was associated with hair corticosterone and neutrophil counts under more favorable environmental conditions, but that these patterns were absent at our harsher study location. We conclude that mice from high quality habitats are healthier and favorable environmental conditions enable them to mount physiological responses to disturbance. In contrast, the ability of mice in poor quality habitat to respond to stressors is impaired, and few and only the very fittest mice survive under the harshest environmental conditions. These findings contribute to our understanding of how anthropogenic environmental change can influence wildlife

health, and highlight the complexity of the mechanisms that drive these processes. Our results may be shaped by underlying infectious disease processes, and have important implications for disease transmission in animals and humans.

INTRODUCTION

Human activity can fragment, simplify, and degrade natural landscapes and lead to declines in wild animal populations. Yet, the mechanisms that underlie such ill effects on wild animals are often complex, context-dependent, and mediated by both ecological and physiological processes (reviewed in Wikelski and Cooke 2006). Health in wild animals can be defined as the normal functioning of the physiologic processes that allow individuals to cope with changes in their environment (Stephen 2014). But, the same processes that maintain homeostasis and allow animals to respond to challenges can be impaired by environmental alterations resulting from human activity (Acevedo-Whitehouse and Duffus 2009).

For instance, anthropogenic environmental change can decrease an animal's fitness and survival by altering the presence and abundance of essential resources in an ecosystem. Poor habitat quality heightens competition for food and shelter and can lead to increased aggressive interactions among individuals of the same or competing species (Kie et al. 1991; Madhav et al. 2007). Subpar environmental conditions necessitate increased foraging effort, and can reduce an animal's condition and suppress reproductive activity (Ylönen and Ronkainen 1994; Eccard and Ylönen 2001; Haapakoski et al. 2012). Finally, longer or more frequent foraging bouts, or changes in dispersal behavior that lead to increased movement between habitats in search of mates or nest sites, may increase the risk of predation and affect the populations of both prey and predator species (Yoder et al. 2004).

In addition to directly affecting fitness and survival, environmental changes can impact wild animals more subtly by acting as acute or chronic stressors (Frid and Dill 2002). In response to stress, vertebrate animals release glucocorticoid hormones, which drive physiologic and behavioral responses that enable them to contend with unexpected environmental challenges (Romero 2004; Reeder and Kramer 2005). The

magnitude and duration of such stress responses depend on the stressor itself (Bowers et al. 2008), but are also shaped by the animal's environmental, nutritional, and social context. In wild animals, natural (e.g. seasonal) fluctuations in glucocorticoid hormones, genetic variation at the individual and population scale, and unknown historic circumstances (e.g. stressors present in utero; exposure to disease) further complicate the response to multiple stressors acting in concert, making the outcome difficult to predict (Dallman et al. 1992; Frid and Dill 2002; Romero 2004). Glucocorticoid hormone levels may increase in an individual acutely exposed to a single stressor such as a predator cue or capture, but return to baseline levels after the stimulus is removed (Dhabhar et al. 1995; Kenagy and Place 2000; Figueiredo et al. 2003; Martin et al. 2010; Graham et al. 2012). In contrast, in animals facing persistent or repeated stressors, such as frequent human activity, continuous heightened risk of predation, increased competition, or poor food or habitat quality, stress hormones may be chronically elevated. But, through negative feedback of circulating glucocorticoids on the hypothalamus, animals may also acclimate to the stressor and reduce circulating stress hormone levels. However, in an acclimated animal, a new or additional stressor can facilitate a disproportionate release of glucocorticoids with potentially dire consequences for other physiological processes (Kenagy and Place 2000; Romero 2004; French et al. 2010; Martin et al. 2010).

One complex suite of components and processes directly affected by acute and chronic release of glucocorticoid hormones is the immune system (Dhabhar 2008; Martin et al. 2010). Glucocorticoids can act on immune function either by suppressing protective responses, or by inducing potentially harmful, systemic inflammatory reactions (Dhabhar et al. 1995; Dhabhar 2008; Graham et al. 2012). For example, Galapagos marine iguanas (*Amblyrhynchus cristatus*) exposed to frequent ecotourism – a constant, low-level stressor – showed significantly higher stress-induced plasma corticosterone levels, and suppression of several immune measures compared to conspecifics from undisturbed populations (French et al. 2010). In contrast, in lemurs (*Indri indri*) inhabiting a fragmented forest in Madagascar that experiences tourism

and nearby mining activity, white blood cell counts were significantly higher than cell counts from individuals from an undisturbed, protected area (Junge et al. 2011).

Both natural fluctuations (e.g. seasonal changes in temperature or food availability) and anthropogenic changes in environmental conditions have been shown to suppress certain immune processes, while upregulating others (Nelson and Demas 1996; Demas and Nelson 1998a; Dhabhar 2008; Kusumoto 2009; French et al. 2010; Junge et al. 2011). Studies that demonstrate declines in protective immune responses under challenging environmental conditions lend support to the notion that mounting an immune response is costly and may require a trade-off with other energetically-demanding mechanisms such as growth or reproduction (Nelson and Demas 1996; Lochmiller and Deerenberg 2000). However, circumstances may also exist under which animals benefit from developing and mounting a protective immune response that immediately improves fitness, but that comes at the expense of long-term survival or reproduction (Rauw 2012). Finally, under desperate conditions, some animals may take an "all or nothing" approach and develop both protective immune defenses and invest energy into growth and reproduction, which likely shortens their long-term survival. This approach seems especially relevant for short-lived, "fast-paced" species such as rodents that mature quickly, have short gestation periods, and produce a large number of small offspring with each litter (Promislow and Harvey 1990; Ricklefs and Wikelski 2002).

Ecoimmunological theory posits that specific, acquired (adaptive) immunity that confers long-term protection requires more energetic input to develop (but not necessarily to maintain) than non-specific, immediate, innate immune defenses (Lee 2006; Sparkman and Palacios 2009; Previtali et al. 2012). Considering that the development of new cells also requires more energy than acellular immune system components (e.g. proteins), we can hypothesize that, under ideal energetic conditions, the development of both acquired and cell-mediated immunity may be favored. But, when an animal is in poor condition and/or stressed and coping with environmental challenges, immune investment may shift towards less costly and more immediately deployable humoral and innate immune responses. Shifting the type of immune

response an animal mounts when faced with an antigenic challenge can have consequences for pathogen transmission and disease prevalence (Martin et al. 2010). This is especially important for wildlife species that act as reservoirs for infectious agents that can spill over into domestic animal or human populations (Mills and Childs 1998; Van Hemert et al. 2014).

Changes to a wild animal's environment can fundamentally affect its health and fitness, induce the release of stress hormones, and modulate potentially protective immune responses (Acevedo-Whitehouse and Duffus 2009). Ultimately, changes in wildlife health can influence dynamics of infectious diseases harbored in wildlife populations (Boughton et al. 2006; Van Hemert et al. 2014), with potentially devastating consequences for other animals, including humans. Here, we investigated the effects of intensive forest management (IFM), a severe type of anthropogenic environmental disturbance pervasive in the northwestern United States, on wildlife health. We used deer mice (*Peromyscus maniculatus*), a small, generalist rodent species ubiquitous to pristine and disturbed habitats across North America (Maser et al. 1981), and a known reservoir for several zoonotic infections (Mills and Childs 1998), to evaluate health effects across replicated forest plots managed at different levels of intensity and situated in two locations differing in their underlying environmental conditions. We quantified chronic stress, observed basic health measures, and assessed immune function in mice across management levels and locations. Using a subset of our data, we then examined the effects of chronic stress on both health and immune function.

We hypothesized that IFM would have negative effects on stress, health, and immune function in deer mice. Specifically, we predicted that chronic stress, measured as glucocorticoid levels in hair, would be highest in animals captured on intensively managed plots (i.e. clearcut and treated with herbicides), and would have a negative effect on both health and immune function in deer mice. Similarly, we expected mice on intensively managed plots, where resources and suitable habitat are sparse, to be more likely to show evidence of aggressive interactions in the form of scars, be in poorest body condition, and adult females to be least likely to be reproductively active

compared to animals inhabiting less severely managed plots. We also anticipated that immune function would generally be suppressed in mice inhabiting intensively managed sites, and that animals on these plots might favor non-specific, humoral innate immune responses over costly, cellular and adaptive responses. Finally, we predicted that negative effects of forest management on all aspects of deer mouse physiology would be intensified by harsher underlying environmental conditions. We found evidence that both forest management intensity and location can affect demographic and physiologic parameters in deer mice, but several of our findings suggest that the most important consequences for wildlife health are driven by the interaction of multiple levels of environmental disturbance. We conclude by discussing the implications of our results for infectious disease dynamics.

METHODS

Study sites and location

Between June and September 2011–2013, we sampled managed forest plots in the coastal mountain range of northwestern Oregon, USA. Plots were grouped into two general locations corresponding to local Oregon Department of Forestry (ODF) districts. Forest Grove district plots (centered on latitude: 45.6212; longitude: -123.4010) were located at mid- to high-elevation (250-500 m) to the east of the mountain ridge with yearly rainfall around 250-360 centimeters. In contrast, plots located in the Tillamook district (centered on latitude: 45.6330; longitude: -123.6135) were situated at slightly higher elevations (600-700 m) on the ridge and west-facing slopes of the mountain range with slightly higher yearly rainfall (360-460 cm; PRISM Climate Group 2016).

We used twelve large (12–16 ha) plots spanning three management intensities (4 plots per management level; Figure 3.1). Details regarding stand locations and structures, as well as chemical treatment prescriptions and schedules are described in Betts et al. (2013). In brief, eight of our twelve plots were clearcut in late 2009 and replanted with Douglas fir (*Pseudotsuga menziesii*) seedlings in spring 2010. Four of these clearcut plots were aerially sprayed with a mixture of chemical herbicides before

planting, and were retreated in late summer of 2010, and during spring and fall of 2011 (hereafter treatment; 2 plots each in Forest Grove and Tillamook districts). Starting in 2012, treatment plots were sprayed either once (two plots) or twice (two plots) a year. However, since all four treatment plots remained barren throughout the three sampling seasons (2011–2013), the four sprayed plots were treated as replicates.

The four remaining plots that were clearcut in 2009 and replanted in 2010 were not treated with herbicides before or after replanting (hereafter control). In addition to Douglas fir saplings, the vegetation on control plots included early successional shrubs and herbaceous plants typical for the region (e.g. bigleaf maple (*Acer macrophyllum*), Oregon grape (*Mahonia nervosa*), and swordfern (*Polystichum munitum*; Betts et al. 2013). In 2011, we sampled two control plots in each forestry district (Tillamook and Forest Grove). However, control plots in the same district were located very close to one another (< 1 km), which, although not observed in this study, posed the risk of animals moving between adjacent plots (Hooven 1958). Therefore, in 2012 and 2013, we replaced one of the original 2011 control plots in each district with two more isolated plots (both located in the Forest Grove district). These new control plots had been clearcut, replanted, and left untreated on a comparable time scale as the original control plots.

Finally, at each sampling location, we identified two 40–50-year-old planted stands dominated by Douglas fir and mixed hardwoods that had not been actively managed for at least 40 years. These four stands served as pre-disturbance reference plots (hereafter uncut; Figure 3.2).

Study species

The deer mouse (*Peromyscus maniculatus*) is one of the most ubiquitous rodent species in the Pacific Northwest (PNW; Maser et al. 1981). Deer mice are omnivorous, are highly adaptable to changes in their environment, and, therefore, often persist in disturbed habitats (Santillo et al. 1989). These characteristics, along with their relatively high abundance at all of our study sites, and the fact that this species is known to host a variety of infectious organisms, including several zoonotic

pathogens (Mills and Childs 1998), make the deer mouse an excellent model organism in which to study the impacts of intensive forest management on wildlife health and immunocompetence.

Animal trapping

We trapped wild deer mice using Sherman™ live traps along 200-meter transects (2 traps every 10 meters) located at the center of each study plot (Hooven 1958; Pearson and Ruggiero 2003). Between late June and early September, each transect was sampled monthly for two consecutive nights. Transects were sampled four times in 2011 and 2012, and twice in 2013.

Since deer mice are primarily nocturnal, all trapping occurred at night (Maser et al. 1981). Traps were outfitted with natural cotton bedding and were baited with peanut butter and oats. Traps were opened before dusk and checked early the following morning. Traps containing deer mice were collected and transported to a central location for processing. All new animals were identified with a uniquely numbered metal ear tag (National Band & Tag Company, # 1005-1). Mice that were recaptured the day after initial capture were released immediately at the site of capture without further processing. Individuals captured during a previous sampling period (~30 days prior) were processed along with new animals. After processing, all mice were transported back to their original site of capture and released.

Sample collection

For each animal, we recorded date, capture and processing time, transect and trap number, and collected demographic parameters. Mice were sexed and the reproductive status of females was noted (visibly pregnant/lactating or not; Lehmer et al. 2007). Animals under 14 g without signs of reproductive activity were classified as juveniles, with all other mice considered adults. Body mass was measured to the nearest 0.5 g using a hanging Pesola™ scale, and body length (snout to base of tail) was measured in millimeters.

Animals were briefly anesthetized with isoflurane and a blood sample was collected from the retro-orbital sinus using a heparinized glass hematocrit tube (Hoff 2000). Blood smears were prepared immediately and stored at room temperature. Blood was collected into heparinized collection vials (BD microtainer, # 365958) and stored on ice until further processing. After recovery from anesthesia, animals were kept in their traps in a sheltered area for at least 6 hours.

All persons involved with trapping and handling deer mice used personal protective equipment (gloves and N95 face mask) to prevent potential transmission of zoonotic agents (Mills et al. 1995). All animal procedures were approved by the Oregon Department of Fish and Wildlife and the Institutional Animal Care and Use Committee at Oregon State University (ACUP #4195).

Hair corticosterone

In 2012 and 2013, we measured corticosterone in hair collected from mice captured on different forest plots as a measure of potential stress associated with environmental changes resulting from forest management and location (Sheriff et al. 2011). In temperate climates such as the northwestern United States, deer mice undergo major molts that tend to coincide with the post-breeding season when energetically demanding processes such as reproduction are minimal but energetic resources remain plentiful. During the spring and summer breeding season, deer mice undergo a partial molt, shedding their winter coat and continuously replacing some of their hair without undergoing a full molt (Tabacaru et al. 2011). This means that hair hormone levels in adult mice captured early in the season (June) during 2012 and 2013 likely reflect stress experienced during the fall and winter months prior to the capture year (2011 and 2012 respectively). Hair corticosterone levels measured during mid and late summer correspond to stress experienced earlier during the same year. Finally, for juvenile mice, hair corticosterone levels mirror circulating hormone levels during the capture year, since juveniles have not yet experienced a full molt, but also undergo continuous partial molting during the summer (Tabacaru et al. 2011).

Hair was clipped over the right hip and stored in plastic microtubes. Hormone extraction was performed adapting published procedures (Koren et al. 2002; Davenport et al. 2006; Martin and Réale 2008). Briefly, we washed each hair sample with 1 ml of isopropanol by vortexing, then centrifuging for 5 min. Isopropanol was decanted and hair was allowed to air dry in the laminar flow hood for 72 hours. Once dried, we weighed samples to the nearest 0.001 gram and transferred hair to 2 ml plastic tubes containing six 2.8 mm ceramic beads (Omni International, Kennesaw, GA; # 19-628). We added 1 ml of methanol to all tubes and again vortexed and centrifuged tubes to fully mix solvent and hair. Finally, we pulverized hair using an Omni Bead Ruptor (Omni International, Kennesaw, GA; # 19-040). Tubes containing pulverized hair and methanol were placed in a MaxQ™ 4450 Orbital Shaker (Thermo ScientificTM; # 4333) and mixed at 100 rpm for 24 hours at room temperature. After a final centrifuge step to separate pulverized hair from methanol (14,000 rpm x 5 min), we transferred 750 µl of the methanol extract to a clean plastic microtube. Microtubes were left uncapped in a laminar flow for 48 hours to allow methanol to evaporate. Corticosterone in each tube was measured using a radioimmunoassay (RIA) at the Endocrine Technologies Support Core (ETSC) at the Oregon National Primate Research Center/Oregon Health & Science University (Rasmussen et al. 1984).

Briefly, hormone was re-suspended using 150 µl phosphate buffered saline (PBS) and analyzed by specific corticosterone RIA. Due to the large number of samples, RIA was performed in three batches. Assay sensitivity was 5 pg/tube with an average intra-assay variation of 6.0%. Average inter-assay variation for the corticosterone RIA at ETSC is 7.6%. Results in ng corticosterone per tube were converted to ng/g hair using the exact methanol volume (µl) recovered and known starting hair sample weights (g). To control for variation in the amount of hair sample available for hormone extraction, hair sample weight was included as an offset term in all statistical models.

General health measures

We were interested in examining the effects of forest management and location on three general measures of health in deer mice. We used the residuals of least squares regression of mass on body length as a measure of condition (Schulte-Hostedde et al. 2005). For females, we noted evidence of reproductive activity (pregnant or lactating vs. not) to gauge fitness. Finally, we determined the presence of visible scarring (usually the result of aggressive encounters with conspecifics) on ears and tail (Calisher et al. 1999).

White blood cell counts

To examine constitutive innate and adaptive immunity, we determined total and differential white blood cell counts. The total number of circulating white blood cells per microliter of whole blood was quantified using a commercially available acetate red blood cell lysis buffer with gentian violet white blood cell stain (Leuko-TIC®, Bioanalytic, Product # 004013-0007), which we adapted for use with small blood volumes and performed in the field. Briefly, 5 µl of whole blood were used to prepare a 1:20 solution of blood and Leuko-TIC® buffer. Following manufacturer instructions, we filled both chambers of a Neubauer counting chamber (Hausser Scientific, Product # 3500) and, in each chamber, counted all cells in the 9 large squares using 100X magnification. Total white blood cell counts per microliter of whole blood were computed by multiplying the average number of cells in the two chambers by the dilution factor (20), and dividing by the product of the number of squares counted and each square's volume (9 squares x 0.1 µl; (Voigt and Swist 2011). Dried blood smears were stained using a commercially available Romanowsky stain (DiffQuik™) and examined under oil immersion (1000X) to determine the proportion of granular (neutrophils, eosinophils, basophils) and agranular (lymphocytes, monocytes) white blood cells per one hundred cells. Lymphocytes and neutrophils are the most common white blood cell type in rodents (Pilny 2008). For these two cell types, we calculated absolute cell counts per microliter of blood by multiplying the proportional cell count determined from the blood smears by the total

white blood cell count. We used absolute lymphocyte and neutrophil counts as indicators of constitutive adaptive and innate immunity respectively. Since the absolute number of each cell type depended on the total number of white blood cells/µl, we included total white blood cell counts as an offset term in all statistical models examining absolute cell counts.

Whole blood bactericidal ability

Induced innate cell-mediated and humoral immune function was measured *in vitro* using a bactericidal assay adapted from (Beechler et al. 2012), which we optimized for *P. maniculatus* and performed in the field. Whole blood bactericidal ability is thought to be mediated by both cellular and humoral processes, with phagocytic neutrophils, macrophages, and platelets working in tandem with complement protein and natural antibodies to kill bacteria (Tieleman et al. 2005; Millet et al. 2007). We quantified the ability of whole blood to kill a non-pathogenic, gentamicin-resistant Dh5a strain of *Escherichia coli* by comparing bacterial growth after reaction with whole blood to uninhibited bacterial growth for each sample (Beechler et al. 2012).

Briefly, 2.5 µl fresh whole blood was diluted with 117.5 µl sterile CO2-independent medium (Thermo Fisher Scientific, # 18045-088), reacted with 150-200 colony forming units (CFU) of *E. coli* suspended in 15 µl PBS, and incubated at 37 ºC for 30 minutes. Controls were prepared by mixing the same number of CFUs with 120 µl of CO2-independent medium and incubating under identical conditions. After 30 min, 27 µl of sample or control mixture was plated in duplicate on lysogeny broth (LB) agar plates, prepared with 1:1000 gentamicin (VWR, Product # 97062-974) to prevent growth of bacterial contaminants. Plates were allowed to sit at ambient temperature for 10 minutes after which they were stored in a heavy-duty cooler (YETI, Product # 31102). In order to keep blood-bacteria reaction time consistent (30 minutes), bactericidal assays were conducted in batches of 8-10 samples. New controls were prepared and plated for each batch. All reagents used for the assay were stored on ice and warmed to ambient temperature before use. Upon return to the laboratory,

plates were incubated at 37 ºC for 24 hours. Negative differences resulting from higher bacterial growth on sample compared to control plates were rounded to zero indicating that the blood sample did not successfully kill bacteria (Matson et al. 2006; Beechler et al. 2012). Since all assays were conducted in the field, bacterial growth in culture and on plates was subject to variation in ambient temperature and varied with each assay. To account for this variation in our statistical analyses, we used the mean number of colonies killed as our outcome measure and included the average number of colonies grown on control plates associated with each sample as an offset term (Beechler et al. 2012).

Phytohemagglutinin skin swelling

To quantify induced cellular innate and adaptive immunocompetence *in vivo*, we used a phytohemagglutinin (PHA) skin swelling assay for *P. maniculatus* adapted from (Lehmer et al. 2007). Briefly, the circumference of the left hind limb at the tibiotarsal joint was measured to the nearest 0.001 mm using a digital micrometer (Mitutoyo, # 293-831-30) in fully anesthetized animals. Crystalline PHA (Sigma-Aldrich® L9017) was diluted in sterile PBS at 0.5 mg/ml and a volume equivalent to 0.5 mg PHA per kg body weight was injected under the skin over the dorsal aspect of the joint using an insulin syringe (Becton Dickinson, # 324910). Volumes injected were rounded to the nearest 0.005 ml based on body weight (e.g. a 20 g mouse received 0.020 ml of solution equivalent to 0.01 mg PHA). The exact time of injection was noted. After 6 hours, mice were re-anesthetized and their left hind limb circumference was re-measured (Lehmer et al. 2007). The tissue swelling associated with PHA injection was computed as the difference between the pre- and post-injection circumference in mm. Negative values resulting from post-injection circumference being smaller than pre-injection limb circumference were rounded up to zero (i.e. no measurable swelling). To account for swelling attributed to slight body mass-based differences in volume of PHA injected, volume injected (ml) was included as an offset term in all statistical models. Finally, since the skin swelling response

increased in recaptured mice that were exposed to PHA multiple times, we controlled for capture number statistically by including it as a fixed effect in all models.

