



Special Section on Mountain Sheep Management

Pneumonia in Bighorn Sheep: Risk and Resilience

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ABSTRACT Infectious disease contributed to historical declines and extirpations of bighorn sheep (*Ovis canadensis*) in North America and continues to impede population restoration and management. Reports of pneumonia outbreaks in free-ranging bighorn sheep following contact with domestic sheep have been validated by the results of 13 captive commingling experiments. However, ecological and etiological complexities still hinder our understanding and control of respiratory disease in wild sheep. In this paper, we review the literature and summarize recent data to present an overview of the biology and management of pneumonia in bighorn sheep. Many factors contribute to this population-limiting disease, but a bacterium (*Mycoplasma ovipneumoniae*) host-specific to Caprinae and commonly carried by healthy domestic sheep and goats, appears to be a primary agent necessary for initiating epizootics. All-age epizootics are usually associated with significant population declines, but mortality rates vary widely and factors influencing disease severity are not well understood. Once introduced, *M. ovipneumoniae* can persist in bighorn sheep populations for decades. Carrier females may transmit the pathogen to their susceptible lambs, triggering fatal pneumonia outbreaks in nursery groups, which limit recruitment and slow or prevent population recovery. The demographic costs of disease persistence can be equal to or greater than the impacts of the initial epizootic. Strain typing suggests that spillover of *M. ovipneumoniae* into bighorn sheep populations from domestic small ruminants is ongoing and that consequences of spillover are amplified by movements of infected bighorn sheep across populations. Therefore, current disease management strategies focus on reducing risk of spillover from reservoir populations of domestic sheep and goats and on limiting transmission among bighorn sheep. A variety of techniques are employed to prevent contacts that could lead to transmission, including limiting the numbers and distribution of both wild and domestic species. No vaccine or antibiotic treatment has controlled infection in domestic or wild sheep and to date, management actions have been unsuccessful at reducing morbidity, mortality, or disease spread once a bighorn sheep population has been exposed. More effective strategies are needed to prevent pathogen introduction, induce disease fadeout in persistently infected populations, and promote population resilience across the diverse landscapes bighorn sheep inhabit. A comprehensive examination of disease dynamics across populations could help elucidate how disease sometimes fades out naturally and whether population resilience can be increased in the face of infection. Cross-jurisdictional adaptive management experiments and transdisciplinary collaboration, including partnerships with members of the domestic sheep and goat community, are needed to speed progress toward sustainable solutions to protect and restore bighorn sheep populations. © 2017 The Wildlife Society.

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Infectious disease has influenced bighorn sheep (*Ovis canadensis*) population dynamics at least since the westward expansion of the United States, and plausibly since the Spanish colonization of Mexico and the American Southwest. The importance of disease in the historical decline and extirpation of bighorn sheep across much of their range from southern Canada to Mexico is unique among North American ungulates. Early naturalists described catastrophic die-offs and suggested that disease outbreaks and disappearance of wild sheep might be attributed to the introduction of domestic sheep and goats into bighorn sheep range (Brooks 1923, Grinnell 1928). Shillinger (1937) reported on an experiment in which Rocky Mountain bighorn sheep (*O. c. canadensis*), after surviving well in captivity by themselves, all died when healthy-appearing domestic sheep were introduced to the enclosure. Shillinger speculated “The only evident explanation is that some infectious organism well tolerated by the domestic sheep. . . was transferred to the wild animals with disastrous results” (Shillinger 1937:301). Since then, many more disastrous disease outbreaks have occurred in free-ranging wild sheep populations and another 12 domestic-wild sheep commingling experiments have been conducted with similar deadly results for bighorn sheep (Wehausen et al. 2011, Besser et al. 2012a). Together these observations have culminated in the recognition that management of bighorn sheep also involves management of pathogen transmission from domestic sheep (Council for Agricultural Science and Technology 2008, Western Association of Fish and Wildlife Agencies Wild Sheep Working Group 2012, The Wildlife Society 2015).

