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Beyond mice and men: Environmental change, immunity and infections in wild ungulates

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Abstract

In the face of rapid environmental change, anticipating shifts in microparasite and macroparasite dynamics, including emergence events, is an enormous challenge. We argue that immunological studies in natural populations are pivotal to meeting this challenge: Many components of environmental change – shifts in biotic assemblages, altered climate patterns, and reduced environmental predictability – may affect host immunity. We suggest that wild ungulates can serve as model systems aiding the discovery of immunological mechanisms that link environmental change with parasite transmission dynamics.

Our review of eco-immunological studies in wild ungulates reveals progress in understanding how co-infections affect immunity and parasite transmission; and how environmental and genetic factors interact to shape immunity. Changes in bioavailability of micronutrients have been linked to immunity and health in wild ungulates. Although physiological stress in response to environmental change has been assessed, downstream effects on immunity have not been studied. Moreover, the taxonomic range of ungulates studied is limited to bovids (bighorn sheep, Soay sheep, chamois, musk oxen, bison, African buffalo) and a few cervids (red deer, black-tailed deer). We discuss areas where future studies in ungulates could lead to significant contributions in understanding patterns of immunity and infection in natural populations and across species.

Keywords

coinfection; nutrition; stress; bovid; cervid; ruminant

Introduction

Almost everything we know about mammalian immunity is the result of decades of work on immune responses of mice and humans (176). Indeed, the use of experimental studies in highly controlled laboratory environments, using genetically homogeneous laboratory animal populations, has allowed immunologists to make enormous progress in defining the cellular and molecular mechanisms of host defense. Although the immunological analogy between mouse and man may have limitations (1-2), it has thus far been overwhelmingly

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successful, enabling the development of a remarkable panacea of life-saving drugs and vaccines.

There is, however, much that is not discoverable with this approach. Extrapolating from laboratory animals to natural host populations is fraught with difficulties, because genetic and environmental variation are likely to interact in shaping patterns of immunity and infection. Patterns in natural populations may therefore differ qualitatively from those observed in laboratory settings (3,4). Similarly, scaling up from molecular immunological mechanisms to population level effects on parasite transmission dynamics is challenging. Hosts and parasites interact with the biological community – including other hosts and parasites, their vectors, predators, mutualists and competitors - and the effects of these interactions on immunity cannot be mimicked in the lab. Controlled experiments with human populations are often not possible for ethical reasons. Consequently, population level outcomes of immunological interventions are typically assessed using observational studies, often leading to contradictory results (e.g. effects of helminth co-infections on HIV: (5); malaria: (6-8); all three: (9)) and weak causal inference (10). Yet, some of the most pressing challenges in public and animal health require understanding the effect of genetic and environmental variation on immunity and infections, and predicting the outcomes of environmental change at the population level: How will climate change affect the emergence of infectious diseases? What about land use changes, or pollution? How does the loss of predators, or of large herbivores affect infectious disease dynamics? Will health interventions have unanticipated consequences for non-target organisms? How will new or invasive parasites change the dynamics of endemic infections? What about invasive host or vector species? These questions conventionally fall within the purview of disease ecology. Here we argue that they are fundamentally about immunological variation among individuals and species, as much as they are about ecological and behavioural factors such as community structure and contact networks (4, 29 Schulenburg et al. 2009; and Box 1). As such, there is tremendous opportunity, and need, to broaden the scope of immunological investigations into natural study systems (3, 11).