Statistical analyses

To examine the effect of intensive forest management and location on linear, normally distributed measures of health and immunocompetence (i.e. hair corticosterone; body condition; white blood cell counts transformed with a natural logarithm; PHA skin swelling) we developed linear mixed effects models. For total and absolute white blood cell counts, we chose to apply a natural logarithm transform and use a general linear mixed effects model instead of using models that assume Poisson, quasi-Poisson, or negative binomial error distribution (Ives 2015). This decision was made by evaluating model goodness-of-fit based on the Pearson's goodness of fit test (Dean and Lawless 1989; Dean 1992), which was best for models assuming normal distribution with log-transformed data, but was poor for all other error distributions examined. In addition, evaluation of diagnostic quantile-quantile and model residual vs. fitted values plots confirmed that log-transformation and normal distribution were appropriate for these data.

We constructed generalized linear mixed effects models to examine binomial outcomes (i.e. reproductive activity; scarring) and linear measures with negative binomial error distribution (i.e. bacterial colony counts). The negative binomial model is appropriate for count data with high variance (overdispersion). For bacterial colony counts we again determined variable distribution based on goodness of fit tests. We chose to represent these count data with negative binomial errors and a log link function, rather than with models assuming Poisson or quasi-Poisson errors, for two reasons. First, the variance of each of these dependent variables was greater than its mean value. This was reflected in Poisson models having a poor goodness-of-fit based on the Pearson's goodness of fit test (Dean and Lawless 1989; Dean 1992). Second, diagnostic plots of model residuals vs. fitted values suggested that the negative binomial was a better fit than the quasi-Poisson distribution for bacterial colony counts.

For each outcome measure, we constructed mixed models including management intensity (uncut; control; treatment) and location (Forest Grove; Tillamook) as environmental predictor variables. To examine if effects of forest management intensity on health and immune measures differed by location, we also included a management by location interaction term in all of our full models. During model selection, the interaction term was only considered if the main effects of management intensity and location were also retained in the model.

In many vertebrate animals, condition is influenced by their reproductive status (and vice versa). Pregnant or recently pregnant individuals are often in better condition than non-reproductive females and/or males (Weimerskirch 1992; Eccard and Ylönen 2001; Speakman 2008). Similarly, sex and reproductive status influence behavior and can drive the frequency and severity of aggressive interactions between individuals (Wolff 1989). To account for interactions between these demographic variables and our measures of interest, we controlled for animal-level variation in all statistical models. When modeling condition and scarring, we constructed full models including age (juvenile; adult) and a three-category variable describing an animal's reproductive status (male; female pregnant or lactating; female not pregnant or lactating). For models evaluating reproductive activity, we only considered adult female mice. When building models for measures of immunocompetence, we included animal age, condition, reproductive status, and scarring as fixed effects in all full models. Scarring was included because bites and scratches from aggressive interactions can expose animals to infectious diseases, induce immune responses, and could thereby confound our results. To control for variation in stress, health, or immune measures over time, we included season (early-summer; mid-summer; late-summer) and sampling year (2011; 2012; 2013) as fixed effects in all models. To account for slight variation in dates across the three sampling years, we defined season categories as 30-day increments spanning the period starting on the earliest Gregorian calendar date sampled during all three study years (June 21 = day 1) and ending on the latest date sampled during all three study years (September 15 = day 87). Finally, to account for the fact that some animals were caught multiple times during the study period,

whereas others were only caught once, we included the interaction between individual animal ID and recapture status (0/1) as a random effect in all of our models (Telfer et al. 2007).

For each outcome measure, we constructed separate full models including all variables and the two-way interaction term. We then explored the effect of dropping each term on model quality using Akaike's information criterion (AIC) and reconstructed increasingly simpler models eliminating terms identified based on lower model AIC until removal of additional terms did not lower AIC any further. The model with the lowest AIC was chosen as the final model. Finally, to evaluate model fit, marginal R^2 and conditional R^2 were computed for all final models. These R^2 measures describe the proportion of variance explained by the fixed effects alone (R_m^2), and by both the fixed and random effects (R_c^2) in a mixed effects model (Nakagawa and Schielzeth 2013). For BKA, model fit could not be evaluated because these measures were not available for negative binomial models.

Finally, we were interested in exploring the effect of chronic stress on animal health and immunocompetence in the face of forest management and environmental conditions. To this end, we used a subset of our data for which hair corticosterone levels were available to construct mixed effects models including corticosterone as a fixed effect and following the same procedures described for each health (condition; reproductive activity; scarring) and immune (total and differential white blood cell counts; BKA; PHA) measure above.

All statistical analyses were performed using R versions 3.0.1. and 3.2.0. (R Development Core Team 2013, 2015). Specialized packages used were bbmle (Bolker and R Development Core Team 2016), glmmADMB (Fournier et al. 2012; Skaug et al. 2014), lme4 (Bates et al. 2015), lmerTest (Kuznetsova et al. 2015), MASS (Venables and Ripley 2002), MuMIn (Barton 2011), and R2admb (Bolker 2015).

RESULTS

Description of study population

Between late June and mid-September 2011 and 2012, and between late June and early August 2013, we captured 218 individual deer mice. Of these, 143 animals were caught only once, whereas 75 animals were caught more than once. Specifically, 41 mice were captured a second time, 20 were caught a third time, and 14 mice were caught four times, yielding a total of 341 capture events (143*1 + 41*2 + 20*3 + 14*4 = 341) of which approximately 58% ((82+60+56)/341) were recaptures. We account for recaptures in statistical analyses, but, unless explicitly noted, we present and discuss data points as if they were independent events. None of the mice were captured during multiple years. Captures by year were $n_{2011} = 57$, $n_{2012} = 190$, and $n_{2013} = 94$. Due to consistently higher capture success in July (mid-season) and a shortened sampling season in 2013, relatively more animals were captured mid-season compared to early or late season over all three sampling years ($n_{early} = 92$; $n_{mid} = 159$; $n_{late} = 90$). In addition, more than twice as many animals were caught on Forest Grove (FG) plots compared to Tillamook (TM) plots ($n_{FG} = 235$ vs. $n_{TM} = 106$) and this pattern was true for all management levels (uncut: $n_{FG} = 41$ vs. $n_{TM} = 11$; control: $n_{FG} = 123$ vs. $n_{TM} = 52$; treatment: $n_{FG} = 71$ vs. $n_{TM} = 43$). Despite equal trapping efforts on all plots, most mice were captured on control plots compared to uncut or treatment plots ($n_{Uncut} = 52$; $n_{Control} = 175$; $n_{Treatment} = 114$). Mice were never captured on more than one plot and we did not find any evidence for mice moving between plots or locations. Finally, most mice were captured as adults, while juveniles were caught infrequently ($n_A = 314$ vs. $n_J = 27$).

Hair corticosterone

Levels of hair corticosterone were available for 101 samples from 2012 and 88 samples from 2013 (166 unique animals). Median hair corticosterone was 97.5 ng/g (range: 0.2 – 290.2 ng/g). The final model included management intensity, location, and the interaction between management and location, while controlling for age, season, and study year, and accounting for hair sample weight as an offset term (AIC

= 2079.7; R_m^2 = 22.8% and R_c^2 = 22.9%; Table 3.1; Supporting Information S3.1). We observed some variation in hair corticosterone levels across plots of differing management intensities, but this effect depended on location. In Forest Grove, corticosterone levels in hair from mice captured on treatment plots were higher than in animals from control plots (T vs. C: β = 30.104, P = 0.013), but we did not see significant differences between treatment or control and uncut plots (all P > 0.1 Figure 3.3a). In contrast, in animals captured on Tillamook plots, we did not observe any associations between hormone levels and management intensity (all P > 0.3; Figure 3.3b).

General health measures

Condition.–Body mass and length measurements were available from 336 captures. Means ± standard deviations of body mass and length were 19 ± 3.7 g and 90 ± 7 mm respectively. Residuals of ordinary least squares regression of mass on length ranged from -7.67 to 13.17 (median = -0.278; mean = 0.000). The final model selected for body condition included management intensity and location, and controlled for reproductive status, age, season, and sampling year (AIC = 1586.3; R_m^2 = 15.0% and R_c^2 = 38.0%; Table 3.1; Supporting Information S3.1). Mice from Tillamook plots generally appeared to be thinner than animals caught in Forest Grove (F = 5.083, β = 0.766, P = 0.025; Figure 3.4a) and this was true across all forest management levels. We also observed that, at both locations, mice captured in treatment plots appeared to be in slightly better condition than mice from control plots (T vs. C: β = 0.724, P = 0.038; Figure 3.4b and c), but did not observe any differences in condition between mice from treatment and uncut, or between uncut and control plots (all P > 0.3).

Female reproductive activity.–We captured 196 male and 145 female mice. Of 136 adult females, 56% were visibly pregnant or lactating at time of capture. We found some evidence that reproductive activity in our study population was associated with forest management and location. The final model selected was the full model, which included management intensity, location, and the management intensity by location interaction term, and controlled for season and sampling year (AIC = 191.6;

R_m^2 = 16.0% and R_c^2 = 20.2%; Table 3.1; Supporting Information S3.1). We observed slight variation in reproductive activity between animals captured from different plots, but this effect was dependent on location and was true only for forest plots located in Tillamook. In Forest Grove, we found no differences in female reproductive activity across management levels (all P > 0.3; Figure 3.5a). But, in Tillamook, we observed a higher proportion of pregnant and/or lactating mice on treatment compared to control plots (T vs. C: β = 1.843, P = 0.026; Figure 3.5b), but did not note any other differences in reproductive activity across forest management intensities (all P > 0.5).

Scarring.–The presence / absence of scarring was noted for 338 captures. Approximately 62% of the sample population had visible scars. The proportion of scarred males (69%) was higher than females (53%; χ^2 = 7.365, P = 0.007), but reproductive status did not affect scarring in females (57% vs. 50% in pregnant/lactating vs. non-reproductive females respectively; χ^2 = 0.416, P = 0.519). And, adult mice were more likely to have scars (65%) compared to juveniles (28%; χ^2 = 11.85, P = 0.0006). We did not find any association between the presence of scars and forest management or location. The final model included reproductive status, age, season, and sampling year (AIC = 395.9.00; R_m^2 = 26.2% and R_c^2 = 37.5%; Table 3.1; Supporting Information S3.1).

White blood cell counts

Total and differential white blood cell counts were available for 341 samples. Median total white blood cell count was 3,289 cells/µl (range: 356 – 38,610 cells/µl). Lymphocytes consistently made up the majority of white blood cells (median = 52%, range: 7 – 87%), followed closely by neutrophils (median = 38%, range: 8 – 93%). Monocytes (median = 4%, range: 0 – 28%), eosinophils (median = 2%, range: 0 – 28%), and basophils (median = 0%, range: 0 – 6%) were significantly less common and these cell types were not considered in subsequent statistical analyses or model selection.

Total white blood cells.–We found associations between total white blood cell counts and management intensity as well as location. The final model for total white

blood cell counts included management intensity, location, and controlled for condition, reproductive status, season, and year (AIC = 713.7; R_m^2 = 13.9% and R_c^2 = 23.1%; Table 3.1; Supporting Information S3.1). Animals sampled on Tillamook plots appeared to have slightly higher white blood cell counts overall compared to animals from Forest Grove (Figure 3.6a), but this effect was only suggestive (F = 3.456, β = 0.169, P = 0.064). Similarly, total white blood cell counts were slightly higher in mice from uncut plots than in mice from control stands (β = 0.221, P = 0.056), but we observed no other differences across management levels (all P > 0.2; Figures 6b and c).

Lymphocytes.–Median lymphocyte count for our study population was 1,496 cells/µl (range: 149 – 19,110 cells/µl). We found some associations between lymphocyte counts and forest management, but this effect was dependent on plot location. The final model for lymphocytes included management intensity, location, and the interaction between forest management and location, and controlled for condition, reproductive status, age, season, and sampling year (AIC = 268.3; R_m^2 = 17.7% and R_c^2 = 32.9%; Table 3.1; Supporting Information S3.1). In Forest Grove, mice from uncut plots had significantly more lymphocytes than animals caught on either control (β = 0.152, P = 0.024) or treatment (β = 0.196, P = 0.008) plots (Figure 3.7a). In contrast, in Tillamook, we did not observe any differences in lymphocyte counts across the three management intensities (all P > 0.3; Figure 3.7b).

Neutrophils.–Median neutrophil count was 1,246 cells/µl (range: 98 – 29,730 cells/µl). We found associations between the number of neutrophils and forest management, and, again, these relationships were dependent on location. The final model included management intensity, location, and the interaction between management intensity and location, while accounting for age, reproductive status, season, and year (AIC = 429.9; R_m^2 = 17.7% and R_c^2 = 30.1%; Table 3.1; Supporting Information S3.1). In Forest Grove, mice from treatment plots had significantly higher neutrophil counts than mice from uncut plots (β = 0.242, P = 0.010; Figure 3.8a). We also found suggestive evidence that animals from control plots had more neutrophils than mice from uncut plots (C vs. U: β = 0.165, P = 0.053), but saw no significant

difference between treatment and control plots (T vs. C: $\beta = 0.077$, P = 0.305). Mice captured in Tillamook did not show any differences in neutrophil counts across management level (all P > 0.1; Figure 3.8b).

Whole blood bactericidal ability

Bacterial killing ability was available for 340 animals. The median proportion of bacteria killed by whole blood was 0.84 (range: 0.0 - 1.0). The average number of bacterial colonies per plate varied significantly for both control plates (median = 90; range: 6 - 395) and for the number of colonies killed, i.e. the difference between control and sample plates (median = 68, range: 0 - 385). We did not find an association between bactericidal ability and forest management intensity, but we did observe a relationship with location. The final model for the number of colonies killed included location and controlled for sampling year, while accounting for the average number of colonies on control plates as an offset term (AIC = 2912.9; Table 3.1; Supporting Information S3.1). Mice from Tillamook plots had significantly poorer bactericidal ability than individuals captured in Forest Grove ($\beta = -0.256$, P < 0.0001; Figure 3.9a), and this effect was observed across all management intensities (Figure 3.9b).

Phytohemagglutinin skin swelling

Median skin swelling in response to local phytohemagglutinin injection was 2.18 mm (range: 0.0 – 6.38) and was measured in 294 animals. We did not observe a relationship between skin swelling and forest management or location. The final model included only condition, reproductive status, season, sampling year, and capture number, and accounted for volume injected as an offset term (AIC = 895.1; R_m^2 = 35.0% and R_c^2 = 41.8%; Table 3.1; Supporting Information S3.1).

Effects of corticosterone on health and immunity

The effect of hair corticosterone on health and immune measures was evaluated using the 187 animals from 2012 and 2013 for which corticosterone levels

and data for health measures were available. Level of corticosterone in hair samples was not associated with any of the health or immune measures examined and was never retained during model selection (data not shown).

DISCUSSION

To examine the hypothesis that intensive forest management, a severe type of anthropogenic environmental disturbance, has negative consequences for wildlife health, we compared demographic and physiologic parameters in deer mice across three experimentally manipulated levels of forest management intensity. To explore the role of the underlying environmental context for management-mediated effects on health, we replicated the study at two locations that differ in their underlying environmental conditions (i.e. elevation, rainfall). We found evidence that both forest management and location were linked to deer mouse health, but the directions of these relationships varied, some patterns were unexpected, and frequently, associations were shaped by interacting environmental factors.

Our data suggest three types of association between health and environmental conditions in deer mice inhabiting our study sites. First, we found health to vary by location. For instance, mice inhabiting the milder Forest Grove plots where resources were available earlier in the spring and were more plentiful at the time of sampling, especially early during the season, were in better overall condition than their counterparts at the harsher Tillamook sites. Patterns of immunity also differed between the two sites. Mice at Tillamook had slightly elevated white blood cell counts, while displaying reduced blood bactericidal ability compared to mice from Forest Grove. White blood cell counts are highly responsive to infection, and frequently used as a general indication of inflammation (Davis et al. 2008a; Maceda-Veiga et al. 2015). Whole blood kills bacteria via both cellular and humoral mechanisms and has been linked to health and fitness quality in several species (Tieleman et al. 2005; Millet et al. 2007; Beechler et al. 2012). While we cannot differentiate whether cellular or humoral mechanisms predominate in our data, we would expect that mice with access to more plentiful food sources might exhibit a

stronger, cell-mediated BKA response (Millet et al. 2007), while it might be beneficial for energy-deprived individuals to preferentially invest in humoral components (Lee 2006). Comparing results from whole blood to plasma BKA across environmental conditions would be a next step to examine this idea. Taken together, these findings suggest that mice at the harsher Tillamook site may be suffering increased exposure to infectious organisms, but appear less able to mount appropriate innate defenses in response to such challenge.

Of course, numerous other factors can shape the immune responses we measured (Romero 2004; Davis et al. 2008a; French et al. 2010; Neuman-Lee and French 2014; Maceda-Veiga et al. 2015). Nonetheless, our findings lend support to the idea that variation in environmental conditions between the two locations plays an important role in shaping patterns of health and immunity in our study populations, which ultimately may drive local differences in the dynamics of infectious disease.

The second category of association we observed was between animal health and forest management alone. Contrary to our predictions, mice captured on treatment plots were in significantly better condition than those captured on clearcut unsprayed stands in both Forest Grove and Tillamook. In addition, at Tillamook, mice captured on treatment plots were also more likely to be reproductively active than those captured on control or uncut plots. Treatment plots represented the harshest of the habitats examined. These sites were repeatedly sprayed with large quantities of herbicides which resulted in very little ground cover, few plant-based food sources, and exposed animals to both winter and summer weather and temperature extremes. Therefore, we expected animals inhabiting these sites to be in poor health overall. Yet, we observed the opposite pattern. The most plausible explanation for finding fatter animals in the poorest quality habitat builds on the "presaturation hypothesis" (Lidicker 1975), which posits that small mammals that emigrate from a population before resources become limited are generally characterized by good body condition. Therefore, only high quality individuals may immigrate to our treatment plots. Moreover, once established, it is likely that only the fittest mice are able to survive the unfavorable conditions of these habitats long enough to be captured and observed by

us. Small populations on treatment plots are also a plausible consequence of these processes. Although we did not estimate mouse density on our plots, we consistently trapped few mice and had high recapture rates on the most intensively managed plots. These observations lend support for the idea that only few, exceptionally fit animals survive in these habitats.

This leads us to the third, final, and perhaps the most intriguing association we observed between health and environmental conditions. For physiological measures of health, we noted an effect of forest management that depended on the location of the treatment plots. These observations may indicate an interaction between multiple stressors, namely that of the differential limitations posed by underlying environmental conditions and the more radical, superimposed habitat changes resulting from forest management.

The strongest result supporting this idea is that, on the milder Forest Grove sites, we noted variation in hair corticosterone levels associated with forest management. Specifically, mice from treatment plots had higher stress hormone levels than those inhabiting control plots. This finding is in contrast to the harsher Tillamook sites where we did not see any variation in stress hormone across management levels. One possible explanation for this observation is that mice living in a generally more favorable environment can mount a stress response and increase their corticosterone levels to cope with the additional stressor of intensive forest management. Whereas, animals already struggling to survive and reproduce in the face of chronically harsh environmental conditions are unable to respond to added stressors (Romero 2004; French et al. 2010). A second potential explanation has to do with natural, seasonal fluctuations in stress hormones, such as increases of corticosterone during the breeding season (Atkinson and Waddell 1995; Reeder and Kramer 2005). Based on the milder weather conditions at lower elevation, the breeding season for deer mice likely begins a few weeks earlier in Forest Grove than in Tillamook. Therefore, at least early in the sampling season, hair collected from mice at the two locations may in fact reflect slightly different molt cycles: the partial molt in early spring that coincides with the beginning of the breeding season in Forest Grove vs. the winter hair coat

reflective of fall post-breeding season conditions for animals in Tillamook (Tabacaru et al. 2011). During early summer, underlying stress in mice that are already reproductively active could facilitate a heightened stress response associated with forest management, whereas animals that have not yet entered the breeding season may not demonstrate this pattern (Romero 2004). Unfortunately, our sample size did not allow us to examine whether the relationship between forest management and corticosterone varied over the course of the sampling season. However, it is plausible that natural stressors such as breeding, or genetic animal- or population-level differences can modulate the physiologic responses of mice to both underlying environmental conditions and superimposed anthropogenic environmental changes (Romero 2004; French et al. 2010).

As noted, our corticosterone data measured chronic stress experienced in the animal's past, but did not assess whether, when challenged with an acute stressor, animals differed in their responses depending on forest management level and/or location. Examining changes in plasma corticosterone levels from baseline in response to a stressor is a common method to evaluate the ability of animals to mount a stress response (Romero 2004; Reeder and Kramer 2005). However, as a proxy for circulating plasma stress hormones the distribution of white blood cells can be examined. In many mammals, neutrophils increase in response to acute stress, while lymphocytes decrease (Dhabhar et al. 1995; Davis et al. 2008a; Cīrule et al. 2011). Live capture, subsequent handling, anesthesia, and blood collection were almost certainly stressful for the wild deer mice we studied and conceivably increased circulating stress hormones with cascading effects on white blood cell distribution. Therefore, we can use the proportion of neutrophils in our samples to compare the ability of mice to react to the more acute stress of capture and handling across forest management levels. We observed that mice from treatment plots in Forest Grove had more neutrophils (and fewer lymphocytes) than animals from uncut plots, but we did not observe an effect of management on white blood cell distributions in mice from Tillamook. This finding adds further support to the idea that multiple stressors are worse than one; under decent environmental conditions, animals can react when faced

with additional stressors. But, when conditions are already limiting, the ability to respond to added challenges declines. For our population, this appears to mean that, mice in Forest Grove are able to increase their corticosterone levels in response to forest management and the acute stress of capture and handling. While mice in Tillamook show no such responses.

The absence of association between the PHA response and environmental conditions warrants brief discussion. The skin swelling resultant from subcutaneous injection of phytohemagglutinin is commonly used to assess both innate and adaptive cellular immune function in wildlife (Martin et al. 2006; Demas et al. 2011). The magnitude of the tissue swelling has been shown to be positively associated with resource availability and fitness in numerous species. But, several studies failed to identify a relationship between environmental contamination and PHA response (reviewed in Martin et al. 2006). Our finding that both condition and female reproductive activity were positively associated with skin swelling, but that neither location or forest management appeared to affect PHA response may indicate that this measure is more sensitive to animal-level factors than to environmental disturbance.

In conclusion, we observed several strong associations between intensive forest management and health in deer mice. In an attempt to clarify some of the complex relationships observed in our study, we organized our results into three categories of association. First, we discussed how underlying environmental conditions appear to shape condition and innate immunity in deer mice. Next, we explored reasons for which animals on most intensively managed plots appear to be of superior quality. And, finally, we examined the consequences that interacting effects of environmental conditions and forest management can have for measures of stress. Our data suggest that underlying habitat conditions play a significant role in determining animals' physiologic responses to additional, drastic changes in their environment. Under favorable conditions, deer mice appear to be able to cope with environmental challenges resulting from clearcutting and intensive herbicide application and responses are relatively predictable. In contrast, when underlying conditions are challenging in themselves, animals faced with additional stressors may

not be able to respond as expected or in a manner ideal to maximize their fitness. Examining the role of disease in this system presents an important next step towards understanding the complex interactions between environmental conditions, wildlife health, and the implications for disease transmission, including the risk for spread to domestic animals and humans.