The susceptibility of bighorn sheep to infectious agents carried by domestic sheep is not unexpected given that genetic similarity with domestic hosts is a key risk factor for pathogen spillover and associated disease-induced population declines in wildlife (Pedersen et al. 2007). The bighorn sheep is the only North American ungulate with a congeneric domesticated relative. Although species divergence occurred over a million years ago (Rezaei et al. 2010), domestic and bighorn sheep are still sufficiently similar that they can interbreed and produce viable offspring (Young and Manville 1960). Bighorn and domestic sheep and goats share lineages of immune-associated genes in the major histocompatibility complex (Gutierrez-Espeleta et al. 2001), but inherent differences in immune systems likely contribute to the disparity in effects of pathogens across species (Silflow et al. 1989, Dassanayake et al. 2009, Highland et al. 2016).

Understanding and acknowledging the importance of pathogen spillover from domestic sheep and goats has provided valuable perspective and direction for management of respiratory disease in bighorn sheep and, at the same time, has complicated it. Wildlife biologists managing bighorn sheep are now faced with an uncomfortable choice between promoting connectivity and gene flow to restore remnant populations and increasing fragmentation and limiting dispersal to reduce the risk of pathogen spillover and transmission. The impact of disease persistence in the aftermath of all-age epizootics is also a serious obstacle to population management. In this paper, we review the

literature and include a synthesis of data from our respective jurisdictions and from members of the Western Association of Fish and Wildlife Agencies Wild Sheep Working Group to provide an overview of the current state of knowledge about pneumonia in bighorn sheep. We report on impacts to individuals and populations, describe current management directions, and discuss potential strategies for moving forward.

CAUSES OF PNEUMONIA IN BIGHORN SHEEP

Pneumonia in bighorn sheep is a microbiologically complex disease, and many diverse bacteria are detected in the lungs of fatally affected animals, including pathogens that cause pneumonia and other diseases in livestock such as *Mannheimia haemolytica*, *Pasteurella multocida*, and *Fusobacterium necrophorum*. Some of these pathogens are toxigenic and lethal to captive bighorn sheep in experimental trials (Foreyt et al. 1994, Dassanayake et al. 2009), but they do not exhibit a clear and consistent association with disease epizootics in free-ranging populations (Singer et al. 2000b, Weiser et al. 2003, Rudolph et al. 2007, Besser et al. 2012b, Shanthalingam et al. 2016). Over time, paradigms of disease etiology have shifted, reflecting the diversity of pathogens and nonpathogenic agents detected in the lungs of pneumonic bighorn sheep. Suspected causes have ranged from lungworm infection (*Protostrongylus* spp.) to leukotoxin positive Pasteurellaceae, to a multi-factorial respiratory disease complex (Besser et al. 2013). Much attention has focused on virulent Pasteurellaceae bacteria where problems with accurate detection and classification have also complicated efforts to establish an association with pneumonia outbreaks in wild sheep (Angen et al. 2002, Walsh et al. 2012, Miller et al. 2013, Shanthalingam et al. 2014, Walsh et al. 2016).

In 2006, by applying culture-independent methods to high-quality samples of the lung microbiome obtained from free-ranging bighorn lambs in early stages of disease, researchers discovered that *Mycoplasma ovipneumoniae* was the pathogen that first invaded the lungs and predisposed affected animals to polymicrobial pneumonia (Besser et al. 2008). This pathogen does not act alone but appears to be a necessary agent for initiating epizootics. Further research is needed on the role of co-infection by known and perhaps as yet unrecognized pathogens as well as other factors that may contribute to disease outcomes by affecting transmission, carriage, and immunity (Dassanayake et al. 2010, Besser et al. 2012b, Fox et al. 2015, Wolff et al. 2016). Clarity on the significance of these interactions will help provide a more complete understanding of the variation observed in the course of infection and disease. We focus our discussion of microbial etiology on *M. ovipneumoniae* because, based on the experimental and empirical data which we review here, it currently presents the most parsimonious and well-supported model for a primary agent of bighorn sheep respiratory disease. For this reason it is also an important focus for management.