Ungulates as model species for wild immunology

In this review we focus on studies in wild ungulates (terrestrial hoofed mammals of the orders Perissodactyla and Cetartiodactyla) that are beginning to uncover how environmental change may affect patterns of immunity and infection. Ungulates are large and long-lived compared to other groups of mammals that currently function as viable models for immunologic research in natural populations – such as rodents or primates. Size and longevity bring considerable challenges to studying wild ungulates: capture can be difficult and expensive, attaining significant sample sizes is harder in large animals, and measuring fitness effects of disease takes time in long-lived animals. Large animals are also more difficult to maintain in captive settings, which limits the potential for combining experiments in controlled environments with field studies in ungulates. Despite these challenges, ungulates can provide good model systems for studying environmental change, immunity and infection in natural populations (11): Ungulates are herbivores that respond directly to climate change –mediated shifts in plant growth and phenology. They are diverse, with 250-450 species recognized (12), and occur in almost every terrestrial ecoregion, from

arctic tundra, to savannas and forests in temperate to tropical climates. The abundance and wide geographic distribution of many ungulate species make them highly suitable for wild immunology research, and allow sampling across meaningful environmental gradients. Ungulates are the only mammalian group for which active management of wild populations is common practice worldwide (13). Management activities can dovetail with eco-immunological research, enhancing study feasibility through access to animals, samples, and population data. The large size of most ungulates means that sample volume is usually not limiting for multiple immunologic and physiologic assays. Diagnostic, immunologic and genetic resources developed for domestic ungulates can often be adapted for use in closely related wild ungulate species (14-19). Immunity in ungulates is relatively well-studied because of the importance of domestic members of this group for food security and economics. Immunologic studies in domestic ungulates have revealed several idiosyncracies in their immune function, which may need to be considered when studying wild ungulate species (Box 2). Wild ungulates are thus one of only a few mammalian groups where interdisciplinary research at the interface of ecological and biomedical science can occur. Immunological studies in an increasing number of wild ungulate study systems attest to this idea (Table 1). However, studies in species outside the families Bovidae and Cervidae would be desirable to improve the taxonomic coverage of eco-immunological studies in wild ungulates.

A new frontier: How will anthropogenic environmental change affect immunity in natural host populations, and what are the consequences for infectious disease dynamics?

The likely effects of anthropogenic environmental change -- climate change, habitat fragmentation, pollution and biotic homogenization -- on infectious disease dynamics and emergence are an active area of scientific investigation and debate (20-23). Assessments of infectious disease responses to environmental change have focused strongly on the density and species composition of host communities (24-27), and the potential for changes in contact rates between hosts, vectors and parasites (28), whereas the impacts of shifts in host immunity due to environmental change have received less consideration. Even where immunological variation among individuals or over time has been measured, it has not been translated to disease transmission parameters (29), leaving a significant gap in the chain of causality linking environmental change with altered patterns of immunity and infections. Environmental change might affect immunity through several mechanisms, which in turn could profoundly alter infectious disease dynamics. Here we focus on three such mechanisms - co-infections, timing and quality of nutritional resource availability, and stress.

(i) Co-infections—Climate and land use changes are causing shifts in the geographic distributions of host, vector and parasite populations (30), resulting in novel species assemblages and host-parasite interactions. Invasion of parasite species into host populations that were not previously in their range, or changes in parasite abundance, are likely to have direct effects on host health. In addition, the host's immune responses to these novel challenges may alter its interactions with other, endemic parasites, potentially changing disease dynamics and clinical outcomes for the host. Shifting immunity due to novel parasite exposures may thus result in emergence or re-emergence of disease due to previously prevalent parasites.