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TABLES

Table 3.1.—Analysis of variance model output for (**a**) linear mixed effects models (linearly modeled response variables: hair corticosterone ng/mg; condition; ln(white blood cells/µl); PHA skin swelling mm), and (**b**) generalized linear mixed effects models (non-linearly modeled response variables, i.e. binomial: scarring; reproductive activity; and negative binomial: bacterial colony counts) examining relationships of forest management and location on stress, health, and immune measures in deer mice (*Peromyscus maniculatus*) captured on differentially managed forest plots at two locations in the Oregon Coast Range between June and September 2011–2013. (Chisq = Chi square statistic; df = degrees of freedom; Den df = Denominator degrees of freedom; Loc = Location; Num df = Numerator degrees of freedom; Pr = probability; (Mean) Sum Sq = (Mean) Sums of squares; Tx = management intensity)

a)

Outcome	Predictor	Sum Sq	Mean Sq	Num df	Den df	F.value	Pr(>F)
Corticosterone	Treatment	5633.68	2816.84	2	177.48	0.861	0.424
	Location	15642.08	15642.08	1	178.70	4.783	**0.030**
	Tx*Loc	14530.14	7265.07	2	177.85	2.222	0.111
	Age	6451.17	6451.17	1	178.23	1.973	0.162
	Season	56176.33	28088.16	2	178.92	8.589	**<0.001**
	Year	90412.74	90412.74	1	178.63	27.647	**<0.0001**
Condition	Treatment	23.44	11.72	2	290.33	2.192	0.114
	Location	27.18	27.18	1	284.82	5.083	**0.025**
	Age	21.66	21.66	1	277.20	4.050	**0.045**
	Repro	159.24	79.62	2	305.37	14.891	**<0.0001**
	Season	77.38	38.69	2	284.64	7.236	**<0.001**
	Year	48.76	24.38	2	290.58	4.559	**0.011**
Total WBCs	Treatment	1.79	0.90	2	245.66	2.013	0.136
	Location	1.54	1.54	1	239.85	3.456	0.064
	Condition	1.23	1.23	1	311.68	2.758	0.098
	Repro	2.96	1.48	2	268.44	3.325	**0.037**
	Season	6.84	3.42	2	291.48	7.674	**<0.001**
	Year	5.18	2.59	2	243.31	5.805	**0.003**

Table 3.1. a) cont.

Outcome	Predictor	Sum Sq	Mean Sq	Num df	Den df	F.value	Pr(>F)
Lymphocytes	Treatment	0.06	0.03	2	276.91	0.259	0.772
	Location	0.36	0.36	1	314.05	3.261	0.072
	Tx*Loc	0.55	0.27	2	271.93	2.458	0.087
	Age	0.66	0.66	1	274.58	5.955	**0.015**
	Condition	0.22	0.22	1	317.78	1.962	0.162
	repro	1.04	0.52	2	290.58	4.680	**0.010**
	Season	1.37	0.68	2	282.64	6.158	**0.002**
	Year	0.76	0.38	2	267.79	3.424	**0.034**
Neutrophils	Treatment	0.18	0.09	2	268.17	0.487	0.615
	Location	0.49	0.49	1	310.92	2.634	0.106
	Tx*Loc	1.12	0.56	2	263.62	3.040	**0.050**
	Age	0.57	0.57	1	279.46	3.088	0.080
	repro	1.96	0.98	2	274.08	5.324	**0.005**
	Season	2.11	1.05	2	287.48	5.711	**0.004**
	Year	2.88	1.44	2	251.94	7.813	**<0.001**
PHA	Condition	5.53	5.53	1	280.24	5.019	**0.026**
	repro	5.22	2.61	2	249.17	2.371	0.096
	Season	20.79	10.40	2	249.49	9.441	**<0.001**
	Year	86.15	43.07	2	221.93	39.115	**<0.0001**
	Capno	15.78	15.78	1	94.69	14.326	**<0.001**

Table 3.1. b) cont.

Outcome	Predictor	Chisq	df	Pr(>Chisq)
Repro	Treatment	1.16	2	0.560
	Location	2.76	1	0.097
	Tx*Loc	5.75	2	0.056
	Season	4.58	2	0.101
	Year	4.99	2	0.083
Scarring	Age	6.44	1	**<0.05**
	Repro	11.91	2	**<0.05**
	Season	5.77	2	0.056
	Year	30.85	2	**<0.0001**
BKA	Location	53.33	1	**<0.0001**
	Year	16.88	2	**<0.001**

FIGURES

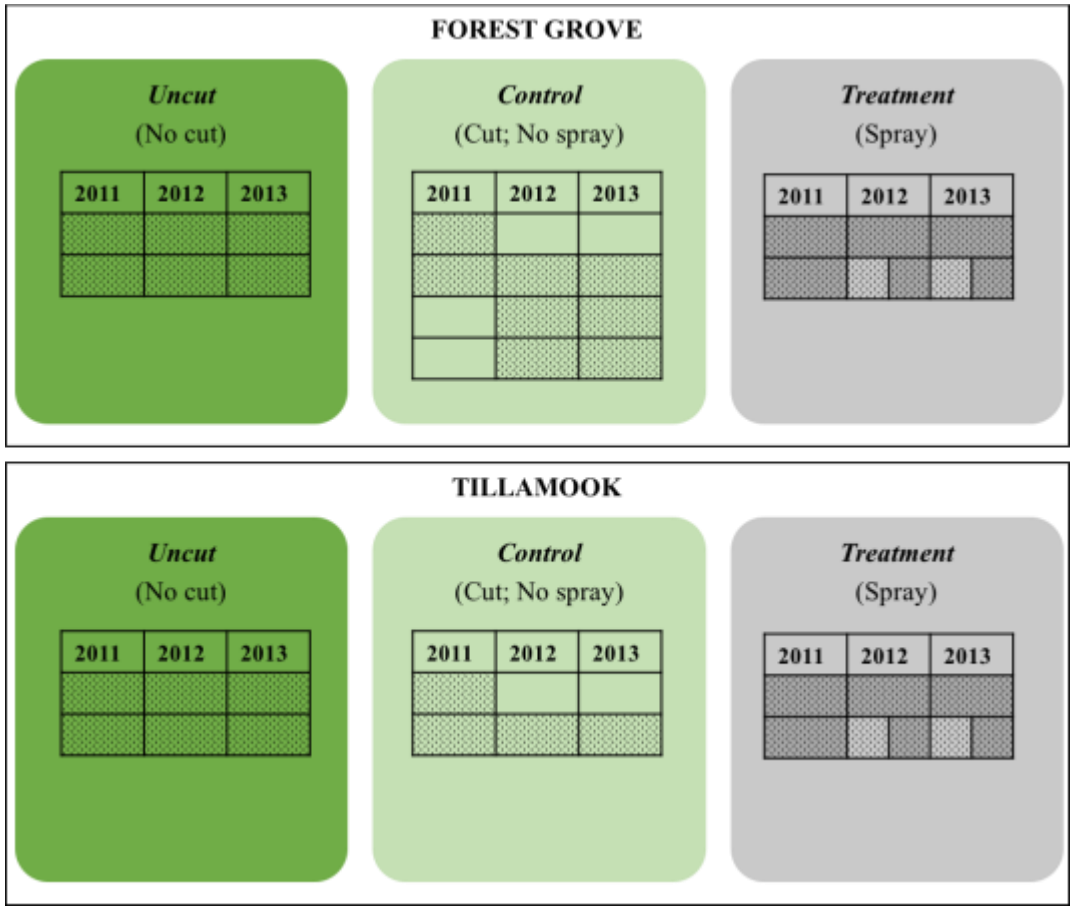

Figure 3.1.—Study design. Between June and September 2011–2013, deer mice (*Peromyscus maniculatus*) were captured along transects at two locations (Forest Grove; Tillamook) in the Oregon coastal mountain range. At each location, trapping occurred across three replicated forest management levels: managed Douglas fir (*Pseudotsuga menziesii*) stands 40-50 years old (uncut); clearcut, replanted, but unsprayed stands (control); and clearcut, replanted stands treated with a mixture of herbicides (treatment). Stippling indicates plots sampled in a given year (four plots per management level per year). Shaded boxes indicate herbicide application during spring and fall (full box) or only fall (half box) of a given year.

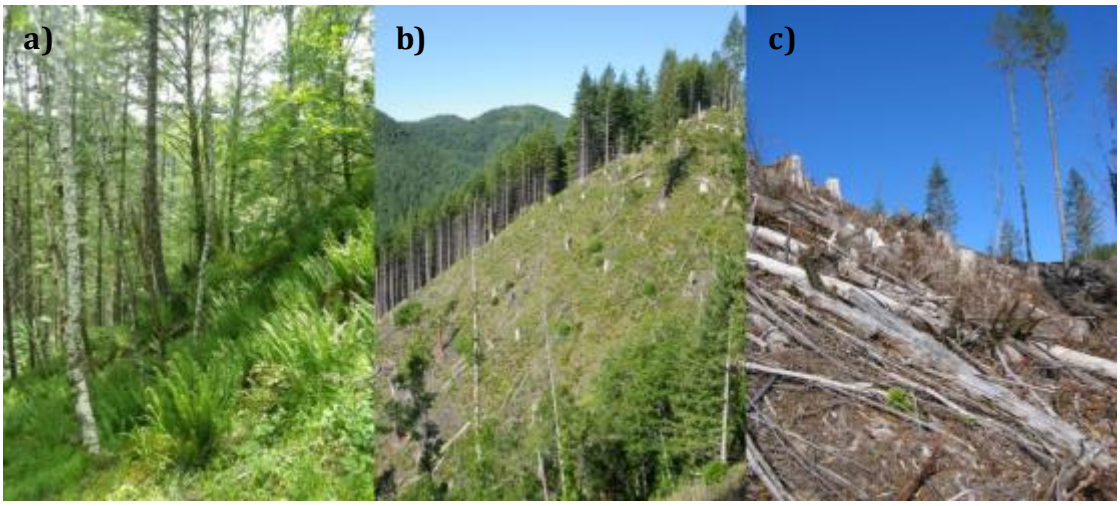

Figure 3.2.—Representative study plots. (**a**) Uncut mixed 40-50 year old Douglas fir (*Pseudotsuga menziesii*) and hardwood stands; (**b**) clearcut and replanted, but unsprayed plots (control); and (**c**) clearcut, replanted stands treated with a mixture of herbicides (treatment). Between June and September 2011–2013, deer mice (*Peromyscus maniculatus*) were captured on four replicates of each plot type at two locations in the Oregon Coast Range.

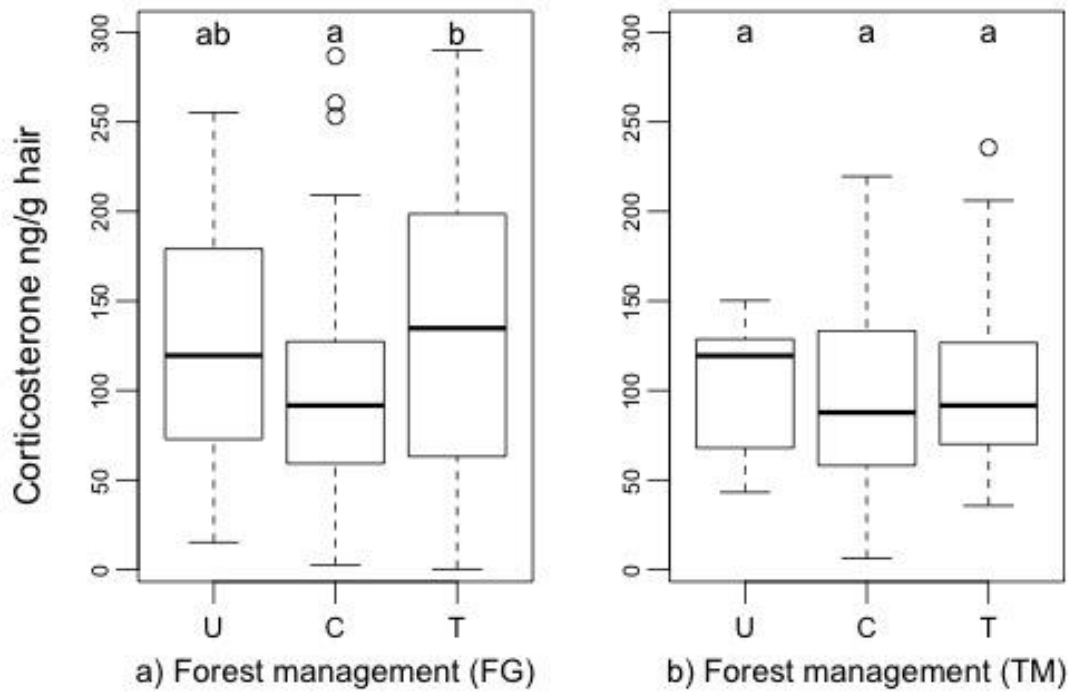

Figure 3.3.—Hair corticosterone levels (ng/g) in 189 deer mice captured on managed forest stands at two locations in the Oregon Coast Range between June and September 2012–2013. In Forest Grove, mice from treatment plots had significantly higher levels of hair corticosterone than animals captured on control plots, while no association between management level and stress hormone level was observed in Tillamook. Different letters denote significant differences at $\alpha = 0.05$. (C = Control; FG = Forest Grove; T = Treatment; TM = Tillamook; U = Uncut; Boxplots represent raw data and do not account for other variables retained in mixed effects models. Boxes represent the two middle and whiskers the lower and upper quartiles. The black band designates the median.)

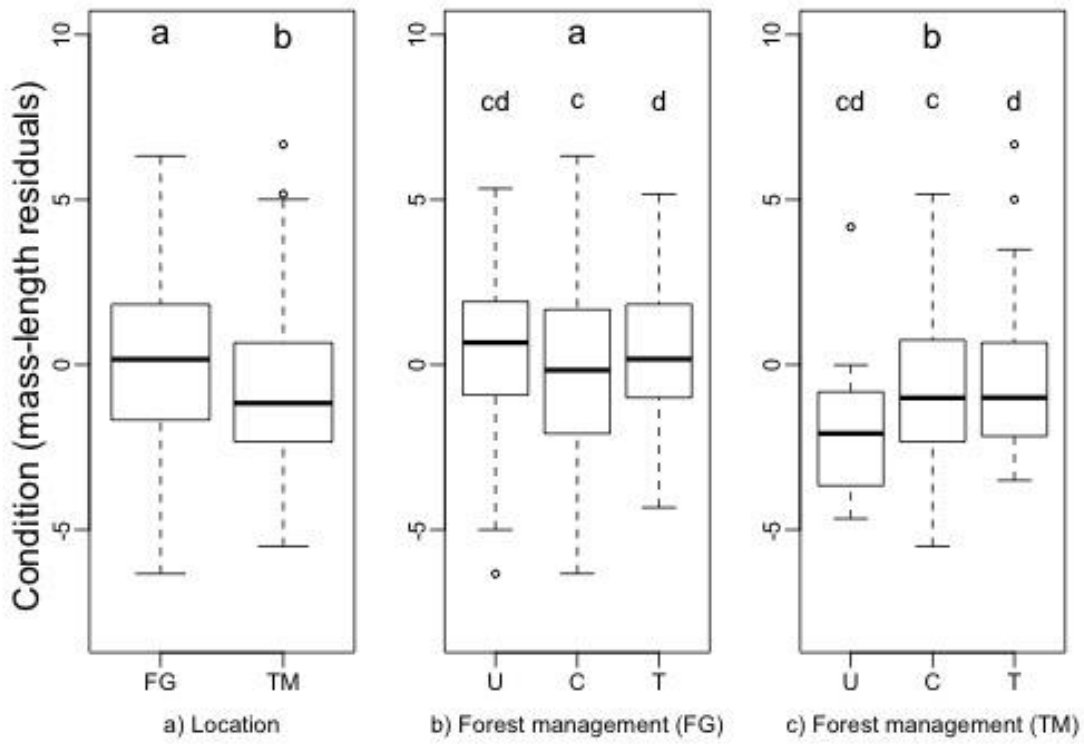

Figure 3.4.—Relationship of management intensity and location to body condition in 336 *Peromyscus maniculatus* captured on differentially managed forest plots at two locations in the Oregon Coast Range between June and September 2011–2013. Mean condition was most influenced by location (**a**) with animals in Tillamook having lower condition across all management levels (**b** and **c**). But, at both locations, mice from treatment plots were in better condition than mice from control plots (**b** and **c**). For visualization purposes, values within +/- 2.5 standard deviations of the mean are displayed, even though outliers did not influence direction or magnitude of outcomes and were retained in statistical analyses. Different letters denote significant differences at $\alpha = 0.05$. (C = Control; FG = Forest Grove; T = Treatment; TM = Tillamook; U = Uncut; Boxplots represent raw data and do not account for other variables retained in mixed effects models. Boxes represent the two middle and whiskers the lower and upper quartiles. The black band designates the median.)

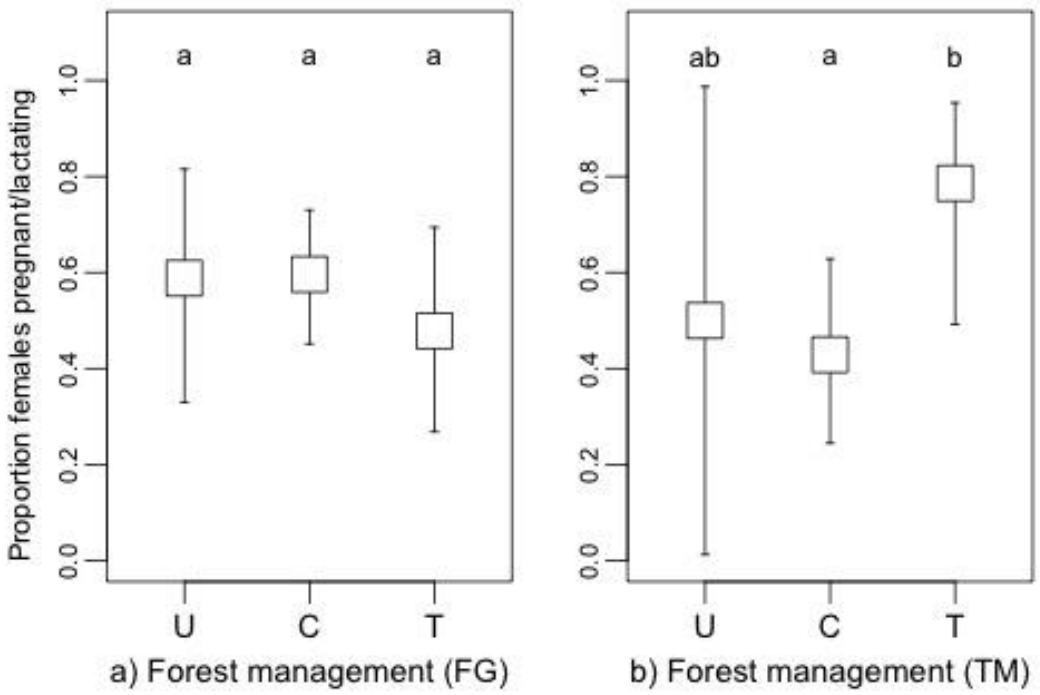

Figure 3.5.—Relationship of management intensity and location to reproductive activity in 136 adult female *Peromyscus maniculatus* captured on managed forest plots in the Oregon Coast Range between June and September 2011–2013. We did not observe any differences in reproductive activity across management intensities in Forest Grove (**a**), but found more pregnant or lactating females on treatment plots compared to control plots in Tillamook (**b**). Proportion estimates are displayed with 95% confidence intervals. Different letters denote significant differences between groups at $\alpha = 0.05$. (C = Control; FG = Forest Grove; T = Treatment; TM = Tillamook; U = Uncut; Plots show mean proportion (box) with 95% confidence intervals (error bars) and do not account for other variables retained in mixed effects models.)

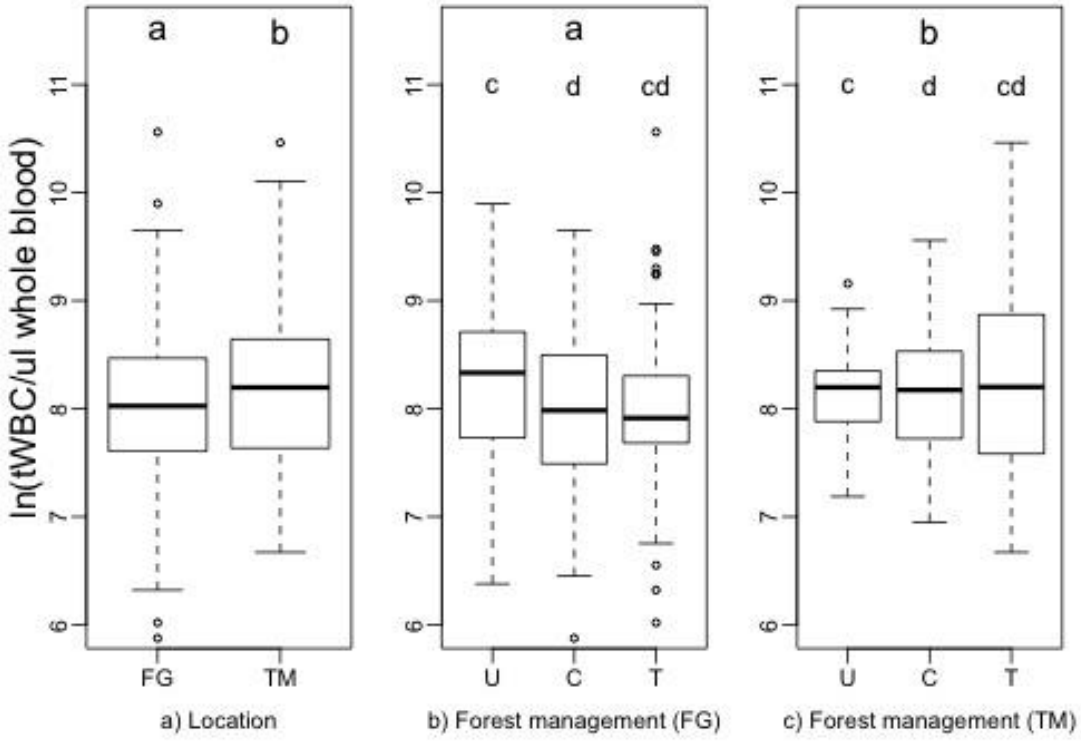

Figure 3.6.—Relationship of total white blood cell counts to location and forest management intensity in 341 deer mice (*Peromyscus maniculatus*) captured on managed forest plots at two locations in the Oregon Coast Range between June and September 2011–2013. Total white blood cells were slightly higher in animals from Tillamook than from Forest Grove (**a**) across all management intensities (**b** and **c**). In addition, mice from uncut plots had more white blood cells than those from control plots (**b** and **c**). These effects were only significant at $\alpha = 0.10$, and, in this figure only, different letters denote significant differences between groups at $\alpha = 0.10$. Cell counts were log-transformed for all analyses and visualization. (C = Control; FG = Forest Grove; T = Treatment; TM = Tillamook; tWBC = total white blood cells; U = Uncut; Boxplots represent raw data and do not account for other variables retained in mixed effects models. Boxes represent the two middle and whiskers the lower and upper quartiles. The black band designates the median.)