M. ovipneumoniae better meets Hill's (1965) causal criteria relevant to infectious diseases: strength of association,

temporality, plausibility, experimental evidence, and analogy than any competing proposed etiology (Besser et al. 2013). *M. ovipneumoniae* also fulfills Koch's postulates (Evans 1976, Walker et al. 2006) for a primary causal agent, with minor modifications. The strong association with disease (i.e., Koch's first postulate) is one of the most convincing lines of evidence for *M. ovipneumoniae*. Besser et al. (2013) detected *M. ovipneumoniae* in all free-ranging bighorn sheep populations affected by pneumonia epizootics where samples were available for testing ($n = 36$) and 91% (29/32) of bighorn sheep populations unaffected by pneumonia lacked evidence of exposure. Pneumonia outbreaks were associated with introduction of *M. ovipneumoniae* in ≥ 10 previously unexposed free-ranging bighorn sheep populations where testing was done before and after the epizootic (Besser et al. 2008, Bernatowicz et al. 2016; M. Cox, Nevada Department of Wildlife, unpublished data; J. Kanta, South Dakota Game, Fish, and Parks, unpublished data; J. Shannon, Utah Division of Wildlife, unpublished data; L. Jones, U.S. Fish and Wildlife Service, unpublished data). Limited information also suggests that free-ranging Dall's sheep (*Ovis dalli*) in Alaska and bighorn sheep populations in northern Alberta where bacterial pneumonia epizootics are not reported, have not been exposed to *M. ovipneumoniae* (Zarnke and Soren 1989, Besser et al. 2013).

Equally compelling, in 2 recent experiments 5 of 6 bighorn sheep survived when commingled with domestic sheep in the absence of *M. ovipneumoniae* (Besser et al. 2012a, Kugadas 2014). In contrast, virtually no (2%) bighorn sheep survived in 12 previous commingling experiments with domestic sheep, including only 1 of 26 in 4 experiments where presence of *M. ovipneumoniae* was reported or could be confirmed retrospectively (Foreyt and Jessup 1982; Foreyt 1989, 1990; Lawrence et al. 2010; Table S1, available online in Supporting Information).

Although Koch's second postulate (i.e., isolation of the agent in pure culture; Walker et al. 2006) has been repeatedly fulfilled, the ability of those cultures to reproduce the disease in healthy bighorn sheep (i.e., Koch's third postulate) is limited, perhaps because of virulence attenuation during cultural passage (Gilmour et al. 1979, Niang et al. 1998a, Besser et al. 2008). However, nasal washes from *M. ovipneumoniae*-colonized domestic sheep, treated to remove any detectable viable bacterial species other than *Mycoplasma*, do reproduce the disease in healthy bighorn sheep and the challenge strain of *M. ovipneumoniae* can be recovered from the pneumonic lungs of the affected animals, thereby fulfilling postulate 4 (i.e., re-isolation of the originally inoculated pathogen; Besser et al. 2014).

Many *Mycoplasma* spp. are host-specific, and the host range of *M. ovipneumoniae* is considered to be limited to Caprinae (Nicholas et al. 2008). Respiratory disease following infection with *M. ovipneumoniae* also has been reported in captive Dall's sheep and other wild Caprinae, including mountain goats (*Oreamnos americanus*), and muskox (*Ovibos moschatus*; Black et al. 1988, Handeland et al. 2014, Wolff et al. 2014). In a recent National Animal Health Monitoring System survey, Sheep 2011, the Animal and Plant Health

Inspection Service tested up to 16 adult females each in 453 randomly selected domestic sheep flocks from across the United States for *M. ovipneumoniae* nasal carriage and serum antibody. Most flocks (88%) tested positive for carriage (as determined by polymerase chain reaction [PCR] on nasal swabs). Larger operations were more likely to be PCR positive and all flocks with ≥ 500 adult females were PCR positive (USDA Aphis Veterinary Services 2015). Less extensive surveys of domestic goats reported 37.5–88% of flocks to be PCR positive on nasal swabs. Larger flocks were more likely to be positive for carriage (Heinse et al. 2016; Table S2, available online in Supporting Information). A host-specific pathogen commonly carried by domestic sheep and goats is consistent with the high mortality observed in captive bighorn sheep when commingled with domestic sheep but not when commingled with non-Caprinae livestock including cattle, horses, and llamas (Foreyt 1992, Foreyt and Lagerquist 1996, Besser et al. 2012a).