Parasites and pathogens have the potential to interact within a host, either by directly competing with each other for space or resources (31), or by altering the immune response (32). Immune responses may be mutually antagonistic (33) where an immune response to one type of parasite prevents the host from mounting appropriate immune defenses against a secondary infection (34). This results in a facilitative effect of one parasite species on another. For example, parasites eliciting a type 2 T helper cell (Th2) response or suppress host immunity, such as gastro-intestinal helminths, might facilitate invasion by microparasites that require an active type 1 T helper cell (Th1) response by the host, due to the well-documented negative feedback between Th1 and Th2 immune responses (35). The role of immunity in coinfection dynamics has been described primarily in mice and birds (36-38). The only ungulate system that has received extensive attention in this context is African buffalo (*Syncerus caffer*), where Th1/Th2 immune co-regulation has been invoked as a mechanism underlying altered dynamics of bovine tuberculosis in buffalo co-infected with gastro-intestinal helminths (39-41): Low natural worm burdens were associated with a higher prevalence of TB infection (41). This could be due to reduced risk of acquiring bTB in animals with low worm burdens, or improved survival of TB-infected buffalo with few worms. Current work using experimental helminth removal in free-ranging buffalo will distinguish between these mechanisms. Importantly, the two mechanisms generate contrasting predictions for the effect of anthelmintic treatment on bTB dynamics: if treatment reduces bTB infection risk, it could slow the spread of the disease in the population; but if treatment prolongs the survival of infectious hosts, it may increase bTB's reproductive number and speed its spread. In contrast, if the immune response mounted to one parasite is cross-protective against another, then infection with one parasite can prevent the secondary infection from establishing. This has been shown in malarial systems in birds and people (42-43). In African buffalo, competition has been investigated in tickborne pathogens (44) and gastrointestinal parasites (45), but it is as yet unclear to what extent these interactions result from resource competition versus immune-mediated parasite interactions.

The presence of emerging infectious diseases can impact host population health directly (46); but beyond this, invasive pathogens may change how the host interacts with its endemic infections (4, 47). For instance, bovine tuberculosis (BTB), an invasive pathogen in southern African wildlife, has been shown to alter the immune response in African buffalo (17, 48), which resulted in increased risk of infection with Rift Valley fever virus (48) as well as increasing the consequences of Brucellosis infection (18) (Box 3).

BTB has changing effects on host immunity throughout its course, characterized by an initial pro-inflammatory, which is later downregulated. These patterns reflect a dynamic interplay between host and pathogen that typically results in persistent infection by the pathogen and limitation of immunopathology by the host: Upon initial infection, hosts upregulate their Th1 immune response to suppress BTB (49-50). Once the pathogen has established itself, hosts develop a chronic infection, remaining infected for the duration of their lives with few overt clinical signs (51), but experiencing significant long-term effects on condition and fitness (41,52-53). During the chronic phase of BTB, the immune response is altered, with changes in cellular protein expression (17, 54) resulting in a skew towards a T-helper cell 0 (Th0) phenotype instead of the initial Th1 responses (49). These dynamic

immunologic effects of BTB may be reflected in changing effects of BTB on subsequent microparasitic infections in the acute versus chronic phase (18).

(ii) Timing and quality of nutritional resource availability—Climate change is altering weather patterns, including the amount and predictability of precipitation (55-57), temperature variability (55), and the frequency of extreme weather events (55), leading to changes in plant growth and phenology (55, 58-59). Animals relying on plants as their food source are thus likely to experience changing patterns of forage availability and quality, and duration of seasonal nutrient restriction. Nutritional condition has the potential to affect immunity in natural populations profoundly, perhaps altering seasonal patterns of disease occurrence and outcomes for the host.

Animals must balance their investment in basic physiological functions including immunity, growth, reproduction and somatic maintenance over the course of their lifetime (60-61). These investments are likely to change with life history stage, season, and resource availability (62-64). Eco-immunological experiments have shown that immune responses depend on resource availability to the host (65-67); but vary among individuals (68); studies explicitly including disease have demonstrated that animals tend to suffer increased susceptibility to disease under nutrient-restriction (69-71). The cost of immunity in the face of limited resources has been investigated in birds (e.g. 172), reptiles (e.g. 173), rodents (e.g. 174). In wild ungulates, resource-mediated changes in immunity and disease susceptibility have been investigated in Soay sheep and African buffalo.