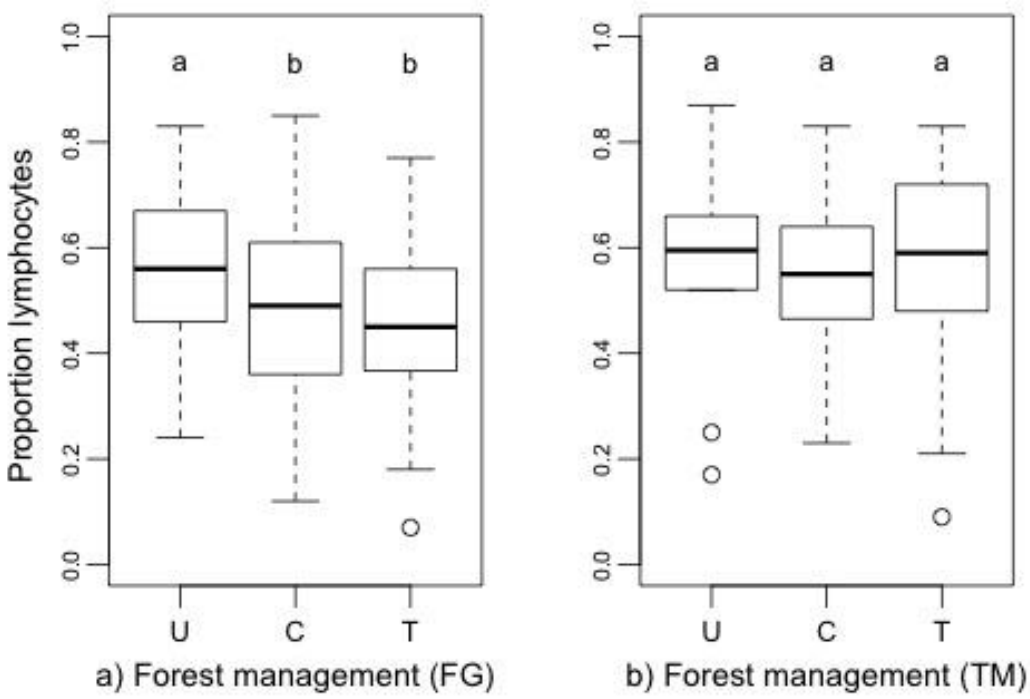

Figure 3.7.—Associations between the proportion of white blood cell made up of lymphocytes and forest management intensity by location in 341 deer mice (*Peromyscus maniculatus*) captured on managed forest plots in the Oregon Coast Range between June and September 2011–2013. In Forest Grove, mice from uncut plots had significantly more lymphocytes than animals from control and treatment plots (**a**), while, in Tillamook, we did not find a relationship between lymphocyte counts and forest management (**b**). Lymphocyte counts are depicted as proportions since total white blood cell count was included as an offset term in all statistical models predicting lymphocyte counts. Different letters denote significant differences at $\alpha = 0.05$. (C = Control; FG = Forest Grove; T = Treatment; TM = Tillamook; U = Uncut; Boxplots represent raw data and do not account for other variables retained in mixed effects models. Boxes represent the two middle and whiskers the lower and upper quartiles. The black band designates the median.)

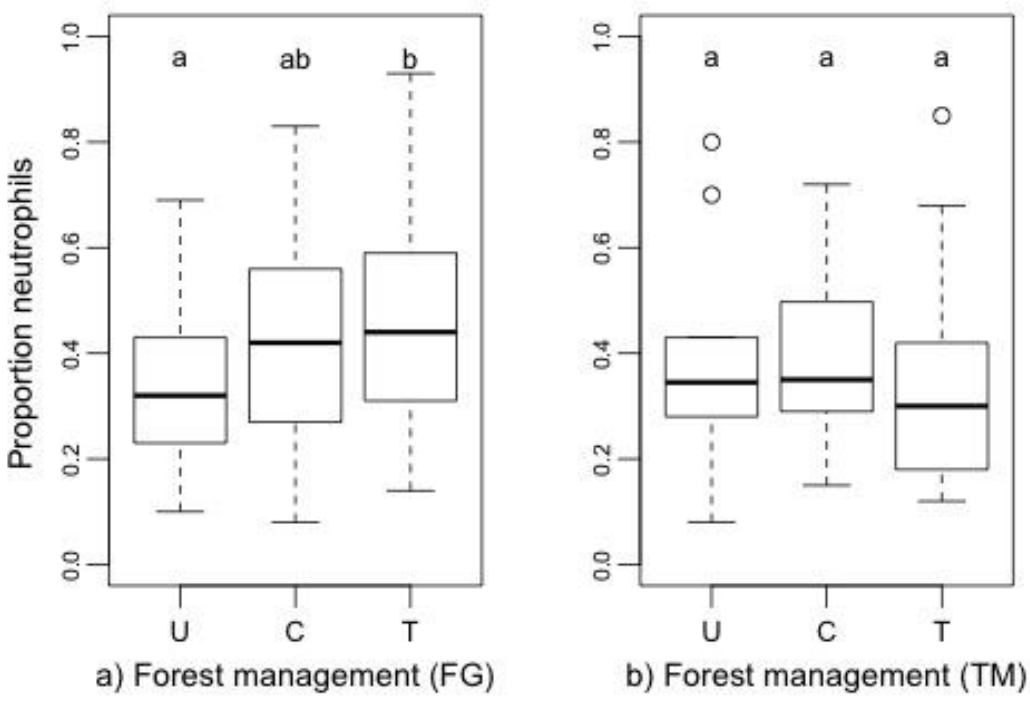

Figure 3.8.—Associations between the proportion of white blood cells made up of neutrophils and forest management intensity in 341 deer mice (*Peromyscus maniculatus*) captured on managed forest plots at two locations in the Oregon Coast Range between June and September 2011–2013. In Forest Grove, mice from treatment plots (and from control plots at $\alpha = 0.10$) had significantly more neutrophils than animals from uncut stands (**a**). In Tillamook, we found no variation in neutrophil counts across the three forest management intensities (**b**). Neutrophils are depicted as proportions since total white blood cell count was included as an offset term in all statistical models predicting neutrophil counts. Different letters denote significant differences at $\alpha = 0.05$. (C = Control; FG = Forest Grove; T = Treatment; TM = Tillamook; U = Uncut; Boxplots represent raw data and do not account for other variables retained in mixed effects models. Boxes represent the two middle and whiskers the lower and upper quartiles. The black band designates the median.)

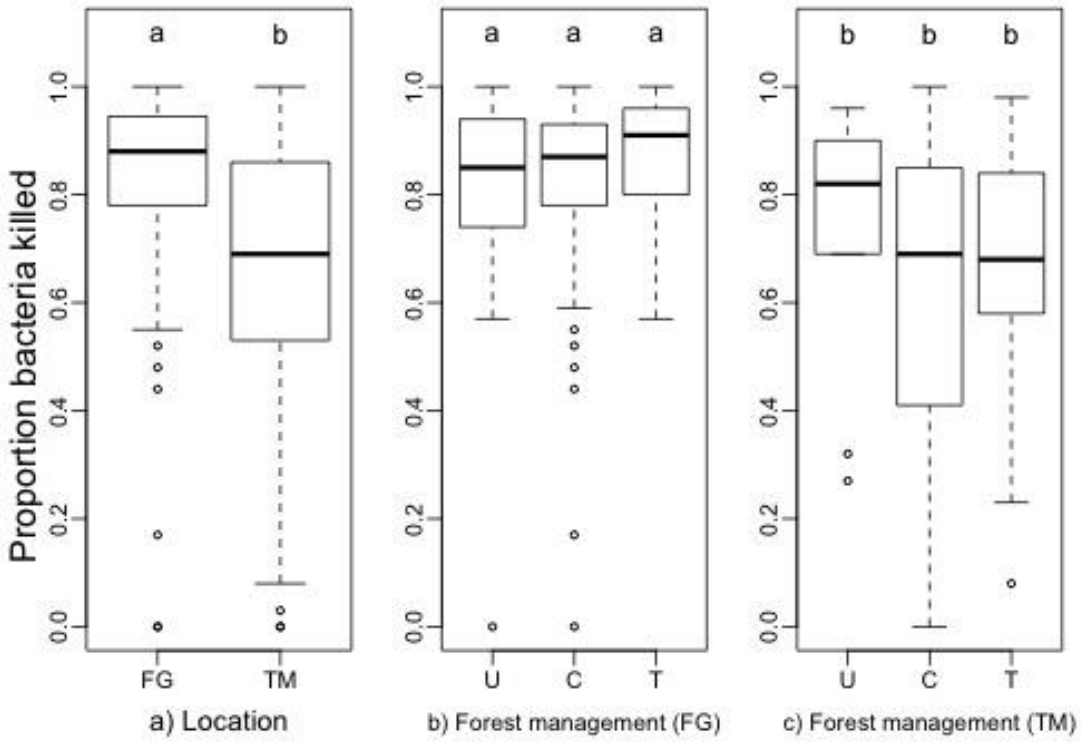

Figure 3.9.—Proportion bacterial colonies killed by whole blood from 332 deer mice (*Peromyscus maniculatus*) captured on managed forest plots at two locations in the Oregon Coast Range between June and September 2011–2013. Bactericidal ability was significantly lower in mice from Tillamook plots compared to mice sampled in equivalent plots in Forest Grove (**a**), and this pattern was observed for all management levels (**b** and **c**). Statistical models for whole blood bactericidal ability predicted the number of colonies killed and included the number of control colonies as an offset term. For visualization purposes, the proportion of colonies killed is presented in the figures. Different letters denote significant differences at $\alpha = 0.05$. (C = Control; FG = Forest Grove; T = Treatment; TM = Tillamook; U = Uncut; Boxplots represent raw data and do not account for other variables retained in mixed effects models. Boxes represent the two middle and whiskers the lower and upper quartiles. The black band designates the median.)

Chapter 4 – Intensive Forest Management May Increase Zoonotic Disease Risk from Small Mammals

Rhea Hanselmann, Laurie J. Dizney, Erin E. Gorsich, and Anna E. Jolles

ABSTRACT

Consequences of human modification of ecosystems for wild animals become especially important when zoonotic disease hosts are affected and shifting disease dynamics can impact public health. We examined the association between intensive forest management and the prevalence of three important zoonotic pathogens in wild deer mice (*Peromyscus maniculatus*), Townsend chipmunks (*Tamias townsendii*), and creeping voles (*Microtus oregoni*) on differentially managed forest plots in the coastal mountain range of Oregon, USA. We determined Sin Nombre virus prevalence in deer mice using a species-specific ELISA, estimated leptospirosis prevalence in the three rodent species based on microscopic agglutination test (MAT) antibody titers against six *Leptospira interrogans* serovars, and examined fleas collected from rodents for *Yersinia pestis* using PCR. SNV prevalence was highest on experimental plots from Forest Grove in 2011 (25%) and, for this disease focus, SNV appeared to be positively associated with forest management intensity, although this effect was not statistically significant. Prevalence of leptospirosis was 31, 17, and 15% in Townsend chipmunks, creeping voles, and deer mice respectively. We found a significant weak but positive association between leptospirosis and forest management intensity in voles (P = 0.047). We observed a similar, albeit non-significant, pattern for chipmunks in one, but not the other forestry district, and saw no effect of forest management on Leptospira prevalence in deer mice. We did not find *Y. pestis* in any of the 145 fleas tested. Our results provide baseline data for northwest Oregon on the prevalence of three zoonoses with high relevance for public health, and underline the importance of considering the potential impact that anthropogenic environmental change can have for disease dynamics in wildlife. Changes in transmission and distribution of diseases in wild animals can have far-reaching consequences for affected wildlife, and for domestic animal and human health. We briefly discuss potential mechanisms and suggest areas for future research.

INTRODUCTION

Unprecedented human population growth is accompanied by a mounting need for food, space, and natural resources to support the increasing number of persons sharing our planet's surface. Expansion of human settlements into previously undisturbed areas encroaches on wildlife habitat; roads and conversion of natural areas to agricultural lands lead to fragmentation and overt habitat loss (Vitousek et al. 1997). The detrimental consequences that anthropogenic environmental change can have for wild animal populations and biodiversity at large have been documented time and again (reviewed in Pimm et al. 1995; Vitousek et al. 1997; Chapin III et al. 2000; Dirzo et al. 2014). It is also becoming increasingly apparent, however, that human-induced changes to the integrity and composition of natural communities can drive the dynamics of infectious diseases. And, when shifting disease dynamics involve zoonoses (diseases transmitted from animals to humans), considering the potential outcomes for human health becomes paramount (reviewed in Daszak et al. 2000; Patz et al. 2000; Bradley and Altizer 2007; Aguirre and Tabor 2008; Keesing et al. 2010). However, forecasting the emergence, re-emergence, or spread of pathogens in relation to environmental change is complicated by the ecology of both hosts and pathogens, which may respond unpredictably and variably influence the direction and magnitude of disease dynamics (Brearley et al. 2012).

For instance, decreased biodiversity, a common result of human disturbance, has been shown to increase the risk of exposure to several zoonotic diseases (Keesing et al. 2010). This includes vector-borne infections such as Lyme disease (Ostfeld and Keesing 2000) and West Nile virus (Ezenwa et al. 2006; Swaddle and Calos 2008), but also directly transmitted diseases such as Sin Nombre virus (Clay et al. 2009b; Dizney and Ruedas 2009; Carver et al. 2010) and other hantaviruses (Tersago et al. 2008; Blasdell et al. 2011). For other diseases, however, the relationship between biodiversity and disease risk is reversed, with higher risk associated with increased species diversity (Saul 2003). In addition to altering host communities, human-induced environmental change can stress wild animals persisting in disturbed habitats. Stress, in turn, can alter protective immune responses, change individuals'

susceptibility to disease, and alter disease prevalence at the population scale (Anderson 1990; Bartolomucci 2007; Martin et al. 2010). The complexity and interconnectedness of the animal-, population-, and ecosystem-level factors that can influence disease dynamics make predicting the consequences for disease transmission in wildlife populations and the potential risks for human health difficult (Lafferty and Holt 2003; Wilcox and Gubler 2005). To begin to understand and forecast the implications of environmental change for zoonotic disease risk, it is essential first to determine existing patterns of disease in wildlife populations and examine the impact of differing habitat quality on disease prevalence (Gubler et al. 2001).

Timber production is an important and widespread agricultural industry in many areas of the Pacific Northwest (PNW) of North America (Swanson and Franklin 1992; Larson and Oliver 1996). In the US, forests are managed intensively, which significantly alters the landscape and simplifies community structure (Lehmkuhl and Ruggiero 1991). Management practices include clearcut harvesting of expansive mature tree stands, mechanical vegetation removal, immediate replanting, usually with a single focal species, and application of large quantities of herbicide mixtures (Tatum 2004; Wagner et al. 2004). Studies evaluating environmental impacts of the most commonly used herbicides state that the majority of these compounds neither persist nor bioaccumulate in the environment and are thought to pose little direct risk to wildlife (Giesy et al. 2000; Lautenschlager and Sullivan 2004; Tatum 2004). However, both laboratory investigations into direct effects of herbicides on animal physiology and survival (Luster et al. 1993; The ICICIS Group Investigators 1998; McComb et al. 2008), and field studies examining indirect consequences of intensive forest management (IFM) on vertebrate diversity and abundance (Santillo et al. 1989; Tew et al. 1992; Cole et al. 1998; Betts et al. 2013) show conflicting results.

Combined, direct toxicity and indirect consequences resulting from changes in habitat quality (e.g. stress, condition, immune function) have the potential to modify the susceptibility of wild animals to disease (Rohr et al. 2008b; Martin et al. 2010). For zoonotic diseases typically endemic in the environment at low levels, changes in host susceptibility can provide an opportunity for pathogens to emerge and invade a

community (Graham et al. 2011). Despite serious implications for human health, few studies have evaluated the potentially transient, non-lethal impacts of intensive agricultural practices on wildlife health and zoonotic disease prevalence (but see Tersago et al. 2004; Mills 2005; Rohr et al. 2008a), especially in relevant mammalian host species and in a large-scale, experimental, multi-host, and multi-pathogen system (but see Lehmer et al. 2008).

Among mammalian disease hosts, rodents play a central role in numerous pathogen life cycles (Meerburg et al. 2009). In addition to comprising the most abundant and diverse order of mammals (Nowak 1999), members of the order Rodentia harbor a multitude of diseases that affect wildlife, domestic animals, and humans. Zoonotic pathogens transmitted by rodents include viruses (e.g. hantaviruses), bacteria such as the causative agents of Leptospirosis (*Leptospira* spp.) and Plague (*Yersinia pestis*), and numerous protozoa and helminth (worm) parasites (Vance and Duszynski 1985; Mills and Childs 1998; Meerburg et al. 2009). Besides being important disease hosts, many rodents are highly adaptable to changes in their environment, often persisting in disturbed habitats and predominating in simplified communities (Coppeto et al. 2006; Bordes et al. 2015). Therefore, wild rodents are useful model organisms in which to study the association between anthropogenic environmental change and the prevalence of zoonotic diseases (Sánchez-Chardi et al. 2007; Meerburg et al. 2009).

The deer mouse (*Peromyscus maniculatus*) is one of the most widespread and abundant rodent species in the PNW and is of particular interest due to its role as the primary reservoir for Sin Nombre virus (SNV; Childs et al. 1994). Sin Nombre virus (family Bunyaviridae, genus *Hantavirus*) is the causative agent of Hantavirus Pulmonary Syndrome, a frequently fatal pneumonia affecting humans exposed directly to the virus via infected rodent bites or inhalation of aerosolized viral particles in rodent excrement (Mills and Childs 1998; Mills et al. 1998, 1999). In North America, SNV is most prevalent in rodents in the southwestern and western United States (Calisher et al. 1999; Orrock and Allan 2008; Dizney et al. 2010). Infection prevalence varies both spatially and temporally in natural populations, with isolated foci of

infection detected in rodents in close proximity to uninfected populations (Otteson et al. 1996; Kuenzi et al. 1999; Douglass et al. 2001; Carver et al. 2010). In *P. maniculatus* captured in parks and wildlife refuges in and around the Portland, Oregon metropolitan area, virus prevalence was found to be as high as 14.8% (0.0–14.8%; Dizney and Ruedas 2009; Dizney et al. 2010). The ubiquity of its primary host, the relatively high local pathogen prevalence, and existing evidence that SNV prevalence in deer mice can vary across a range of habitat types and qualities motivated our investigation into the association between intensive forest management and SNV (Mills et al. 1998; Calisher et al. 2001; Mackelprang et al. 2001; Lehmer et al. 2008).

Rodents are also considered fundamental in the transmission cycle of Leptospira, a generalist bacterial spirochete that infects a multitude of hosts (Meerburg et al. 2009; Wasiński and Dutkiewicz 2013; Cosson et al. 2014). Leptospirosis is one of the most geographically widespread zoonotic diseases in the world. Thirteen known pathogenic species of bacteria cause disease in both humans and animals (Evangelista and Coburn 2010). Leptospira bacteria are enzootic in many sylvatic and domestic wild rodent populations and produce persistent, asymptomatic infection in many rodent reservoirs. Bacteria colonize the kidneys and can be shed in urine for months after initial infection with the potential to infect other wild and domestic animals causing a range of disease or carrier states (Thiermann 1981; Monahan et al. 2008). Humans are incidental hosts infected either via direct contact with animal urine or, more commonly, exposure to contaminated soil or water (Ko et al. 2009). Disease severity ranges from mild flu-like symptoms to organ failure and death (Evangelista and Coburn 2010). Human migration and travel have changed the epidemiology of leptospirosis and increased the incidence of the disease in areas where it was previously uncommon or non-endemic (Bandara et al. 2014). In the continental United States, for instance, recent outbreaks of leptospirosis have occurred in participants of recreational and sporting events involving natural water bodies (Monahan et al. 2009). The re-emergence of leptospirosis as a human disease risk in the US and its common occurrence in wild rodent populations underline the importance of evaluating the prevalence of this disease in wild rodent reservoirs affected by anthropogenic

environmental change. This is especially relevant in an area such as northwest Oregon where heavy rainfall may promote leptospires reaching natural water ways and widespread outdoor and water recreation activities increase human and domestic animal risk of exposure.

Bubonic, pneumonic, and septicemic plague are all versions of a highly fatal disease caused by the gram-negative bacterium *Yersinia pestis*, which infects the lymphatic system, respiratory tissues, and blood stream respectively of susceptible hosts (Centers for Disease Control and Prevention 1996; Gage and Kosoy 2005). Since the last pandemic in Eastern Asia and Europe more than a century ago, the geographic range of *Y. pestis* has expanded to previously unaffected regions around the globe, including the western United States. Humans usually become infected with *Y. pestis* through bites from fleas associated with wild rodent or other mammalian hosts, or directly from handling infected animals (Weniger et al. 1984; Gage et al. 2000; Gubler et al. 2001; Gage and Kosoy 2005; McElroy et al. 2010). In the western USA, *Y. pestis* is thought to be maintained in wildlife, especially rodent, hosts that appear resistant to infection. Transmission to highly susceptible animals is the presumptive cause of intermittent disease outbreaks (epizootics), which are usually associated with high mortality and can significantly increase the risk of human infection (Salkeld and Stapp 2008; Stapp et al. 2008). Deer mice and certain species of voles (*Microtus* spp.) have been implicated in acting as enzootic maintenance hosts for plague, while chipmunks (*Tamias* spp.) appear to be highly susceptible to this bacterial disease (Quan et al. 1956; Gage and Kosoy 2005; Meerburg et al. 2009). Furthermore, in enzootic regions of the US, the incidence of plague in fleas and rodent hosts has been associated with changes in habitat and climate (reviewed in Gubler et al. 2001; Ari et al. 2011). However, despite extensive research into rodent host and flea transmission competence, as well as environmental variables influencing interactions between small mammals, their fleas, and *Y. pestis*, the exact mechanisms driving the often cyclical sylvatic plague dynamics in the United States are still poorly understood (Gage and Kosoy 2005; Salkeld and Stapp 2008; Thiagarajan et al. 2008; Franklin et al. 2010; Griffin et al. 2010).