Additional evidence for *M. ovipneumoniae* as an epidemic agent is the transmission of 1 (or occasionally 2) multi-locus sequence types (strains) within an outbreak and a diversity of strains across outbreaks (Besser et al. 2012b, Cassirer et al. 2017). These strains of *M. ovipneumoniae* also link the all-age epizootics to the recurrent lamb pneumonia epizootics that follow (Cassirer et al. 2017). Strains detected in domestic sheep differ from those detected in domestic goats, suggesting host adaptation and coevolution within old world Caprinae (Maksimović et al. 2017). This divergence also provides a means for inferring the host species of origin.

CHARACTERISTICS OF RESPIRATORY DISEASE IN INDIVIDUALS

The diverse histopathologic lesions observed in experimental and naturally occurring bighorn sheep pneumonia, range from those typical of *Mycoplasma* infections (lymphocytic cuffing around airways and hypertrophy of the bronchial respiratory epithelium) to the often more dramatic and severe hemorrhagic, edematous, and necrotic lesions resulting from secondary bacterial infections (Miller 2001, Besser et al. 2008, Wood et al. 2017). This polymicrobial pneumonia is thought to occur when *M. ovipneumoniae* binds to and degrades the cilia of the trachea and bronchi, resulting in disruption of the mucociliary escalator (Niang et al. 1998c), the physiologic process for clearing bacteria from the lower respiratory tract. The impaired host immune defenses then allow inhaled opportunistic pathogens to establish multiple simultaneous infections of lung tissues with often fatal results.

The clinical course of bighorn sheep pneumonia may appear dramatic and short, but evidence from naturally occurring and experimental infection indicates that sub-clinical disease exists for several days to several weeks prior to development of obvious symptoms (Besser et al. 2008, Besser et al. 2014, Cassirer et al. 2017). This delay presumably represents the time required for *M. ovipneumoniae* to infect the airways and disrupt the mucociliary escalator. The latent period has important implications for management because animals might appear healthy for several weeks following

infection. By the time disease is evident, *M. ovipneumoniae* and other pneumonia pathogens already could be widespread in the population, even in individuals that still look healthy.

The original focus of *M. ovipneumoniae* research was infection in domestic sheep and goats where it is documented as an important, and probably under-diagnosed, cause of pneumonia in lambs and kids (Lin et al. 2008, Rifatbegović et al. 2011). Differences in the disease across host species suggest potential focal areas for research that may reveal why the disease is so devastating in wild sheep (Table 1). Higher nasal carriage rates ($\chi^2_1 = 35.49$, $P < 0.001$) and lower antibody prevalence in domestic sheep ($\chi^2_1 = 33.78$, $P < 0.001$; Table 1, Table S2) are consistent with an evolved tolerance of *M. ovipneumoniae*, defined as the ability to shed high levels of a pathogen with minimal morbidity or mortality (Råberg et al. 2009). Bighorn sheep resist infection and react to *M. ovipneumoniae* exposure with dramatic humoral immune responses, which could reduce carriage (Table 1), but also might trigger an auto-immune reaction. Such a reaction has been described in domestic lambs that develop respiratory disease associated with *M. ovipneumoniae* infection (Niang et al. 1998b). Robust bighorn sheep immune responses may also contribute to their disease.