One of the best studied systems for the interactions between nutrition, disease and immunity is the feral Soay sheep population on the island of St. Kilda (Scotland) which experiences crashes where up to 50% of the population may die off during mortality events. These events are driven by nutritional restriction during harsh winters (72), combined with gastrointestinal helminth burdens (73-74). Helminth burdens are moderately heritable in Soay lambs, but in adults, heritability is low (175). Interestingly, stress, due to harsh winters or years with poor recruitment, appears to mediate the increase in parasite burdens observed in Soays during senescence. Sheep that experienced more stress throughout their lives had higher parasite burdens, suggesting that environmental stress may contribute cumulatively to immunosenescence (75). A recent analysis of long-term data on sheep population dynamics, immunity and parasite infections demonstrated that sheep that survive harsh winters may have invested more in anti-helminth immunity (measured as helminth-specific antibody titres), allowing them to maintain condition and resist the mortality associated with gastrointestinal helminths (76). However, winter survival benefits of high investment in immunity may be balanced by costs to reproductive performance in Soays. Female Soays with high self-reactive antibody responsiveness (which correlated positively with overall antibody responsiveness) showed improved survival during harsh winters, but autoreactive antibodies were also associated with reduced reproductive output (171). This trade-off between winter survival and reproductive performance may be mediated by the energetic cost of maintaining a highly responsive immune system, or immunopathology due to autoimmune responsiveness may be affecting fitness directly.

In addition to these trade-offs between immunity and reproduction, studies in African buffalo suggest that there are resource-dependent trade-offs among different components of the immune system. A trade-off between Th1 responses (measured as IFN γ production in response to *in vitro* stimulation of whole blood with *M. bovis* antigen) and Th2 immunity (measured as circulating eosinophils) was observable in buffalo only during the dry season, when forage quality and availability are low and animals in poor condition (39). Similarly, innate immune responses (measured as bactericidal ability of whole blood and neutrophil counts) were negatively correlated with adaptive immunity (measured as lymphocyte counts) in the dry season, but not in the wet season (17). These findings underline the fundamental importance of nutritional resource availability in mediating immune function in wild animals.

Besides effects on forage availability, environmental change may also result in alterations to the mineral and vitamin content of food – i.e., forage quality. These changes may lead to nutritional effects on immunity that are not related to energy restriction. One of the most researched minerals in this context is selenium, which is decreasing in bioavailability due to anthropogenic causes such as fossil fuel combustion (77) and intensified agriculture (78). Selenium has been linked to immune function in ruminants (79), where it is important in oxidative immunity, fetal development, muscle maintenance and bone metabolism (79-81). A recent review on the role of mineral nutrition in wild herbivore conservation emphasized that selenium deficiency has been implicated as a cause of poor reproductive performance and health in wild elk and bison, and linked directly to reduced immune function in black tailed deer (78). In addition to selenium, mammalian tissues contain more than 50 other minerals, several of which also play a role in immunity. Zinc, iron, copper, cobalt and molybdenum have been linked directly to altered immune function in livestock (82) and are all altered during climate change (8-85) or land use change such as intensified agriculture (86-87).

(iii) Stress—Human encroachment, land use change, habitat fragmentation, unpredictable extreme weather, and toxic pollutants can all act as physiologic stressors in wild animals (88-91). Chronic stressors (longterm periods of stress) cause immunological, endocrinological and physiological responses that could lead to immune suppression and consequently contribute to serious health effects (92-93). When faced with chronic stress events, an animal's hypothalamic pituitary adrenal (HPA axis) responds by increasing the production of ACTH and farther downstream glucocorticoids (94). In many wildlife studies circulating glucocorticoids are measured in plasma, or the byproducts of metabolism are quantified in the feces (fecal glucocorticoid metabolites) (95). Numerous studies have aimed to assess whether plasma glucocorticoids or fecal glucocorticoid metabolites can be linked to changes in immunity (reviews in 96-98). However, the majority of this research in wild animals has occurred in birds (96, 99-100), rodents (101-102) and amphibians (103-105). Very little work has been done in free-living ungulate species on the effects of stress on immunity, or the effects of stress on disease transmission between individuals.