In many areas of Oregon, including coastal Coos County in the southwest, *Y. pestis* is considered enzootic and, as is the case for other areas, plague appears to be maintained in several species of wildlife, including wild rodents (Hopkins and Gresbrink 1982). Since 1995, fewer than ten human cases of plague have been reported in the state, with the two most recent cases reported from central Oregon in 2012 and 2015. In both of these instances, patients were thought to have been infected via flea bites acquired during outdoor recreation activities. Two earlier patients diagnosed with plague in 2010 were thought to have acquired the infection from fleas found on their pet dog (Centers for Disease Control and Prevention 2011). To date, there have been no known occurrences of plague in the area of our study sites in the northwestern coastal mountains of Oregon. However, given that plague is known to exist in the state and is an emerging disease of significant public health concern, it was relevant to survey rodents inhabiting severely altered habitats for *Y. pestis* to gain a preliminary understanding of infection risk in the area.

Little is known about zoonotic infections in wild rodents in northwestern Oregon, and no studies have investigated the influence of anthropogenic environmental change on zoonoses in this region. To fill this knowledge gap, we took advantage of an existing experimental design, unique on spatial and temporal scales. In 2013, Betts et al. (2013) documented decreases in habitat quality and simplification of vegetation and songbird communities associated with increasing forest management intensity on large, replicated experimental forest plots in the central to northern coastal mountain range of Oregon. We examined the relationship between forest management and the prevalence of three regionally important zoonotic diseases in known and potential wild rodent hosts inhabiting a subset of these same differentially managed experimental plots.

The principal objective of our study was to examine if intensive forest management was associated with Sin Nombre virus, *Leptospira interrogans*, and *Yersinia pestis* infection prevalence in small mammals inhabiting our study sites. First, we needed to identify the prevalence of these infections in rodents in the Oregon Coast Range, describe disease distribution within our study area and, for Leptospira and

Yersinia pestis, document differences in prevalence by host species. To account for known risk factors for the three diseases, it was also important that we include animal-level characteristics associated with each infection in our analyses.

We predicted that prevalence of the three focal zoonoses would be associated with the level of forest management intensity. Based on existing reports documenting SNV in Oregon (Dizney et al. 2010) and observed *Leptospira* spp. incidence data in domestic and wild animals in the region (Smith 1959; Hodder et al. 1992; Hamir et al. 2001; Grayzel and DeBess 2016), we expected to find evidence of SNV and *Leptospira interrogans* infection in the wild rodent populations examined. Although occasional cases of plague in humans and domestic animals have been reported in other parts of Oregon (Weniger et al. 1984; Centers for Disease Control and Prevention 2011), there are no reports or known surveys of this disease in our study area. Therefore, our investigation into *Yersinia pestis* prevalence in fleas collected from wild rodents was purely exploratory and represented a preliminary survey of this bacterium in the small mammal populations in northwestern Oregon.

Considering the documented negative consequences of anthropogenic environmental change for the prevalence and dynamics of infectious disease in wildlife (Daszak et al. 2001; Mackelprang et al. 2001; Johnson and Chase 2004; Martin et al. 2010), and the potentially detrimental effects of IFM for wildlife populations (Gashwiler 1970; Santillo et al. 1989; Lehmkuhl and Ruggiero 1991; Cole et al. 1998; Steventon et al. 1998; Betts et al. 2013) and for individual animal health (Chapter 3), we expected disease prevalence to be positively associated with increasing level of forest management intensity.

METHODS

Study sites

During the summers of 2011–2013, we sampled small mammals in the coastal mountain range of northwestern Oregon, USA. Our study sites, as well as trapping and sampling methods, are described in detail elsewhere (Chapter 3). Briefly, we positioned transects at the center of twelve large (12–16 ha) managed forest plots

located in two Oregon Department of Forestry (ODF) districts: Forest Grove (centered on latitude: 45.6212; longitude: -123.4010) and Tillamook (centered on latitude: 45.6330; longitude: -123.6135). Plots located in the two districts differed in their elevation and mean annual rainfall, with stands in Forest Grove located at lower elevation (250–500 m) on the east-facing slopes of the mountain range and experiencing slightly drier weather (250–360 cm/year) compared to Tillamook plots, which were located at 600–700 m along the mountain ridge and west-facing slopes, and, on average, received 360–460 cm of rain per year (PRISM Climate Group 2016).

Eight of our twelve plots were clearcut in late 2009 and replanted with Douglas fir (*Pseudotsuga menziesii*) seedlings in the spring of 2010. Of these, four plots were sprayed with a mixture of herbicides and surfactants before replanting, and again either once or twice a year after replanting (hereafter *treatment* plots). The remaining four clearcut plots were not sprayed or actively managed before or after replanting in 2010 (hereafter *control* plots). By 2011, these plots experienced significant growth and diversity of native and non-native broadleaf and non-woody vegetation (Betts et al. 2013). In 2011, two control plots were situated in each forestry district. However, control plots in the same district used in this study were located very close to one another (< 1 km), which posed the risk of animals moving between adjacent plots (Hooven 1958). Therefore, in 2012 and 2013, we replaced one of the original 2011 control plots in each district with two more isolated plots, both located in the Forest Grove district. These new control plots had been clearcut, replanted, and left untreated on a comparable time scale as the original control plots. Finally, as a baseline habitat type, in each district, we also identified two uncut plots consisting of young, 40–50-year-old mixed Douglas fir and hardwood stands that had not experienced recent management interventions (hereafter *uncut* plots).

Study species

We focused our trapping efforts on three species of locally abundant small mammals: deer mice (*Peromyscus maniculatus*), Townsend chipmunks (*Tamias townsendii*), and creeping voles (*Microtus oregoni*; Sullivan et al. 1997). Deer mice

are one of the most abundant species of rodent in North America (Maser 1998). They are nocturnal omnivores that inhabit a variety of ecosystems, survive across a range of disturbance levels, and are ubiquitous in Pacific Northwest forests (Hooven 1958; Maser et al. 1981; Tallmon et al. 2003; Lehmer et al. 2008). Deer mice are the primary reservoir for SNV and play a role in several other zoonotic disease cycles (Childs et al. 1994; Peavey and Lane 1995; Mills and Childs 1998; Dabritz et al. 2008).

Townsend chipmunks are a medium-sized, primarily diurnal or crepuscular, omnivorous sciurid abundant especially in old-growth, but also in young, managed hardwood and Douglas fir forests throughout the PNW (Maser et al. 1981; Doyle 1987; Rosenberg and Anthony 1993; Carey 1995, 2000). Although little information on disease has been published for Townsend chipmunks (but see Easton 1975; Hill and Duszynski 1986; Fuller and Duszynski 1997), closely related species of sciurids have been identified as reservoirs for several vector-borne zoonotic infections in the United States (McLean et al. 1993; Nieto and Foley 2009).

Finally, *M. oregoni* is a small, nocturnal, herbivorous species of vole found in montane coniferous forests of the PNW (Maser et al. 1981; Doyle 1987). Creeping voles prefer early-successional forest habitats including young stands and clearcuts (Doyle 1987; Sullivan et al. 1997). Similar to chipmunks, data on infections associated with creeping voles is sparse at best (Vance and Duszynski 1985). However, pathogens and parasites have been described in related *Microtus* species and include several zoonotic agents (Rausch 1967; Lee et al. 1985; Song et al. 1995).

Animal trapping

Every 3–4 weeks between June and September, we used Sherman live traps to capture wild rodents along 150-meter (2011) and 200-meter (2012 and 2013) line transects located at the center of each study plot. Along each transect, we set two traps every 10 meters (30 traps/transect in 2011 and 42 traps/transect in 2012 and 2013).

In 2011 and 2012, we visited all plots four times and trapped deer mice, chipmunks, and voles. In 2011, during the first trapping session in June, Forest Grove plots were visited for four consecutive nights, while Tillamook plots were only

sampled for two nights due to exceptionally poor trapping success resulting from cold and wet weather conditions. Visits in July and August of 2011 consisted of four consecutive trapping nights per plot in both districts. Due to logistical constraints during September of 2011, only three plots (one per management level) in each district were sampled for one night each. In 2012, we sampled all plots four times for two consecutive trapping nights per visit. Finally, in 2013, we visited Forest Grove plots once during the early-summer and once during mid-summer and sampled each plot for two nights. Due to loss of processing equipment during the first field visit, we trapped for two consecutive nights on Tillamook plots only during the second visit in mid-summer of 2013. And, throughout the 2013 trapping season we focused our efforts only on deer mice.

On trapping nights, we outfitted traps with clean natural cotton bedding and fresh bait consisting of rolled oats and peanut butter. We opened traps before dusk and checked them shortly after sunrise the following morning. Trapping took place overnight, but included the crepuscular periods to target chipmunks. Traps were closed during the day.

Traps containing rodents were collected and transported to a central location for processing. All new animals were identified with a uniquely numbered metal ear tag (National Band & Tag Company, # 1005-1). Animals that were recaptured the day after initial capture were released immediately at the site of capture without further processing. Individuals captured during a previous sampling period (~30 days prior) were identified as recaptures and processed along with new animals. After processing, all animals were transported back to their original site of capture and released.

Data collection and sampling

We recorded date and transect, and collected demographic parameters for each animal. Rodents were sexed and the reproductive status of females was noted (visibly pregnant/lactating or not; Lehmer et al. 2007). In all species, body mass was measured to the nearest 0.5 g using a hanging Pesola™ scale, and body length (snout to base of tail) was measured in millimeters. Deer mice ≤ 14 g without signs of reproductive

activity were classified as juveniles, with all other mice considered adults. Chipmunks and voles were classified into juvenile or adult age groups based on body size, evidence of reproductive activity, and appearance of hair coat.

All animals were briefly anesthetized with isoflurane and a blood sample was collected from the retro-orbital sinus using a heparinized glass hematocrit tube (Hoff 2000). Blood was collected into heparinized collection vials (BD microtainer) and stored in a portable cooler until centrifugation for 15 minutes at 2000 g (6000 rpm) to separate plasma from cells. Plasma aliquots were stored in liquid nitrogen in the field, transferred to a -80°C freezer upon return to the laboratory, and were kept frozen until further processing. We noted the presence of ectoparasites for all animals. Fleas were collected opportunistically and stored in ethanol.

All persons involved with trapping and handling wild rodents used personal protective equipment (disposable nitrile gloves and a N95 face mask) to prevent potential transmission of zoonotic agents (Mills et al. 1995). Animal procedures were approved by the Oregon Department of Fish and Wildlife and the Institutional Animal Care and Use Committee at Oregon State University (ACUP #4195).

Disease testing

Sin Nombre virus.—Deer mice become persistently infected with SNV and intermittently shed virus in their urine and saliva without suffering significant morbidity or mortality (Otteson et al. 1996; Netski et al. 1999; Botten et al. 2000; Meyer and Schmaljohn 2000; Schönrich et al. 2008). Viral RNA has been detected as early as two days after experimental infection, and viremia has been confirmed for at least ninety days post-inoculation (Schountz et al. 2012; Schountz and Prescott 2014). Once infected, deer mice produce virus-specific anti-SNV antibodies within as little as ten days, and antibodies are thought to persist for life (Botten et al. 2000; Schountz et al. 2012; Schountz and Prescott 2014). Therefore, the presence of circulating anti-SNV antibodies confirms exposure to, and most likely active infection with, Sin Nombre virus and detecting said antibodies is the standard method for testing wild deer mice for SNV (Dizney et al. 2010; Schountz and Prescott 2014). We used an

enzyme-linked immunosorbent assay (ELISA) for immunoglobulin G (IgG) antibodies against SNV to measure prevalence of Sin Nombre virus infection in the deer mouse populations in our study (Feldmann et al. 1993).

Briefly, frozen plasma samples were thawed at room temperature and heat deactivated in a warm water bath for 30 minutes. Each sample, as well as positive and negative controls from mice with known infection status (provided by James Terry, Oregon State Public Health Laboratory, Portland Oregon), were diluted 1:100 with diluent consisting of skim milk powder, phosphate buffered saline, and Tween-20 (Sigma-Aldrich). We added 100 µl of each sample solution in duplicate to adjacent wells on a 96-well flat-bottom polystyrene plate previously coated with SNV nucleocapsid protein, and covered and incubated plates at 37 ºC for one hour. After a washing step, we added 100 µl of horseradish peroxidase-labeled goat anti-Peromyscus antibody solution (1 µg/ml) and again incubated at 37 ºC for one hour. After a second wash step, we added 100 µl of ABTS peroxidase substrate. We incubated the plate for a final 30 minutes and read optical density (OD) at 405 nm using an Epoch Microplate Spectrophotometer (Bio-Tek®). For each sample and for controls, we averaged OD and calculated standard deviation. We determined the cut off for positive samples as three times the mean OD of negative controls and identified samples with mean OD $\geq$ cut off value as positive (L. Dizney, 2011, pers. comm.). Samples with OD greater than twice, but less than three times the mean OD of negative controls, and those demonstrating a high coefficient of variation, were rerun. All samples collected from deer mice were tested for SNV regardless of recapture or previously determined infection status. Due to the species-specific nature of the ELISA, plasma samples from chipmunks and voles were not tested for SNV (T. Schountz 2011, pers. comm.).

Leptospira interrogans.—In wild rodents, *L. interrogans* is the species of Leptospira most commonly implicated in causing persistent infection (Easterbrook et al. 2007; Suepaul et al. 2010; Himsworth et al. 2013a). In most mammalian hosts, with the exception of some rat species, infection with *L. interrogans* induces a strong agglutinating antibody response (Adler and Faine 1977; Ko et al. 2009; Evangelista

and Coburn 2010; Himsworth et al. 2013a). The microscopic agglutination test (MAT) measures antibody titers against Leptospira serovars (bacterial strains) in host serum or plasma with high specificity (i.e. the ability to correctly identify uninfected individuals as negative), and marginal sensitivity (i.e. both poor ability to correctly identify infected individuals as positive, and to identify specifically infecting serovars due to antibodies cross-reacting with different bacterial strains; Levett 2003; Smythe et al. 2009; Limmathurotsakul et al. 2012; Chirathaworn et al. 2014). Since we aimed to determine overall prevalence of Leptospira in the wild rodent population, and since the serovars present in our study populations are unknown, MAT was a convenient and suitable method to assess historic exposure to and/or active infection with *L. interrogans*. This assay enabled us to survey plasma samples collected from our target species for six different serovars known to be regionally endemic in domestic animals and livestock simultaneously, which increased the likelihood of detecting agglutinating antibodies against *L. interrogans*, but did not allow distinction between previous exposure or active infection, or identification of specific infecting serovars.

Samples were submitted to the Veterinary Diagnostic Laboratory (VDL) at Oregon State University's College of Veterinary Medicine. The VDL maintains active *L. interrogans* cultures and tested rodent plasma for agglutinating antibodies against serovars bratislava, canicola, gryppotyphosa, hardjo, icterohemorrhagiae, and pomona following the Center for Veterinary Biologics and National Veterinary Services Laboratories Testing Protocol: Microscopic Agglutination Test (MAT) for Detection of Leptospira Antibodies in Animal Serum (SOP-BI-0038). For a given plasma dilution, agglutination of 50% was considered positive (Saadi and Post 1976).

In animal and human patients, a four-fold increase in antibody titers on MAT measured in paired serum samples is considered diagnostic of leptospirosis (Cole et al. 1973; Cumberland et al. 1999; Bajani et al. 2003; Smythe et al. 2009). Paired samples were not available for most of our study animals. Therefore, we classified animals as positive or negative for *Leptospira interrogans* (hereafter Lepto+ vs. Lepto-) based on combined antibody titers to the six serovars examined via MAT. Specifically, we used the following criteria to identify an animal as positive at the time point of sample

collection: titers ≥ 1:400 for one or more serovars concurrently; two or more concurrent titers ≥ 1:200; three or more concurrent titers of ≥ 1:100. In addition, for animals for which samples from multiple time points were available, we considered samples to be positive if titers to one or two serovars ≥ 1:100 were preceded or followed by titers classified as positive according to the criteria outlined above at the time point immediately before or after the sample in question (Davis et al. 2008b). Deer mouse samples were available from all three study years, whereas plasma samples from chipmunks and creeping voles were available only from 2011 and 2012.

Yersinia pestis.—Susceptible mammals infected with *Yersinia pestis* harbor high bacterial loads in their bloodstream, especially immediately before succumbing to the disease. High bacteremia allows feeding fleas to become infected and transmit *Y. pestis* to new hosts during subsequent feedings (Gage and Kosoy 2005). *Y. pestis* proliferate and form plaques in the flea's gut, which eventually block movement of blood through the gut. Blocked, starving fleas continue to feed, often on multiple hosts, but blood meals are regurgitated back through the flea's mouthparts thereby infecting new hosts (Bacot and Martin 1914; Anisimov 2002; Gage and Kosoy 2005; Franklin et al. 2010).

To examine whether plague was present in the rodent population in northwestern Oregon, we surveyed fleas found on our three target rodent species for *Y. pestis*. Fleas were opportunistically collected from wild rodents and submitted to the United States Geologic Survey National Wildlife Health Center (USGS NWHC) in Madison, Wisconsin, USA for identification and *Yersinia pestis* testing. All fleas were identified to species (or genus) under stereomicroscopy by a trained individual using morphologic and taxonomic reference guides (Hubbard and others 1947; Stark 1958; Furman and Catts 1982).

For each rodent host, fleas of the same species were pooled (1-8 fleas per pool) and homogenized using stainless steel beads in a Bullet blender® (Next Advance). DNA was extracted following manufacturer's instructions including proteinase K digestion using a Quick-gDNA MiniPrep (Zymo Research) and screened for the presence of *Y. pestis* by real time PCR (Applied Biosystems) targeting the *pim*gene on

the pPCP1 plasmid (Hu et al. 1998). Presence of *Y. pestis* DNA in individual or pooled fleas is considered evidence for infection of the mammal host from which said blood meal was obtained (Griffin et al. 2010). However, since fleas can have multiple blood meals in their gut that may originate from more than one host, presence of bacterial DNA does not necessarily indicate plague in the rodent from which the flea was collected (Franklin et al. 2010).

Statistical analyses

Sin Nombre virus.—To direct statistical analyses, we visually explored spatial and temporal patterns of SNV at three levels. First, we computed prevalence of SNV as the number of plasma samples that tested positive for SNV on ELISA divided by the total number of samples tested. We then compared SNV prevalence: 1) in the two forestry districts (Forest Grove and Tillamook) during each of the three sampling years, and 2) at the three forest management levels for each district and year. Finally, to avoid artificially inflating or diluting true SNV prevalence in our sample, we accounted for deer mice that had been recaptured during a single sampling year by determining SNV prevalence across forest management levels for each sampling period in a given year in each district. This exploratory approach allowed us to identify the presence of one distinct SNV focus in the deer mouse populations examined. As a result, we restricted subsequent statistical analyses to the district where and the year during which we found the majority of SNV+ animals.

To examine the association of intensive forest management on SNV prevalence in the identified infection focus, we constructed a generalized linear mixed effects model using a binomial error distribution. We constructed a full model including management intensity (uncut; control; treatment), sampling season (June; July; August; September), and sex (male; female) as fixed effects. Although age, along with sex and season, has been shown to be linked to SNV infection (Dizney et al. 2010), the small number of juvenile mice in the sample selected for statistical analysis prevented us from controlling for age in our model. To account for the fact that some mice were caught during multiple sampling periods, whereas others were captured

only once, we included the interaction between individual animal ID and recapture status (0/1) as a random effect in the model (Telfer et al. 2007). However, since our dataset was small and unbalanced (i.e. certain category combinations did not exist since mice were not captured on all plots during every sampling period in 2011), our models did not converge, which forced us to simplify our approach. For each of the four sampling periods in 2011, we performed a Fisher's exact test to examine the association between SNV infection and forest management level (Ramsey and Schafer 2012). This allowed us to account for forest management and season, but not sex. To correct for multiple hypothesis testing ($m = 4$), we adjusted the level of significance using a Bonferroni correction ($\alpha_{\text{corrected}} = \alpha / m = 0.0125$).

Leptospira interrogans.—We were interested in exploring the effect of forest management level on prevalence of *L. interrogans* in each of our three focal rodent species. To this end, we constructed generalized linear mixed effects models examining Leptospira infection (Lepto+/Lepto-). We developed models including management intensity (uncut; control; treatment) and district (Forest Grove; Tillamook) as environmental predictor variables. Overall environmental conditions varied slightly between the two forestry districts. To control for potential effects of forest management intensity on infection that depended on these varying environmental contexts, we also included a management by district interaction term in all of our full models. During model selection, the interaction term was only considered if the main effects were also retained in the model.

Since susceptibility to Leptospira infection and infecting bacterial strains vary widely across rodent species (Packchanian 1940; McKiel et al. 1961), we constructed separate models for mice, chipmunks, and voles. Within species, infection has also been shown to differ with demographic variables (Himsworth et al. 2013a; b). To account for animal-level variation, we controlled for sex in all models, and included age in models describing Leptospira infection in deer mice and Townsend chipmunks as fixed effects. Since all voles trapped were adults, we did not add an age variable to the model for this species. Leptospira infection prevalence can vary over time (Himsworth et al. 2013a). Therefore, we also included season (early-summer; mid-

summer; late-summer) and sampling year (2011; 2012; 2013) as fixed effects in all models. Exact sampling dates across the three study years differed slightly. To control for this variation, we defined season categories as 30-day intervals spanning the period starting on the earliest Gregorian calendar date sampled during all three study years (June 21 = day 1) and ending on the latest date sampled during all three study years (September 15 = day 87). Finally, to account for the fact that some animals were caught multiple times during the study period, whereas others were only caught once, we included the interaction between individual animal ID and recapture status (0/1) as a random effect in all of our models (Telfer et al. 2007).

For each rodent species, we constructed a separate full model including all variables and the two-way interaction term. We then explored the effect of dropping each term on model quality using Akaike's information criterion (AIC) for deer mice and chipmunks, and corrected for small sample size for voles by using AICc to avoid overfitting models. We reconstructed increasingly simpler models eliminating terms identified based on lower model AIC (or AICc for voles) until removal of additional terms did not lower the information criterion any further. The model with the lowest AIC (or AICc) was chosen as the final model. Finally, to evaluate model fit, marginal R^2 and conditional R^2 were computed for all final models. These R^2 measures describe the proportion of variance explained by the fixed effects alone (R_m^2), and by both the fixed and random effects (R_c^2) in a mixed effects model (Nakagawa and Schielzeth 2013).

Yersinia pestis.—We noted the presence of fleas on rodents and collected fleas when possible. However, our flea sampling technique was not as systematic as described by other authors (e.g. Thiagarajan et al. 2008) meaning that, for numerous rodents for which fleas were observed we were unable to obtain representative samples. For each rodent species, we determined the proportion of animals infested with fleas, and, from these, identified the number of animals from which fleas were collected. We then calculated the prevalence of *Y. pestis* as the number of animals with *Y. pestis*-positive fleas divided by the total number of animals for which fleas were tested. This approach did not take into account flea-infested rodents for which

representative fleas were not collected or assayed for *Y. pestis*. Therefore, our results likely represent a conservative estimate of true *Y. pestis* prevalence in wild rodents in our study area. Based on our findings, we computed Clopper-Pearson exact two-sided 95% confidence intervals for the true prevalence values of *Y. pestis* for each rodent species (Shender et al. 2014). We used this approach because of its ability to handle probabilities equal to zero and its highly conservative approach to interval estimation (Clopper and Pearson 1934; Brown et al. 2001).

All statistical analyses were performed using R version 3.2.3 (R Development Core Team 2015). Specialized packages used were binom (Dorai-Raj 2014), car (Fox and Weisberg 2010), lme4 (Bates et al. 2015), MASS (Venables and Ripley 2002), MuMIn (Barton 2011), and stats (R Development Core Team 2015).

RESULTS

Study population

Over the course of 9668 trap-nights, we sampled 222 unique deer mice (2011–2013), and from 2011 to 2012, 159 Townsend chipmunks and 52 creeping voles from the twelve study plots in the two forestry districts (Table 4.1). Deer mice were most likely (36.6%) and voles least likely (12.1%) to be recaptured. Only one chipmunk was captured during two consecutive years, and we did not trap any individuals along more than one transect, indicating that animals did not move between our study plots. We trapped comparable numbers of voles across the three management levels, but captured most deer mice from control plots and most chipmunks from uncut forest plots. The majority of rodents trapped were adults and we captured comparable numbers of males and females for all three species. Capture success, recapture rates, demographics (age; sex), and morphometrics (mass; length) of our sample population are summarized by species in Table 4.2.

Sin Nombre virus

Over the three sampling years, 22 out of 341 deer mouse plasma samples tested positive for Sin Nombre virus antibodies (SNV+). One mouse was SNV+ on

first capture, but SNV- on second capture and was removed from further analysis. The remaining 21 positive samples represented 14 individuals (3 females; 11 males). Of the 21 SNV+ samples, 19 were from mice captured in Forest Grove and 12 were collected in 2011. Therefore, the prevalence of SNV was highest in samples collected on plots in Forest Grove in 2011 (34.3% of samples tested ≙ 25% of deer mice represented by samples), but declined to near zero in this district over the course of the three sampling years; Supporting Information S4.1). In fact, during the three years of our study, we found only two SNV+ mice from plots located in Tillamook. Therefore, we report statistical analyses only for the 35 samples (24 unique animals) obtained from deer mice captured on Forest Grove plots in 2011 that were tested for SNV.

When visually examining overall SNV prevalence across forest management levels for 2011 (Figure 4.1a) and for each month sampled in 2011 (Figure 4.1b), SNV infection appeared to occur most frequently in mice from treatment plots, and never in mice trapped on uncut plots. However, we did not find statistical support for these observations and SNV prevalence did not differ significantly across forest management levels for any of the four months sampled in Forest Grove in 2011 (P_{June} = 1.000; P_{July} = 0.486; P_{August} = 1.000; $P_{September}$ = 0.083).

Leptospira interrogans

We classified 51 deer mouse, 71 Townsend chipmunk, and 10 creeping vole samples corresponding to 42, 55, and 10 animals respectively, as Lepto+ using the cutoff criteria described above. Based on these criteria, chipmunk samples had the highest (31%) and deer mouse samples the lowest prevalence (15%). The two most common serovars to show agglutination in all three rodent species were bratislava and icterohaemorrhagiae. Deer mice generally had low antibody titers, but reacted frequently and to all six serovars. In contrast, few vole samples appeared to contain agglutinating antibodies and, when present, positive titers were only noted for four of the six bacterial strains. However, the proportion of mice that were classified as Lepto+ based on our criteria was nonetheless lower in deer mice than in creeping voles (Table 4.3).

For creeping voles, forest management level was the only fixed effect included in the final model (AICc = 55.69; R_m^2 = 15.4% and R_c^2 = 15.4%; Table 4.4; Supporting Information S4.2). Leptospira prevalence was slightly higher in voles captured from treatment plots compared to control plots (β = 1.792, P = 0.047; Figure 4.2), and we observed a similar pattern comparing treatment and uncut plots, although the latter was not significant at α = 0.05 (β = 1.504, P = 0.099). For chipmunks, the final model included forest management, location, and the interaction between forest management and location (AIC = 291.5; R_m^2 = 5.0% and R_c^2 = 17.9%; Table 4.4; Supporting Information S4.2). However, although in Tillamook the proportion of Lepto+ chipmunks appeared to be higher on treatment compared to control and uncut plots (Figure 4.3), neither forest management nor district were significantly related to Leptospira infection in chipmunks. Finally, we did not find an association between forest management or location and *L. interrogans* prevalence in deer mice (Figure 4.4). The only fixed effect retained in the final model selected for mice was year (AIC = 290.4; R_m^2 < 0.01% and R_c^2 < 0.01%; Table 4.4; Supporting Information S4.2). The small coefficients of determination obtained for this model indicate that year and the random effect explained only a minute proportion of the data variance.

Yersinia pestis.

Of the 222 deer mice, 159 chipmunks, and 52 creeping voles captured throughout the study, we noted the presence of fleas for 17, 45, and 33% of individuals respectively (n=37 mice, 72 chipmunks, and 17 voles). We tested a total of 145 fleas (3 families; 9 species) collected from 68, 51, and 88% of flea-infested rodents of each of the three species for the presence of *Y. pestis* DNA (Table 4.5). Of the 367 total blood meals examined, we found zero positive for *Y. pestis* (overall prevalence (95% CI) = 0% (0.0–2.5%)). Ninety-five percent Clopper-Pearson confidence intervals for true prevalence in deer mice, Townsend chipmunks, and creeping voles are 0.0–7.9%, 0.0–4.6%, and 0.0–16.1% respectively.

DISCUSSION

The primary objective of this study was to examine the association between intensive forest management and the prevalence of three locally relevant zoonoses in wild rodent hosts. We hypothesized that Sin Nombre virus would be endemic in deer mice inhabiting our study plots, and also expected to find evidence of *Leptospira interrogans* infection in the three rodent species examined. As a result of adverse habitat-, population-, and/or animal-level effects of IFM on small mammals, we predicted that prevalence of SNV and *L. interrogans* in rodent populations would increase with forest management intensity.

During the first year of our study, we found a distinct focus of high Sin Nombre virus prevalence (25%) in the deer mice sampled in Forest Grove. In fact, throughout our study, SNV infection was almost exclusively found in mice trapped on plots located in this district with only two mice testing SNV+ on plots from Tillamook. During the second and third study years, SNV prevalence decreased on all plots sampled and remained very low throughout the season. Similar spatial and temporal variation in SNV prevalence has been previously documented in deer mouse populations in the western USA (Otteson et al. 1996; Kuenzi et al. 1999; Douglass et al. 2001; Carver et al. 2010; Dizney et al. 2010). Most notably, in research carried out approximately 75 kilometers to the east of our study sites, Dizney et al. (2010) described moderate SNV prevalence in one of five urban natural areas studied, but noted very low infection prevalence in all other sites investigated despite similar capture rates and apparent deer mouse population densities. The same authors also observed fluctuations in SNV prevalence both seasonally and between years, comparable to the patterns noted herein.

Given the non-uniform distribution of SNV noted in our study, we concentrated our analysis of the relationship between IFM and SNV prevalence on the area and time of high SNV infection. For this infection focus, we observed a positive trend relating SNV prevalence to forest management intensity. The proportion of deer mice infected with SNV consistently appeared highest on plots that had been intensively sprayed with herbicides, lower on unsprayed control sites, and was absent

from uncut plots. The same pattern was constant throughout the year, even though overall SNV prevalence appeared to gradually decrease over the course of the sampling season, and our overall sample size was small. Capture success for deer mice during the first study year was quite poor, likely due to unusually cold and wet conditions early in the season. As a result, we lacked the power to find statistical support for the apparent association between IFM and the relatively high SNV prevalence observed in Forest Grove in 2011. And, similar to previous work (Dizney et al. 2010), as our capture rates increased in 2012 and 2013, the SNV epizootic in deer mice inhabiting our study sites appeared to dissipate, which prevented us from investigating this relationship in greater depth. It is nonetheless important to note, however, that poor habitat quality resulting from intensive chemical and mechanical forest management strategies has the potential to influence the dynamics of SNV in deer mouse populations and that, during periods and in areas of high SNV prevalence, human disease risk may be increased in intensively managed forests.

We found evidence of *Leptospira interrogans* in all three rodent species examined. However, a significant association between forest management intensity and Leptospira prevalence was observed only in creeping voles. In this species, infection prevalence increased with forest management intensity and was highest on intensively managed forest plots – similar to the trend observed for SNV in deer mice. In our study, voles were the least frequently captured rodent species, but this was also the only species for which we did not observe any apparent preference in habitat type (Sullivan 1990; Sullivan and Boateng 1996). Given their apparent true ubiquity across the three forest management levels sampled, voles may, in fact, be the best of our three model species in which to consider the effects of IFM on disease dynamics since results are least likely to be biased by uneven population distribution across plots. We found evidence that, in creeping voles, IFM may influence the prevalence of leptospirosis and heighten the risk of Leptospira transmission from voles to humans and domestic animals in intensively managed forests. To our knowledge, there has been no previous work examining zoonoses in *Mictrotus* spp. in northwestern Oregon. We suggest that creeping voles may play an important and unrecognized part in

Leptospira transmission in this region. To date, this species' potential as an important disease host may have been overlooked, and future efforts should focus on investigating its role in zoonotic disease cycles.

For Townsend chipmunks and deer mice, we did not find statistical evidence linking forest management to Leptospira prevalence. Yet, in chipmunks, model selection suggested an effect of management intensity that depended on district, and we can visualize this pattern. Leptospira prevalence in chipmunks trapped in Tillamook appeared highest on treatment plots. But, this pattern was not present in Forest Grove. In fact, only one chipmunk from a treatment plot in Forest Grove was positive for *L. interrogans* based on our criteria compared to about one third of animals from both uncut and control plots in this district. We have previously reported on associations between intensive forest management and animal health, and have described how the magnitude of IFM effects on health can depend on the overarching environmental context (Chapter 3). The pattern noted for *L. interrogans* infection in chipmunks seems to follow this same model. The Tillamook forestry district is a generally harsher environment. All study plots were located at higher elevation than Forest Grove plots, were more exposed to the elements, and experienced more rainfall and greater temperature fluctuations. Challenging environmental conditions, together with anthropogenic disturbance, such as occurred repeatedly on treatment plots, could increase the susceptibility of chipmunks to disease and could explain the apparent trend we observed for Leptospirosis in these populations. However, why disease prevalence is lowest in chipmunks captured in the poorest quality habitat in Forest Grove remains unclear. It is unlikely that health, immune function, and the resulting ability of these animals to clear infection is superior on treatment plots compared to the more favorable habitat found on control and uncut plots in this district. Additional work is needed to tease apart whether changes in health and immunity truly drive the disease patterns we observed. Linking animal health measures with disease prevalence may elucidate why, for some host species and pathogens, the effect of forest management alone influences disease prevalence, while for other hosts IFM effect on

disease seems to depend on environmental conditions, and finally, why we see no relationship between IFM and disease in some host-pathogen combinations.

In deer mice, we did not observe an association between forest management and *L. interrogans* prevalence even though deer mice represented the largest sample of the three rodent species examined. Many deer mice had agglutinating antibodies in their plasma, but the majority of their titers were low and did not meet our criteria for designation as Lepto+. Leptospirosis prevalence in wildlife has been estimated using a single positive, low titer (Davis et al. 2008b), and it is possible that inclusion criteria may need to be adjusted for each host species. However, rerunning our analyses for deer mice with relaxed inclusion criteria, which considered any positive titer as evidence for exposure to or infection with *L. interrogans* did not change our findings (data not shown). We therefore conclude that, for deer mice inhabiting managed forests in northwestern Oregon, forest management level does not influence prevalence of leptospirosis.

Specific serovars infecting rodents in northwestern Oregon are unknown and may include rodent strains not included in our assay (e.g. autumnalis, ballum, copenhageni; Bharti et al. 2003; Ko et al. 2009; Himsworth et al. 2013b; Grayzel and DeBess 2016). Different strains of *L. interrogans* can elicit variable immune responses in rodents and it is likely that the immune response to the same strain also differs among species (Ko et al. 2009; Evangelista and Coburn 2010). Furthermore, rodent antibodies against unknown infecting strains can cross-react with other *L. interrogans* serovars. Nonetheless, the agglutination patterns observed in our study population correspond to serovars previously described in wild rodents (Bharti et al. 2003; Ko et al. 2009; Himsworth et al. 2013b). Based on antibody titers categorized as positive according to our selection criteria, *L. interrogans* prevalence in rodent plasma samples ranged from over 30% in chipmunks, to 17% in voles and 15% in deer mice. These percentages are relatively low, but comparable to Leptospira infection prevalence documented in other wildlife and domestic animals in the region (Bender and Hall 1996; Hamir et al. 2001; Colagross-Schouten et al. 2002; Davis et al. 2008b). However, considering the demonstrated low sensitivity of the MAT assay for

detecting Leptospira (Limmathurotsakul et al. 2012) and our relatively conservative cutoff criteria for identifying Lepto+ animals, it is possible that we may be underestimating the true prevalence of Leptospirosis in wild rodents in northwestern Oregon. Investigating a wider array of serovars, including additional bacterial strains known to be associated specifically with rodents, and exact serovars isolated from local human cases of leptospirosis, is necessary to establish true prevalence of Leptospirosis in this region. Additionally, combining molecular, histopathological, bacterial culture, and serological techniques in the diagnosis of leptospirosis from wild rodent samples, although logistically and financially difficult, may improve the accuracy of leptospirosis surveillance and estimate human disease risk from wild rodents in managed forest habitats in Oregon.

A secondary objective of our research was to explore the presence of *Yersinia pestis* in our study area. To this end, we tested fleas collected from wild rodents for evidence of the plague bacterium, and estimated disease prevalence in our three focal rodent species. We found no evidence of *Yersinia pestis* in fleas collected from deer mice, Townsend chipmunks, and creeping voles inhabiting our study sites. Documenting the presence of plague, in both rodent fleas, blood samples, and tissue preparations has been shown to be challenging, even in plague enzootic areas, and immediately following plague outbreaks (Meyer 1938; Stapp et al. 2008, 2009; Thiagarajan et al. 2008; Franklin et al. 2010). Plague has been identified in Oregon wildlife species other than rodents, however (Salkeld and Stapp 2006). A survey of wild carnivores identified *Y. pestis* in coyotes, badgers, raccoons, and striped skunks from 20 of the 36 Oregon counties (Hopkins and Gresbrink 1982). In said study, plague was most prevalent in carnivores east of the Cascade Range and in central Oregon, but was also detected in samples from the south and southwestern coastal areas of the state. Prevalence in carnivores from the Willamette Valley, which is located immediately to the east and south of our study sites, was low, and the authors did not report findings specific to the northwestern counties where we conducted our work. More recently, two cases of *Y. pestis* were reported in mule deer from eastern

Oregon (Edmunds et al. 2008). But, rodent fleas collected from burrowing owls in northeastern and eastern Oregon did not reveal *Y. pestis* (Belthoff et al. 2015). Cases of *Yersinia pestis* have not been documented in humans, domestic animal, or wildlife from northwest Oregon. And, to our knowledge, ours is the first report to survey fleas collected directly from wild rodents for *Y. pestis* in the northwestern part of the state. The fact that we found zero percent prevalence of *Y. pestis* in the fleas tested parallels the absence of reports of human cases of plague in this region and suggests that risk for infection with *Y. pestis* from wild rodents and other wildlife in northwest Oregon is likely to be low. However, more rigorous studies examining blood and tissue samples collected from potential rodent and other wildlife hosts for the bacterium, either via culture or molecular techniques, are needed to confirm the absence of plague in this system. Outdoor recreation is common in this area, which increases the transmission potential of zoonotic infections such as plague to domestic animals and humans, either directly or via flea vectors (Rust et al. 1971; Weniger et al. 1984; Werner et al. 1984; Nelson et al. 1986). In addition, hunting is widespread in the publicly managed forest stands that dominate the landscape of northwestern Oregon and target species include potential plague hosts such as bobcat or deer (Jessup et al. 1989; Salkeld and Stapp 2006; Bevins et al. 2009). Were plague to be identified in northwestern Oregon, examining the relationship of this zoonosis to habitat characteristics, including anthropogenic disturbance levels, will be of utmost interest for public health.

Here, we took advantage of an existing, unique, and large-scale experimental design to investigate the effects of a single type of severe anthropogenic environmental disturbance on the prevalence of three zoonotic pathogens with varying modes of transmission in multiple known or potential rodent host species. All of the pathogens investigated can cause fatal disease in humans.

To our knowledge, we documented for the first time the presence of Sin Nombre virus and Leptospirosis in wild rodents in the Oregon Coast Range. And, for both of these zoonoses, we found evidence that intensive forest management may affect pathogen dynamics in rodent populations. However, the potential mechanisms underlying these patterns remain unclear. Two theories seem most plausible. First,

IFM may alter rodent populations and affect overall community composition with cascading effects on disease dynamics (Keesing et al. 2010). And, second, IFM can adversely affect animal health (Chapter 3), change the susceptibility to disease in individual animals, and alter pathogen dynamics at the population scale.

To elucidate if either of these mechanisms is driving zoonotic disease dynamics in rodent populations inhabiting intensively managed forests in the Pacific Northwest, additional research is needed. For instance, we did not evaluate rodent abundance, estimate population size, or assess the composition of small mammal communities. To relate both presence and abundance of host species to disease prevalence, it will be necessary to thoroughly document and quantify changes in rodent and other vertebrate populations in response to IFM. And, since small mammal populations turn over on a relatively short time scale, assessing populations and community composition over multiple years will reveal whether the observed associations are stable or only a transient effect of severe forest management interventions that occur immediately after harvest. In addition, combining more sophisticated disease diagnostic techniques with long-term and continuous studies (i.e. year-round sampling) will also allow more accurate description of temporal disease patterns in wildlife populations in northwestern Oregon. Knowing the true prevalence of zoonotic diseases in managed forest systems and identifying temporal variation in disease will enable health workers to better inform the public, especially forest workers and recreationists visiting the area, about potential human and animal health risks. Finally, examining the association between rodent health measures and infection prevalence is an important next step that will bring us closer to understanding how intensive forest management specifically, and anthropogenic environmental change in general, can drive zoonotic disease patterns in wildlife. Using diseases with high local prevalence, including parasitic infections ubiquitous in wildlife populations, presents one feasible approach to examining the link between forest management, animal health, and infection, with the goal of ascertaining the implications for human health.

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TABLES

Table 4.1.—Trapping success by year and season for deer mice (*Peromyscus maniculatus*), Townsend chipmunks (*Tamias townsendii*), and creeping voles (*Microtus oregoni*) captured on differentially managed forest plots in two districts in the Oregon Coast Range, USA between June and September 2011–2013. (C = control plot; Early = mid-June–mid-July; FG = Forest Grove district; Late = mid-August–mid-September; Mid = mid-July–mid-August; T = treatment plot; TM = Tillamook district; U = uncut plot)

District-Forest management	2011			2012			2013		Total
	Early	Mid	Late	Early	Mid	Late	Early	Mid	
P. maniculatus									
FG-U	0	2	3	6	10	10	5	7	43
FG-C	5	3	17	30	25	22	11	13	126
FG-T	1	3	5	9	13	11	15	15	72
FG Total									*241*
TM-U	0	2	1	0	1	2	Not sampled	5	11
TM-C	1	3	9	7	17	6		9	52
TM-T	0	1	2	3	16	6		15	43
TM Total									*106*
Grand Total	*7*	*14*	*37*	*55*	*82*	*57*	*31*	*64*	*347*

Table 4.1. cont.

District-Forest management	2011			2012			2013		Total
	Early	Mid	Late	Early	Mid	Late	Early	Mid	
T. townsendii									
FG-U	2	9	9	14	8	6			48
FG-C	1	15	11	9	5	8	Not sampled		49
FG-T	1	0	6	1	3	2			13
FG Total									*110*
TM-U	1	6	13	11	24	12			67
TM-C	0	6	12	2	4	7	Not sampled		31
TM-T	0	3	9	0	8	5			25
TM Total									*123*
Grand Total	*5*	*39*	*60*	*37*	*52*	*40*			*233*

Table 4.1. cont.

District-Forest management	2011			2012			2013		Total
	Early	Mid	Late	Early	Mid	Late	Early	Mid	
M. oregoni									
FG-U	0	6	5	1	0	1			13
FG-C	0	1	2	2	5	5	Not sampled		15
FG-T	0	0	2	0	0	1			3
FG Total									*31*
TM-U	0	1	2	1	1	0			5
TM-C	0	2	4	1	0	1	Not sampled		8
TM-T	0	2	2	0	6	4			14
TM Total									*27*
Grand Total	*0*	*12*	*17*	*5*	*12*	*12*			*58*

Table 4.2.—Demographic and morphometric description of deer mice (*P. maniculatus*), Townsend chipmunks (*T. townsendii*), and creeping voles (*M. oregoni*) captured between June and September 2011–2013 from differentially managed forest plots in two districts in the Oregon Coast Range, USA. (Body length was measured from the tip of the snout to the base of the tail.)

P. maniculatus	Captures		347	
	(Unique)		(222)	
	Recapture (%)		36.6	
			Female	Male
	Adult		130	174
		Mass (g)	20.7 ± 3.34	18.4 ± 2.48
		Length (cm)	9.2 ± 0.56	8.9 ± 0.56
	Juvenile		17	23
		Mass (g)	12.7 ± 1.31	12.4 ± 1.68
		Length (cm)	7.8 ± 0.69	7.9 ± 0.67

Table 4.2. cont.