Conventionally it was believed that physiological stress decreased immune response and increased the likelihood of disease transmission (106-107). However, more recently it has been shown that physiological stress has a variety of effects on the immune system and that

some – typically acute - physiological stress events may enhance immune responses while decreasing the risk of disease transmission (106, 108), while other – often more chronic - physiological stressors may provide the classic picture of suppressed immunity (106). Moreover, the effect of stress on immunity varies by the type of stressor, other ecological pressures (nutrition, reproduction) and the species being investigated (96, 109-110). Wild ungulate study systems provide opportunities to disentangle these complex eco-physiological relationships, because their comparative longevity allows for observation of temporal variation in environmental stressors, the animals' stress responses and their effects on immunity, and potentially disease transmission. For instance human presence in the environment has been linked to a stress response in elk (111), and caribou (112), but no links to immunity or disease were made in these studies. Indeed, despite plausible connections between stress, immunity and disease, these links have not been investigated in most wild mammalian systems (113-114, but see 115).

Future directions and conclusions

With intersections between disease ecology and immunology just beginning to be explored (4, 116), the field is wide open for future discovery. In the following, we highlight some obvious gaps in knowledge in applied and basic aspects of wild immunology; we focus on the scientific underpinnings for anticipating and managing emerging infectious diseases, and on basic comparative immunology in ungulates. Our summary is intended only as a menu of enticing and important research opportunities in wild immunology, where ungulates might serve as appropriate study systems – it is not by any means an exhaustive list.

Applied focus areas that deserve urgent consideration include: (i) linking temporal and inter-individual variation in immunity with heterogeneity in disease susceptibility and transmission – that is, providing an explicit connection between patterns of immunity and disease dynamics in natural populations. There has been enormous progress in investigating environmental and host drivers of immunological variation in natural populations – and this has been a major focus of eco-immunology as a discipline. However, the immune measures typically used in eco-immunological studies have rarely been linked to actual disease transmission. It thus remains unclear how variation in immune measures such as swelling responses to mitogen injection, *in vitro* bactericidal ability, cytokine production or lymphocyte proliferation relates to disease dynamics. Anticipating and managing the effects of anthropogenic environmental change on infectious disease dynamics is one of the most daunting public and animal health challenges of our time: translating immunologic variation to disease dynamic parameters is a necessary step, if immunology is to contribute to a predictive framework linking environmental change and infectious disease dynamics. (ii) Understanding how different environmental stressors mediate immune function at different temporal scales is an important priority in the face of rapidly changing environmental parameters. This includes defining the limits of “normal” environmental variability that organisms can adjust to during the course of their lives, versus variability that exceeds their physiological limitations, causing stress that impairs immune function and may contribute to disease emergence. (iii) Which wild species are the most likely sources of new infections that can spillover into human and domestic animal populations is an urgent question in targeting surveillance for disease emergence. Ungulates play a prominent role in this

context, because they share many parasites with related livestock species and are a frequent source of infection spillover (30). A comparative immunological framework that relates behavioural and life history traits to interspecific variation in immune function could help identify key species that are more likely to harbor the next emerging infections (117).

In addition to these applied questions that are driven by our need to understand how environmental change is likely to change infectious disease dynamics, future research in wild ungulates might also address basic immunological questions about the function and consequences of differences in immunity among mammalian species. For example, how does transfer of maternal antibodies primarily through colostrum affect disease dynamics in ungulate populations? Maternal antibody transfer occurs in a much shorter time period in ungulates than in other mammalian groups (118), in part reflecting the mother's antibody repertoire during the few days surrounding parturition. This snapshot of maternal immunity might accentuate variability in neonatal and juvenile immunity in ungulates, compared to other taxa which receive maternal antibodies throughout pregnancy. It may also limit the breadth of the antibody repertoire that is transmitted, and result in more synchronized loss of maternal immunity in young ungulates – all of which could profoundly affect disease dynamics in ungulate populations. The functional significance of large numbers of $\gamma\delta$ T cells observed in ungulates is another conundrum in comparative immunology. Work in domestic cattle has revealed a reliance on $\gamma\delta$ T cells in controlling a variety of diseases such as FMDV and Mycobacterial infections (119-120) and in sheep, resistance to nematode infection has been linked to the presence of $\gamma\delta$ T cells (121). Compared to humans and laboratory mice, ungulates have more V, D, and J $\gamma\delta$ gene segments to create, and presumably, more diverse T cell receptors (122-124). In cattle, $\gamma\delta$ T cells appear to use all segments, and evidence exists for junction diversity (125), suggesting that perhaps ungulates rely on a more diverse pool of “innate” T cells to provide immunological protection. If ungulates balance the roles of innate and adaptive immune mechanisms differently than other mammalian groups, this may be reflected in distinct patterns of resistance and tolerance to infections, which could set the stage for taxon-specific ecological and evolutionary disease dynamics.