T. townsendii	Captures	233		
	(Unique)	(159)		
	Recapture (%)	32.6		
			Female	Male
	Adult		106	100
		Mass (g)	78.7 ± 10.77	71.8 ± 7.88
		Length (cm)	14.1 ± 0.60	13.9 ± 0.61
	Juvenile		8	17
		Mass (g)	57.9 ± 7.52	67.8 ± 12.03
		Length (cm)	12.6 ± 0.76	13.6 ± 0.62
M. oregoni	Captures	58		
	(Unique)	(52)		
	Recapture (%)	12.1		
			Female	Male
	Adult		35	20
		Mass (g)	16.6 ± 2.65	15.9 ± 4.18
		Length (cm)	9.3 ± 0.81	9.7 ± 0.74
	Juvenile		0	0
		Mass (g)	-	-
		Length (cm)	-	-

Table 4.3.—Agglutinating antibody titers against each of six *Leptospira interrogans* serovars for plasma samples collected from deer mice (*P. maniculatus*), Townsend chipmunks (*T. townsendii*), and creeping voles (*M. oregoni*) captured between June and September 2011–2013 on differentially managed forest plots in two districts in the Oregon Coast Range, USA. Antibody titers were determined via microscopic agglutination test (MAT). (ictero = icterohaemorrhagiae; grippo = grippotyphosa; n = number of unique animals sampled)

	Leptospira interrogans serovars						
Titer	bratislava	canicola	grippo	hardjo	ictero	pomona	Total
Peromyscus maniculatus: prevalence = 15% (51 positive / 343 total samples; n = 42)							
100	15	5	2	9	18	14	63
200	25	-	3	4	13	11	56
400	12	2	5	1	13	2	35
800	8	1	1	1	3	1	15
1600	1	-	-	-	-	1	2
3200	1	-	-	-	2	-	3
Total	62	8	11	15	49	29	174

Table 4.3. cont.

Tamias townsendii: prevalence = 31% (71 positive / 233 total samples; n = 55)							
100	32	4	7	16	31	21	111
200	28	2	16	11	15	10	82
400	7	2	8	2	8	5	32
800	5	-	7	2	3	3	20
1600	2	-	1	1	1	1	6
3200	-	-	1	-	-	-	1
Total	74	8	40	32	58	40	252
Microtus oregoni: prevalence = 17% (10 positive / 58 total samples; n = 10)							
100	3	1	-	-	3	1	8
200	8	-	-	-	2	-	10
400	4	-	-	-	3	-	7
800	-	-	-	-	1	-	1
1600	-	-	-	-	-	-	0
3200	-	-	-	-	-	-	0
Total	15	1	0	0	9	1	26

Table 4.4.—Analysis of variance model output for final generalized linear mixed effects models selected for *Leptospira interrogans* prevalence in deer mice (*Peromyscus maniculatus*), Townsend chipmunks (*Tamias townsendii*), and creeping voles (*Microtus oregoni*) captured on differentially managed forest plots at two locations in the Oregon Coast Range between June and September 2011–2013. (Chisq = Chi square statistic; df = degrees of freedom; Pr = probability)

Species	Predictor	Chisq	df	Pr(>Chisq)
P. maniculatus	(Intercept)	16.6	1	<0.001
	Year	4.80	2	0.091
T. townsendii	(Intercept)	2.09	1	0.149
	Management level	2.24	2	0.326
	District	0.20	1	0.655
	Management level x District	3.70	2	0.157
M. oregoni	(Intercept)	7.16	1	0.007
	Management level	5.06	2	0.080

Table 4.5.—Flea families and species, and the number of fleas (number of rodents infested) that were tested for *Yersinia pestis* via PCR at USGS NWHC, Madison, WI, USA. A total of 145 fleas (367 blood meals) were collected from 27 deer mice (*Peromyscus maniculatus*), 43 Townsend chipmunks (*Tamias townsendii*), and 15 creeping voles (*Microtus oregoni*) trapped on differentially managed forest plots in the Oregon Coast Range, USA between June and September 2011–2013. The number of blood meals tested for each rodent species was 98, 225, and 44 respectively; all were negative for *Y. pestis*. (C = control; FG = Forest Grove forestry district; T = treatment; TM = Tillamook forestry district; U = uncut)

		2011						2012						2013						
		FG			TM			FG			TM			FG			TM			
Flea family	Flea species	U	C	T	U	C	T	U	C	T	U	C	T	U	C	T	U	C	T	Row Total
P. maniculatus																				
Ceratophyllidae	*Monopsyllus*	1	1			1			1			1								5
	ciliatus protinus	(1)	(1)			(1)			(1)			(1)								(5)
	Opisodasys	2	5	1	1				5	3			2	8	2	6	1	1		37
	keeni	(2)	(4)	(1)	(1)				(4)	(2)			(1)	(2)	(1)	(1)	(1)	(1)		(21)

Table 4.5. cont.

		2011						2012						2013					
		FG				TM			FG			TM			FG			TM	
P. maniculatus																			
Hystrichopsyllidae	*Delotelis*							1											1
	telegoni							(1)											(1)
	Epitedia jordani	1																	1
		(1)																	(1)
	Rhadinopsylla						1												1
	spp.						(1)												(1)
	Column total	4	6	1	1	1	1	1	6	3	1	2	8	2	6	1	1		45
		(2)	(5)	(1)	(1)	(1)	(1)	(1)	(5)	(2)	(1)	(1)	(2)	(1)	(1)	(1)	(1)		(27)

Table 4.5. cont.

		2011						2012						2013						
		FG			TM			FG			TM			FG			TM			
Flea family	Flea species	U	C	T	U	C	T	U	C	T	U	C	T	U	C	T	U	C	T	Row Total
T. townsendii																				
Ceratophyllidae	*Monopsyllus ciliatus protinus*	10 (5)	29 (6)	2 (2)	6 (5)	8 (6)	2 (2)	7 (4)	2 (2)	1 (1)	9 (7)	2 (2)								78 (42)
	Opisodasys keeni								1 (1)											1 (1)
	Column total	10 (5)	29 (6)	2 (2)	6 (5)	8 (6)	2 (2)	7 (4)	3 (3)	1 (1)	9 (7)	2 (2)								79 (43)

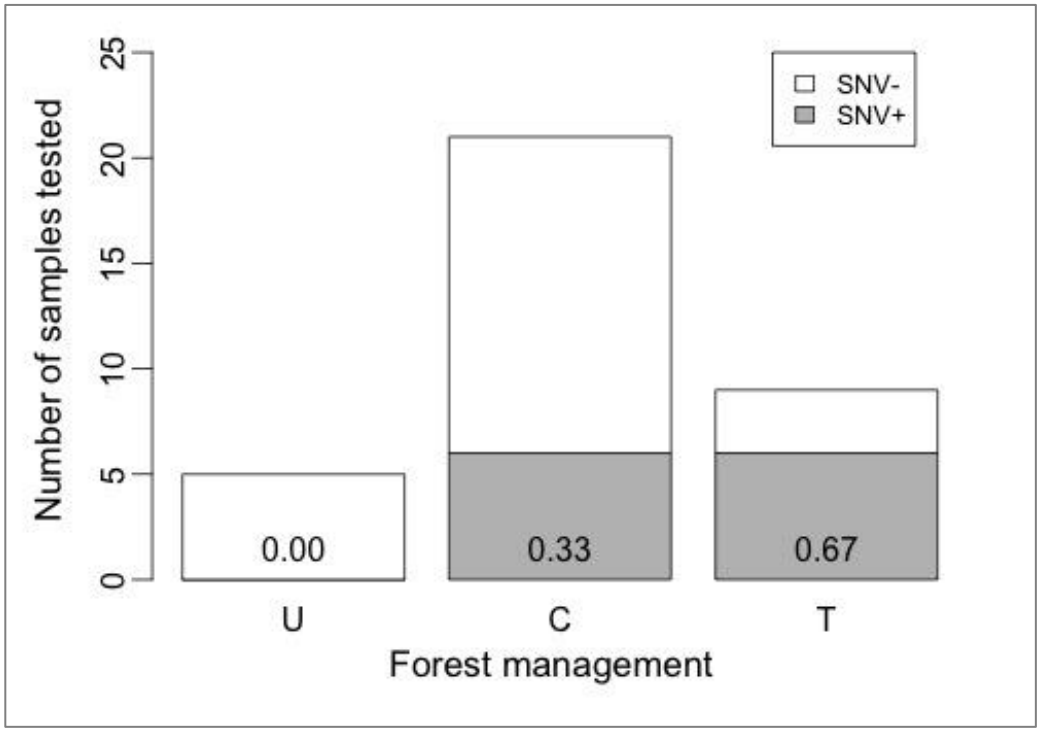
Table 4.5. cont.

		2011			2012		2013	
		FG	TM		FG	TM	FG	TM
M. oregoni								
Ceratophyllidae	*Monopsyllus*				1			1
	ciliatus protinus				(1)			(1)
	Megabothris				3			3
	abantis				(2)			(2)
Hystrichopsyllidae	*Atyphloceras*	1						1
	multidentatus	(1)						(1)
	Epitedia jordani	1	2	1	1	1	1	7
		(1)	(2)	(1)	(1)	(1)	(1)	(7)
	Hystrichopsylla	1						1
	dippiei	(1)						(1)

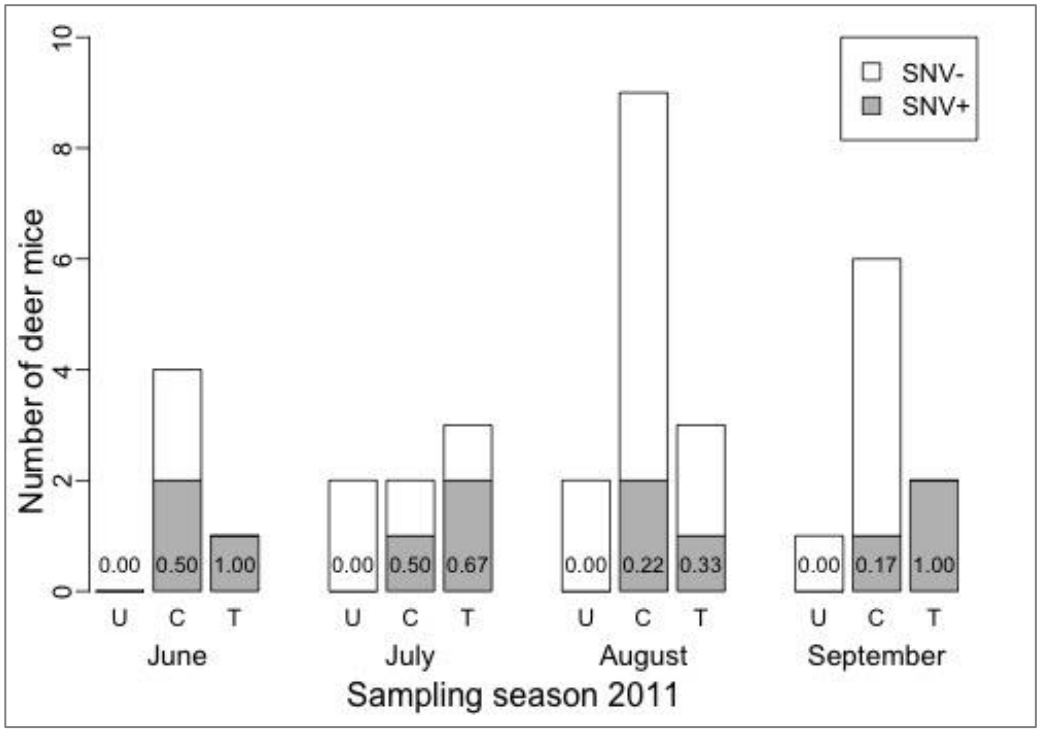
Table 4.5. cont.

		2011							2012						2013					
		FG				TM			FG				TM			FG			TM	
M. oregoni																				
Leptopsyllidae	*Peromyscopsylla selenis*	1 (1)		1 (1)		2 (1)			3 (1)				1 (1)							8 (5)
	Column total	4 (3)	2 (2)	2 (1)		3 (2)	1 (1)		8 (5)				1 (1)							21 (15)
	Grand total	18 (10)	37 (13)	5 (4)	7 (6)	12 (9)	4 (4)	8 (5)	17 (13)	4 (3)	9 (7)	3 (3)	3 (2)	8 (2)	2 (1)	6 (1)	1 (1)	1 (1)	145 (85)

FIGURES


Number of samples tested
0
5
10
15
20
25
SNV-
SNV+
0.00
0.33
0.67
U
C
T
Forest management

a)


Number of deer mice
0
2
4
6
8
10
SNV-
SNV+
0.00
0.50
1.00
0.00
0.50
0.67
0.00
0.22
0.33
0.00
0.17
1.00
U
C
T
June
July
August
September
Sampling season 2011

b)

Figure 4.1.—Prevalence of SNV by forest management level in deer mice (*Peromyscus maniculatus*) trapped on differentially managed forest plots in the Forest Grove district of the Oregon Coast Range, USA between June and September 2011. In (**a**), the overall prevalence of SNV in all 35 plasma samples collected from mice in Forest Grove in 2011 that were tested for SNV is displayed, which includes recaptured animals. In (**b**), for each sampling month and forest management level, we show prevalence as the number of SNV+ samples / the total number of samples tested, which does not include recaptured mice. The proportion of SNV+ mice consistently appeared highest on treatment plots. However, this observation was not supported statistically for any of the four sampling months in 2011 (Fisher's exact tests comparing SNV infection across forest management level for each sampling month: $P_{\text{June}} = 1.000$; $P_{\text{July}} = 0.486$; $P_{\text{August}} = 1.000$; $P_{\text{September}} = 0.083$; significance level α was adjusted for multiple comparisons with P-values < 0.0125 considered significant). (Numbers appearing in each bar indicate prevalence; C = control; T = treatment; U = uncut)

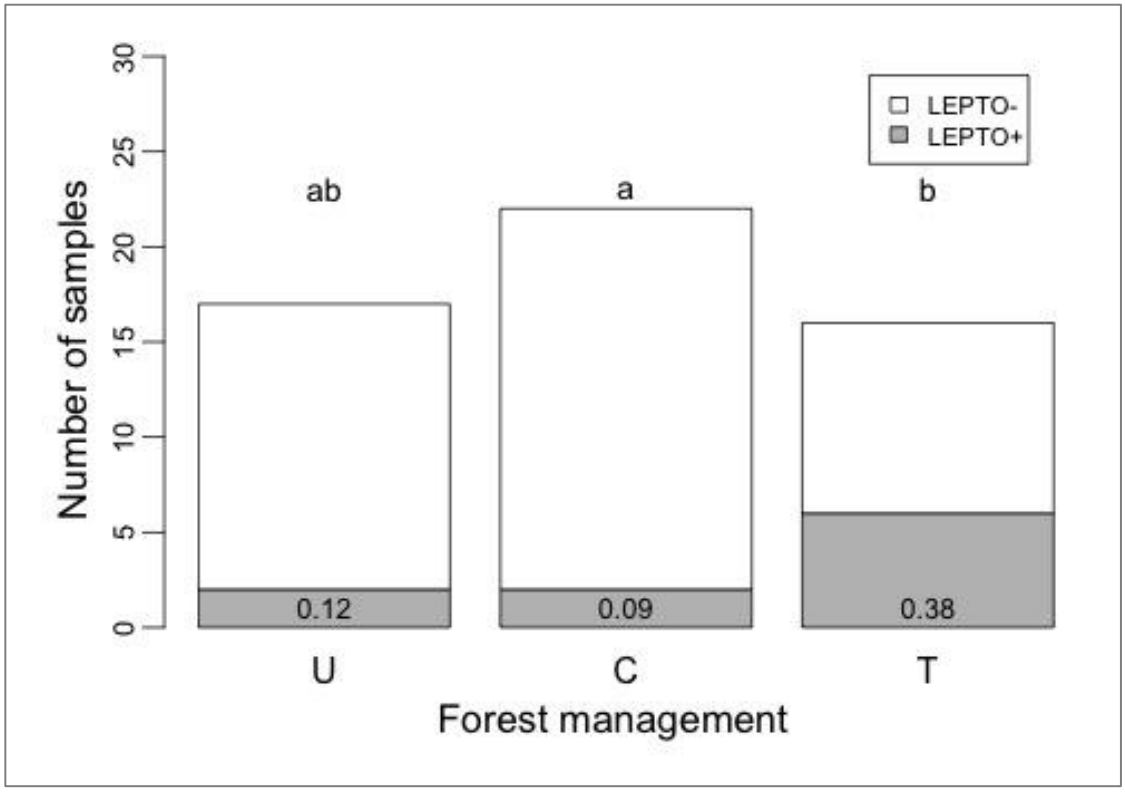


Figure 4.2.—Overall prevalence of *Leptospira interrogans* by forest management level in 55 plasma samples collected from creeping voles (*Microtus oregoni*) captured on differentially managed forest plots in two forestry districts in the Oregon Coast Range, USA between June and September 2011–2012. Although only 16 samples were collected from voles on treatment plots compared to 22 from control plots, a larger proportion of voles from treatment plots were infected with *L. interrogans (P* = 0.047*). L. interrogans* prevalence for each forest management level was computed as the total number of Lepto+ samples divided by the total number of samples collected from said management level across both forestry districts and sampling years and did not control for multiple samples from the same animal collected during repeat captures. However, only 6 animals were resampled and none of them were Lepto+ at any time point. (Numbers appearing in each bar indicate prevalence; different letters indicate statistically significant differences at $\alpha = 0.05$; C = control; T = treatment; U = uncut)

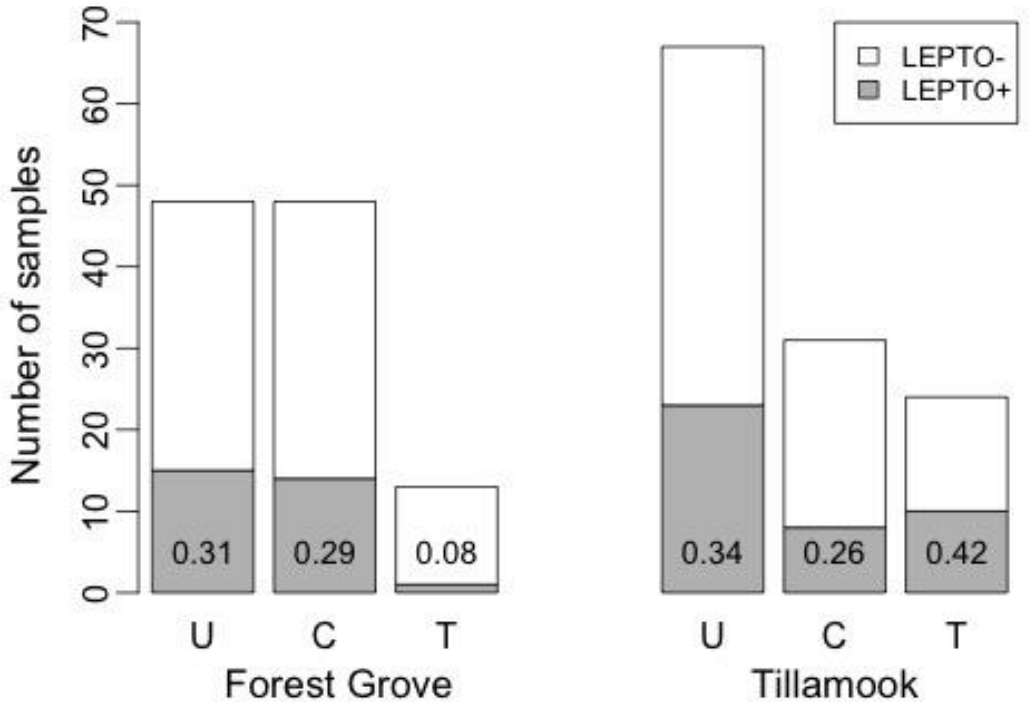


Figure 4.3.—Prevalence of *Leptospira interrogans* in Townsend chipmunks (*Tamias townsendii*) captured on differentially managed forest plots in two forestry districts in the Oregon Coast Range, USA between June and September 2011–2012. Fewer chipmunks were trapped and sampled on treatment compared to control and especially compared to uncut plots in both districts. Yet, in Tillamook, the proportion of Lepto+ animals appeared largest on treatment plots, although this observation was not supported statistically. For each district, Leptospira prevalence for each forest management level was computed as the number of Lepto+ samples divided by the total number of samples collected from said management level in 2011 and 2012 combined and did not control for multiple samples from the same animal collected during repeat captures in each of the two years. (Numbers appearing in each bar indicate prevalence; C = control; T = treatment; U = uncut)

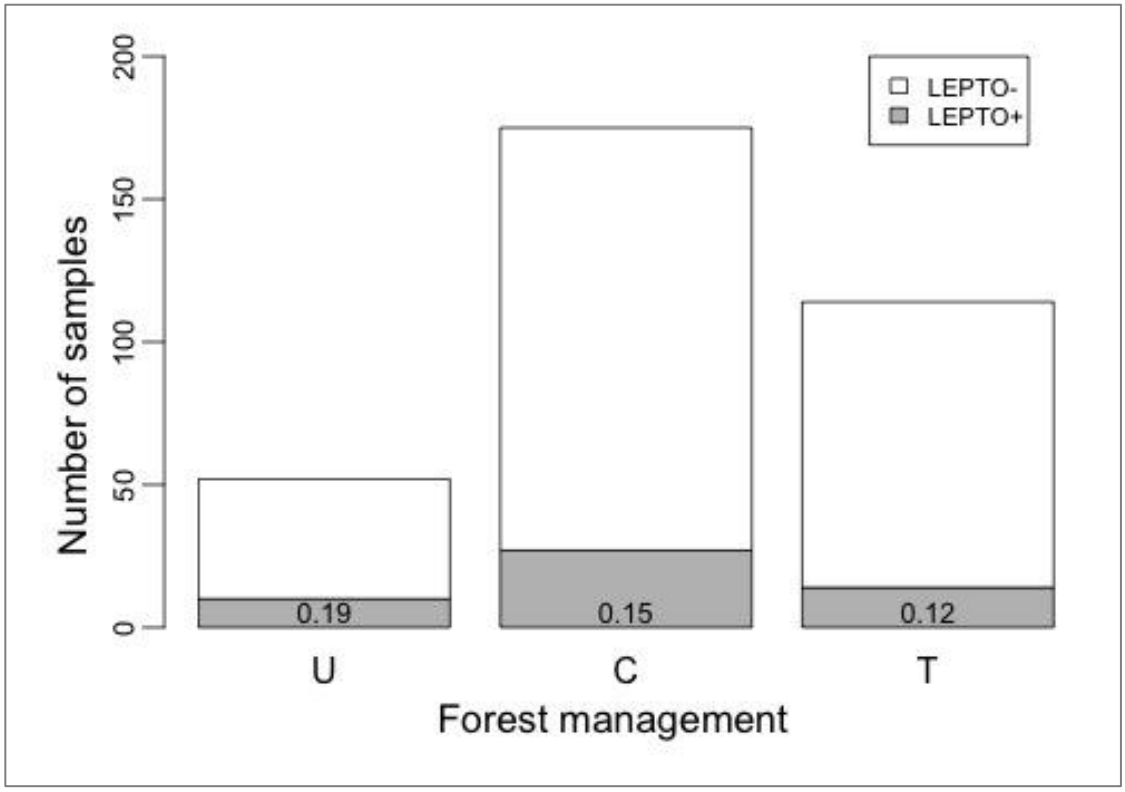


Figure 4.4.—Prevalence of *Leptospira interrogans* in deer mice (*Peromyscus maniculatus*) trapped on differentially managed forest plots in two forestry districts in the Oregon Coast Range, USA between June and September 2011–2013. Forest management did not appear to influence Leptospira prevalence in deer mice. In this figure, Leptospira prevalence for each forest management level was computed as the number of Lepto+ samples divided by the total number of samples collected from said management level in all years in both districts and did not control for multiple samples from the same animal collected during repeat captures in any one year. (Numbers appearing in each bar indicate prevalence; C = control; T = treatment; U = uncut)

Chapter 5 – Conclusion

Human actions have wide-reaching consequences for the integrity of ecosystems around the world (Pimm et al. 1995; Vitousek et al. 1997; Dirzo et al. 2014). Intensive agricultural practices are one important and common way in which we change our environment. In the Pacific Northwest (PNW) of the United States, most forests are managed for timber production to supply local and international markets (Swanson and Franklin 1992). The management strategies employed to promote rapid tree growth and maximize harvest efficiency are intensive and include clearcutting and monoculture. Not surprisingly, these practices severely alter the structure of plant and animal communities (Betts et al. 2013), create a patchwork of habitat fragments (Lehmkuhl and Ruggiero 1991), and introduce large quantities of herbicides into the ecosystem (Tatum 2004).