In this review, we have argued that there is much to learn about mammalian immune function by studying immunity in natural populations (echoing 3, 29). Our aim is to stimulate interest, especially among immunologists, in working with wild mammals, and we suggest that ungulate study systems offer some unique opportunities for pursuing this type of research – especially in the context of anthropogenic environmental change. The comparatively long life spans of many ungulate species can allow for longitudinal observation of immune patterns across relevant time scales during which environmental change can occur; and effects of season and reproductive cycles on immunity can potentially be disentangled from those of secular environmental trends. Similarly, ungulate species are often abundant throughout broad geographic ranges, enabling comparisons of immunity across meaningful environmental gradients. These features, along with the availability of genetic, immunologic and diagnostic tools developed for closely related domestic species, set ungulates apart as one of the most tractable groups for the study of wild immunology – despite logistic challenges associated with capturing and sampling large animals. As such, studies in wild ungulates stand to contribute significant insights on immunologic processes

in natural populations, and how they are likely to change in the face of shifting environmental baselines.

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Box 1. Disease dynamics result from the interplay of host behavior and immunity

Dynamics of infectious diseases are driven by disease transmission (rate β) and loss of infectious hosts through death (rate α) or recovery (rate γ). Host behaviour determines the rate at which infectious (I) and susceptible (S) hosts come into contact ($c(S, I)$). Host immunity mediates the likelihood of transmission given a contact ($P(I/c)$), the fraction and rate at which hosts recover (R, γ) or die (D, α) from infection. Diagram is based on directly transmitted infection, but principles apply regardless of transmission pathway.

Box 2: Unique aspects of ungulate immunology

Many aspects of mammalian immunity, as revealed by studies in mice and humans, are conserved in ungulates. However, studies of domesticated ungulates (cattle, sheep, goats, pigs, and horses) have yielded some notable exceptions.

(1) Transfer of maternal antibodies via colostrum. Ungulates do not actively transfer immunoglobulins from mother to the developing fetus and therefore, neonatal ungulates are born without the protection of passively acquired maternal antibodies (150,151). Newborns acquire maternal immunoglobulins, including IgG, IgM, IgA, and IgE during the first colostrum feeding, which freely diffuse through the developing GI tract in the first 1-2 days following birth (152-155). This unusual timing of transfer of maternal antibodies may lead to differences in the repertoire of antibodies in both the neonate and mother, which could affect disease transmission in natural ungulate populations.

(2) MHC organization and usage have noticeable difference from humans. Bovids have an MHC gene organization not seen in other mammals whereby the class II region of the MHC is divided into MHC IIa and MHC IIb regions (156, 157). Further, domestic cattle can often express 1-6 different MHC genes, demonstrating plasticity in MHC expression (158). These idiosyncrasies may need to be considered when interpreting MHC genetic data from wild ungulates.

(3) The presence of a large number of $\gamma\delta$ T cells. All mammals examined to date have $\gamma\delta$ T cells, which use relatively conserved T cell receptors and are activated by pathogen associated molecular patterns often in an MHC-independent manner (159). However, ungulates have unusually high numbers of these T cells in their circulation (160), especially younger animals (161-163) - suggesting functional differences in immune mechanisms and effectors deployed. Researchers need to account for these cells when quantifying the lymphocytic compartment and interpreting cytokine responses in wild ruminants.

Box 3: Emerging infections might alter immunity, and hence native disease dynamics

Case study: Emerging bovine tuberculosis alters dynamics of Rift Valley fever and brucellosis in African Buffalo in Kruger National Park, South Africa (18, 48).

Table 1

Immunological studies in wild ungulates. We used the Web of Science to search for immunological studies of wild ungulates, using the keywords immun*, wild and ungulate (62 results); or the ungulate families - equid /equine (3/168 results respectively), tapir (2 results), rhinoceros (18 results), bovid/bovine (3/849 results respectively), cervid (9 results), suid (7 results), giraffe (5 results), and camelid (4 results) - since the year 1980. The majority of papers on immunity focused on immune response to vaccines or immunologic assays designed to test for diseases, but a few were relevant to understanding immunity in the context of environmental change. Relevant studies in feral Soay sheep and African buffalo are reviewed in the text, studies in other wild ungulate species are summarized in the table.

Study Species	Geographic Region	Key Questions	Key Findings	Key References
Bighorn Sheep (<i>Ovis canadensis</i>)	Western United States	Is pneumonia the result of increased contact between domestic sheep and wild bighorn sheep? Differences in maternal immunity that can explain why lambs of domestic sheep are far less susceptible than bighorns? Why do effects of pneumonia seem to vary dramatically across bighorn sheep populations? Does variation in immunity play a role? Role of coinfection in disease?	Ovine pneumonia involves bacterial and sometimes viral pathogens, and most likely entered bighorn sheep populations due to increased contact with domestic livestock. Domestic sheep are less susceptible to mortality from pneumonia, perhaps due to differences in maternal antibody transfer.	Origin of pneumonia in bighorn sheep: 126-129 Causative agents: 130 Maternal Immunity: 131-132
Red Deer (<i>Cervus elaphus</i>)	Europe	Role of immunity in determining patterns of mycobacterial infections (paratuberculosis)? Role of acquired immunity - natural or through vaccination - in driving bluetongue disease dynamics?	Red deer have been studied to understand the role of immunity in determining resistance to paratuberculosis. Red deer have been proposed as a relevant and cost effective system to study mycobacterial infection in wildlife. They are also susceptible to bluetongue virus and it has been suggested that acquired immunity may have helped reduce infection rates between 2008 and 2010, in addition to a mass vaccination protocol of domestic ruminants.	Paratuberculosis: 133-135 Bluetongue: 136
Alpine Chamois (<i>Rupicapra rupicapra</i>)	Europe	Tradeoffs between immunity and reproduction, mediated by nutritional status? Importance of immunity in mediating <i>Mycoplasma conjunctivae</i> infection? Did it come from domestic sheep and goats?	Male Chamois who invest heavily in mating activities during rut experience decreased immunological defense and may be more susceptible to parasites. Chamois appear to be more susceptible than other wild caprines to <i>Mycoplasma conjunctivae</i> transmitted from domestic sheep and goats.	Tradeoffs: 137-139 <i>Mycoplasma Conjunctivae</i> : 140-141
Musk Oxen (<i>Ovibos moschatus</i>)	Canada, Alaska, Northern Europe	Effect of changes in nutrition on immune function? Effect of heavy metal contamination on immune function? Effect of heat stress on immune function? Why do musk oxen have such low MHC diversity?	Low Copper in milk of mothers and in forage may impair immune function of musk oxen. Exceptionally high levels, and exceptionally low levels of heavy metals reduced lymphocyte proliferation of musk oxen. Epizootic of fatal pneumonia in musk oxen hypothesized to be due to immunosuppression during heat stress. Low MHC diversity in musk oxen may be due to limited exposure to parasites and pathogens.	Nutrition: 142-143 Heavy Metals: 144 Heat Stress: 145 Coinfection: 146

Study Species	Geographic Region	Key Questions	Key Findings	Key References
Bison (<i>Bison bison</i>)	Greater Yellowstone Area, United States	How does infection spillover from domestic livestock affect immunity in wild bison?	Sheep associated malignant catarrhal fever recently emerged in bison. It seems to cause significant immune dysregulation, which is unlike the response of domestic hosts.	Infection spillover: 147-149