The effects on wildlife populations of habitat loss secondary to conversion of undisturbed, old-growth to managed forests in general, and of intensive forest management (IFM) in particular, have been studied for several species with variable results (Santillo et al. 1989; Sullivan and Boateng 1996; Cole et al. 1998; McComb et al. 2008; Betts et al. 2013). But, data on the consequences of these severe environmental changes for wildlife health are still lacking. My dissertation research aims to fill this gap in knowledge by reporting on how physiological, and especially immunological parameters, as well as infectious disease prevalence respond to environmental changes resulting from intensive management practices in PNW forest ecosystems.

Infectious diseases can be detrimental to wildlife populations and can hamper species conservation efforts (Daszak et al. 2000; Deem et al. 2001). At the same time, wild animals are an important source for emerging diseases, including infections that can spill over into domestic animal and human populations (Daszak et al. 2001; Jones et al. 2008). Rodents are especially important players in many disease cycles as they are primary hosts for numerous zoonoses, diseases transmissible from animals to humans (Mills and Childs 1998; Meerburg et al. 2009). Using rodents native to forests of northwestern Oregon, I measured health and immune variation in one species, then

examined how different habitat conditions can influence animal health and immunity, and, finally, determined how the prevalence of three zoonoses related to forest management.

In Chapter 2, I describe how animal-level characteristics (i.e. condition and age) shape immunity in a unique native rodent species, the red tree vole (*Arborimus longicaudus*). The rare opportunity to study this species in captivity allowed me to collect data from animals kept in a relatively controlled environment, which omitted the additional variation that can result from differences in foraging or nesting success, predators, or disease in the wild. My results illustrate the importance of taking into account within species variation when examining external influences, such as habitat quality, on animal health. The findings presented in Chapter 2 also underline the importance of considering the potential implications of changing environmental conditions for animal health when working to conserve threatened or endangered species (Daszak et al. 2000; Deem et al. 2001; Acevedo-Whitehouse and Duffus 2009).

In Chapters 3 and 4, I dovetailed with ongoing research that investigates intensive forest management effects on wildlife populations. With the aim of exploring the influence of anthropogenic environmental change on wildlife health and zoonotic infection prevalence, I used a unique experimental set-up consisting of large forest plots spanning three levels of forest management intensity located in the coastal mountain range of northwest Oregon. I examined health and immune measures (Chapter 3), and determined infectious disease prevalence (Chapter 4) in three pervasive wild rodent species inhabiting these differentially managed plots.

In Chapter 3, I discovered that environmental disturbance can drive health and immunity in wild deer mice (*Peromyscus maniculatus*). But, I observed these associations to be complex and dependent on underlying environmental conditions. Specifically, I found that, together, multiple stressors, namely inherently harsh environmental conditions and poor habitat quality secondary to intensive forest management, can have detrimental consequences for animal health. Yet, the difficulty in detecting these disturbance effects and the dependency of their direction and

magnitude on environmental context emphasize the challenges associated with predicting consequences of anthropogenic environmental change for wildlife health (Lafferty and Holt 2003; Brearley et al. 2012).

Finally, in Chapter 4, I investigated how infectious diseases might be affected by intensive forest management. I found spatially and temporally clustered prevalence of Sin Nombre virus in deer mice. Leptospirosis was present at low to moderate levels in all three rodent species. And, I did not find evidence of plague (*Yersinia pestis*) in any of the fleas collected from study animals. Disease prevalence appeared to vary across forest management levels. However, patterns were not consistent across pathogens or host species. For creeping voles (*Microtus oregoni*), I found prevalence of Leptospirosis to increase with the level of forest management. A saw a similar pattern with Sin Nombre virus in deer mice, but did not find an association between Leptospirosis and forest management in deer mice or chipmunks. From these data, I conclude that environmental disturbance can indeed influence infectious disease prevalence in wild rodents. But, it appears that, in the case of disease, the direction and magnitude of the disturbance effect depends on the host-pathogen context. Therefore, it is important first to know which diseases are present in an ecosystem and to identify the specific reservoirs for said pathogens, taking into consideration even animal species previously discarded as important disease hosts. Understanding the ecology of infectious diseases in disturbed ecosystems is fundamental to bringing us closer to predicting the effects of anthropogenic environmental change for animal and human health (Gubler et al. 2001).

My dissertation research contributes to our understanding of how human-induced changes to our surroundings can impact the health of wild animals surviving in disturbed ecosystems, and also illustrates the relevance of this knowledge for human health. Using approaches from epidemiology, disease ecology, immunology, wildlife biology, and veterinary medicine, I have begun to tease apart some of the complex ecosystem-, animal-, and disease-level processes that occur secondary to anthropogenic environmental change. However, much work remains to be done. Most importantly, I must examine whether changes in animal health in the individual are

indeed linked to the prevalence of pathogens at the population scale. Connecting my findings in health and immunity in Oregon rodents to the infectious disease patterns I observed will allow me to determine the true impact of intensive forest management for disease risk. This information will inform predictions regarding the implications of intensive agricultural practices for animal and human health, and may direct policy regulating such practices.

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APPENDICES

Appendix A Supporting Information for Chapter 2

Supporting Information S2.1.—Results of simple linear regression models examining: (**a**) covariation between sex, age (days), and growth – body mass (g), length (mm), and condition (mass-length residual) – in 46 captive red tree voles (*Arborimus longicaudus*) sacrificed at Oregon State University between October 2013 and July 2014; and (**b**) difference in mean body condition (mass-length residuals) between the captive tree vole population and 260 wild red tree voles caught and measured in Oregon between 1955 and 2012. (Associations significant at $\alpha = 0.05$ appear in bold font.)

Growth metric	Variable	β	$F_{(d.f.1,d.f.2)}$	*P*-value
a)				
Body mass (g)	Age (days)	0.007	$9.61_{(1,44)}$	**0.003**
Body length (mm)	Age (days)	0.021	$12.43_{(1,44)}$	**< 0.001**
Condition	Age (days)	0.002	$1.51_{(1,44)}$	0.226
Body mass (g)	Sex (M vs. F)	-0.992	$2.40_{(1,44)}$	0.128
Body length (mm)	Sex (M vs. F)	-1.75	$0.97_{(1,44)}$	0.331
Condition	Sex (M vs. F)	-0.616	$1.39_{(1,44)}$	0.246
(b)				
Condition	Origin (Wild vs. Captive)	-0.290	$0.207_{(1,304)}$	0.650

Supporting Information S2.2.—Multiple linear regression models considered for examining the effect of condition, age, and sex on immune measures in red tree voles (*Arborimus longicaudus*). Candidate models were identified via backwards selection from the full model (first row) based on lowest Akaike's information criterion adjusted for small sample size (AICc). For each immune parameter, the full model, the final model (bold font) and the two next best models are shown for comparison. (bka = bacterial killing ability; cond = condition; eos + 1 = eosinophil counts + 1 (Since eosinophils were absent from many samples, we added 1 to all eosinophil counts before applying the log-transform for data analysis.); lym = lymphocytes; mon = monocytes; neu = neutrophils; twbc = total white blood cells)

Immune measure	Models considered	AICc	ΔAICc
Total white blood cells	log(twbc) ~ cond + age + sex	62.81	5.28
	log(twbc) ~ cond	58.39	0.87
	log(twbc) ~ age	59.59	2.07
	log(twbc) ~ intercept	**57.52**	**0.00**
Lymphocytes	log(lym) ~ cond + age + sex + log(twbc)	-53.29	1.98
	log(lym) ~ cond + age + log(twbc)	**-55.27**	**0.00**
	log(lym) ~ cond + sex + log(twbc)	-48.79	6.48
	log(lym) ~ cond + log(twbc)	-50.98	4.29
Monocytes	log(mon) ~ cond + age + sex + log(twbc)	**107.50**	2.79
	log(mon) ~ cond + age + log(twbc)	104.91	0.19
	log(mon) ~ cond + log(twbc)	**104.72**	**0.00**
	log(mon) ~ age + log(twbc)	105.20	0.48
Neutrophils	log(neu) ~ cond + age + sex + log(twbc)	103.83	1.32
	log(neu) ~ cond + age + log(twbc)	**102.51**	**0.00**
	log(neu) ~ cond + sex + log(twbc)	104.27	1.76
	log(neu) ~ cond + log(twbc)	102.76	0.24

S2.2. cont.

Immune measure	Models considered	AICc	ΔAICc
Eosinophils	log(eos+1) ~ cond + age + sex + log(twbc)	212.25	5.20
	log(eos+1) ~ cond + log(twbc)	**208.35**	**0.17**
	log(eos+1) ~ cond	207.05	0.00
	log(eos+1) ~ cond + age	208.46	1.41
Proportion lymphocytes	logit(ProLym) ~ cond + age + sex	82.11	1.60
	Logit(ProLym) ~ cond + age	**80.51**	**0.00**
	Logit(ProLym) ~ cond + sex	87.26	6.75
	Logit(ProLym) ~ cond	85.35	4.84
Proportion monocytes	Logit(ProMon) ~ cond + age + sex	113.68	2.76
	Logit(ProMon) ~ cond + age	111.19	0.27
	Logit(ProMon) ~ cond	111.47	0.55
	Logit(ProMon) ~ age	**110.92**	**0.00**
Proportion neutrophils	Logit(ProNeu) ~ cond + age + sex	114.51	1.60
	Logit(ProNeu) ~ cond + age	113.21	0.30
	Logit(ProNeu) ~ cond + sex	114.36	1.45
	Logit(ProNeu) ~ cond	**112.91**	**0.00**
Proportion eosinophils	Logit(ProEos) ~ cond + age + sex	101.64	2.52
	Logit(ProEos) ~ cond + age	**99.11**	**0.00**
	Logit(ProEos) ~ cond + sex	101.58	2.46
	Logit(ProEos) ~ cond	99.20	0.09
Bacterial killing ability	logit(BKA3U) ~ cond + age + sex)	64.38	3.20
	logit(bka) ~ cond + age	61.57	0.39
	logit(bka) ~ age	**61.18**	**0.00**
	logit(bka) ~ intercept	61.88	0.70

Appendix B Supporting Information for Chapter 3

Supporting Information S3.1.—Mixed effects models considered for each health and immune outcome identified via backwards selection from the full model (see Methods) based on lowest Akaike's information criterion (AIC). For each outcome, the final model (bold font) and the two next best models are shown for comparison. All models include as a random effect a unique animal identifier, which takes into account animal ID and recapture status (0/1) at each time point. Models for hair corticosterone include hair sample weight as an offset term. Models for condition assume normal distribution, while models for female reproductive activity and scarring assume binomial distribution. Models for cell counts assume normal distribution after transformation with a natural logarithm. For differential cell counts we also included total white blood cell counts transformed with a natural logarithm as an offset term. Models for bacterial killing ability predict the difference between the mean number of colonies on sample and control plates and include bacterial colony counts on control plates transformed with a natural logarithm as an offset term (equivalent to a log link function). These models assume negative binomial distribution of bacterial colony counts. Models predicting skin swelling in response to phytohemagglutinin injection include PHA volume injected as an offset term and control for differences in swelling in response to previous exposure to PHA (i.e. previous capture) by including capture number as a fixed effect. (cond = condition; control = average number of bacteria on control plates; cort = hair corticosterone; hwt = hair sample weight; ID = unique animal identifier; killed = average number of bacteria killed on sample plates; loc = location; lym= lymphocytes; n = sample size; neu = neutrophils; pha = change in limb circumference; pvol = volume of PHA injected; repro = evidence of reproductive activity; scar = presence/absence of scarring; seas = season; twbc = total white blood cells; tx = forest management level; unique = number of unique animals in sample; yr = study year)

Measure	Outcome	n (unique)	Models considered	AIC	ΔAIC
Stress	Corticosterone	189	cort~tx+loc+tx*loc+age+repro+seas+yr+(1|ID),offset=hwt	2081.7	2.00
		(166)	**cort~tx+loc+tx*loc+age+seas+yr+(1|ID),offset=hwt**	**2079.7**	**0.00**
			cort~tx+loc+tx*loc+seas+yr+(1|ID),offset=hwt	2079.8	0.10
Health	Condition	336	cond~tx+loc+tx*loc+age+repro+seas+yr+(1|ID)	1589.9	3.60
		(215)	**cond~tx+loc+repro+age+seas+yr+(1|ID)**	**1586.3**	**0.00**
			cond~loc+repro+age+seas+yr+(1|ID)	1586.8	0.50
	Female reproduction	136	**repro~tx+loc+tx*loc+seas+yr+ (1|ID)**	**191.6**	**0.00**
		(79)	repro~tx+loc+tx*loc+yr+(1|ID)	192.2	0.60
			repro~tx+loc+tx*loc+seas+(1|ID)	193.5	1.90
	Scarring	338	scar~loc+repro+age+seas+yr+(1|ID)	397.4	1.50
		(214)	**scar~repro+age+seas+yr+(1|ID)**	**395.9**	**0.00**
			scar~repro+age+yr +(1|ID),	398.0	2.10

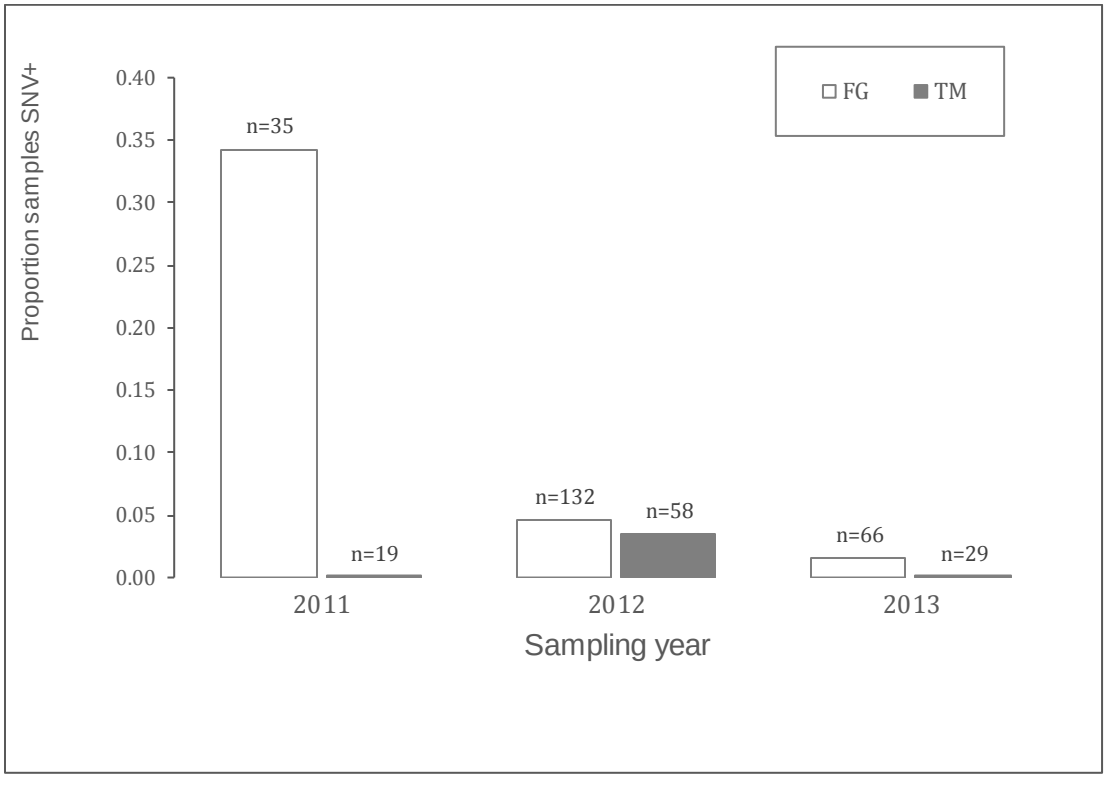
S3.1. cont.

Measure	Outcome	n (unique)	Models considered	AIC	ΔAIC
Immunity	Total WBCs	333 (213)	log(twbc)~tx+loc+cond+repro+scar+seas+yr +(1|ID)	714.9	1.20
			log(twbc)~tx+loc+cond+repro+seas+yr+(1|ID)	**713.7**	**0.00**
			log(twbc)~loc+cond+repro+seas+yr+(1|ID)	713.9	0.20
	Lymphocytes	333 (213)	log(lym)~ tx+loc+tx*loc+cond+repro+age+scar+seas+yr +(1|ID), offset=log(twbc)	270.0	1.70
			log(lym)~tx+loc+tx*loc+cond+repro+age+seas+yr +(1|ID), offset=log(twbc)	**268.29**	**0.00**
			log(lym)~tx+loc+tx*loc+repro+age+seas+yr +(1|ID), offset=log(twbc)	268.34	0.05
	Neutrophils	333 (213)	log(neu)~tx+loc+tx*loc+repro+age+scar+seas+yr+(1|ID),offset=log(twbc)	430.4	**0.50**
			log(neu)~tx+loc+tx*loc+repro+age+seas+yr+(1|ID),offset=log(twbc)	**429.9**	**0.00**
			log(neu)~tx+loc+tx*loc+repro+seas+yr+(1|ID),offset=log(twbc)	431.2	1.30

S3.1. cont.

Measure	Outcome	n (unique)	Models considered	AIC	ΔAIC
Immunity (cont.)	BKA	332 (212)	killed~loc+seas+yr+repro+(1|ID),offset=(log(control))	2913.1	0.30
			killed~loc+seas+yr+(1|ID),offset=(log(control))	2912.9	0.10
			killed~loc+yr+(1|ID),offset=(log(control))	**2912.8**	**0.00**
	PHA	294 (203)	pha~tx+loc+cond+repro+seas+yr+capno+(1|ID),offset=pvol	896.2	1.10
			pha~tx+cond+repro+seas+yr+capno+(1|ID),offset=pvol	895.4	0.30
			pha~cond+repro+seas+yr+capno+(1|ID),offset=pvol	**895.1**	**0.00**

Appendix C Supporting Information for Chapter 4



Supporting Information S4.1.—Sin Nombre virus prevalence in deer mice (*Peromyscus maniculatus*) captured between June and September 2011–2013 on differentially managed forest plots in the Oregon Coast Range, USA. Prevalence of SNV was highest on Forest Grove plots in 2011 (34.3% of samples; 25% of deer mice), but decreased over the course of the three sampling years. In this figure, prevalence was computed for each district and year separately as the number of samples that tested positive via SNV ELISA in a given year divided by the total number of samples obtained during the same year from the same district (n). (FG = Forest Grove district; TM = Tillamook district)

Supporting Information S4.2.—Mixed effect models considered for *Leptospira interrogans* antibody prevalence in deer mice (*Peromyscus maniculatus*), Townsend chipmunks (*Tamias townsendii*), and creeping voles (*Microtus oregoni*) captured across differentially managed forest plots in two districts in the Oregon Coast Range, USA between June and September 2011–2013. Candidate models were identified via backwards selection from the full model (first row) based on lowest Akaike's information criterion (AIC) for *P. maniculatus* and *T. townsendii*, and AICc for *M. oregoni*. For each species, the full model, the final model (bold font) and the two next best models are shown for comparison. All models include as a random effect a unique animal identifier, which takes into account animal ID and recapture status (0/1) at each time point. (ID = unique animal identifier; lepto = *L. interrogans* classification (positive / negative) based on microscopic agglutination test (MAT) and cutoff criteria described in Methods; loc = forestry district; n = sample size; seas = sampling season; tx = forest management level; unique = number of unique animals in sample; yr = study year)

Measure	n (unique)	Models considered	AIC	ΔAIC
P. maniculatus	341	lepto~tx+loc+tx*loc+age+sex+seas+yr+(1|ID)	303.36	12.92
	(219)	lepto~sex+yr+(1|ID)	290.50	0.06
		lepto~yr+(1|ID)	**290.44**	**0.00**
		lepto~(1|ID)	291.77	1.33

S4.2 cont.

Measure	n (unique)	Models considered	AIC	ΔAIC
T. townsendii	231	lepto~tx+loc+tx*loc+age+sex+seas+yr+(1|ID)	296.58	5.07
	(157)	lepto~tx+loc+tx*loc+sex+(1|ID)	291.64	0.13
		lepto~tx+loc+tx*loc+(1|ID)	**291.51**	**0.00**
		lepto~tx+loc+(1|ID)	292.38	0.87
			AICc	ΔAICc
M. oregoni	55	lepto~tx+loc+tx*loc+sex+seas+yr+(1|ID)	69.25	13.56
	(48)	lepto~tx+loc+(1|ID)	57.02	0.08
		lepto~tx+(1|ID)	**55.69**	**0.00**
		lepto~(1|ID)	56.39	0.70