Although *M. ovipneumoniae* may be associated with early pneumonia in domestic lambs (Bottinelli et al. 2017), juvenile domestic sheep are usually resistant to *M. ovipneumoniae* prior to weaning. Lambs born in persistently infected flocks often become infected during their third month of life (Table S3, available online in Supporting Information). Bighorn lambs are apparently completely susceptible to infection from birth (Besser et al. 2013), despite the similar magnitude and timing of passive transfer of maternal immunity in both species (Herndon et al. 2011, Highland 2016). Passively transferred bighorn sheep

antibodies might not protect from colonization or it could be that other forms of immunity are more important than the maternally transferred antibody-mediated immune response in defending the host from this pathogen (Plowright et al. 2013).

Domestic sheep herds usually harbor multiple strains of *M. ovipneumoniae* simultaneously (Thirkell et al. 1990; Ionas et al. 1991a, b; Parham et al. 2006). Therefore, intensive sampling and strain typing are required to confirm or rule out individual flocks as a source of *M. ovipneumoniae* transmission to bighorn sheep populations. In contrast, 1 or occasionally 2 strains appear to predominate in bighorn sheep populations (Cassirer et al. 2017). Immune response to *M. ovipneumoniae* is apparently strain-specific in both species, but disease outcomes of cross-strain infection are more severe in bighorn sheep (Alley et al. 1999, Felts et al. 2016, Justice-Allen et al. 2016, Cassirer et al. 2017).

PNEUMONIA IN BIGHORN SHEEP POPULATIONS

Die-Off Events

Many, if not most, bighorn sheep populations in the lower 48 states have endured all-age pneumonia die-offs (Western Association of Fish and Wildlife Agencies Wild Sheep Working Group 2012). These epizootics are the most obvious and dramatic manifestation of disease in bighorn sheep populations. During pneumonia outbreaks when animals are clinically ill, disease agents such as *M. ovipneumoniae* and Pasteurellaceae, usually transmitted through direct contact, may become airborne for short distances (Dixon et al. 2002, Besser et al. 2014). Pathogens can spread rapidly and expose nearly all individuals to infection (Bernatowicz et al. 2016, Ramsey et al. 2016, Cassirer et al. 2017). Severe, high mortality epizootics can ultimately cause extirpation or functional extinction of populations (Singer et al. 2000b); however, most pneumonia outbreaks do not kill entire populations. We estimated a median population decline of 48% (range = 5–100%) in 82 bighorn sheep disease events reported in 7 states and 2 provinces (Fig. 1, Table S4). Causes of the considerable divergence in mortality rates are not well understood but might be explained by heterogeneity in host immunity, pathogen virulence, and patterns of contact and transmission (Hobbs and Miller 1992).

We detected 28 different strains of *M. ovipneumoniae* in 45 bighorn sheep populations tested in 6 western states (Fig. 2B,C; Tables S5 and S6, available online in Supporting Information), each of which likely represents a separate spillover event that caused an all-age epizootic when first introduced. Domestic sheep and domestic goat *M. ovipneumoniae* lineages were both detected in bighorn sheep populations, but most strains detected in bighorn sheep fell within the domestic sheep clade (Kamath et al. 2016, Cassirer et al. 2017; Fig. 2C).

Clusters of the same strain in inter-connected populations, such as those along the border of Idaho, Oregon, and Washington in Hells Canyon, USA; in the Pancake Range

Table 1. Comparison of *M. ovipneumoniae* infection in domestic and bighorn sheep, USA, 1999–2016.

	Bighorn sheep	Domestic sheep
Infection outcome—naïve adults ^a	Bronchopneumonia	No disease
Infection outcome—lambs ^a	Bronchopneumonia 20–100% mortality	Coughing syndrome <2% mortality
Age of lambs at initial infection ^a	<1 week	Usually 8–12 weeks
Prevalence of carriage ^b	Low (median 22%)	High (median 56%)
Seroprevalence ^c	High (median 67%)	Low (median 30%)
Strain diversity within populations ^d	Usually 1	Usually many

^a Alley et al. (1999); Besser et al. (2008, 2014); Cassirer et al. (2013); USDA (2011).

^b Samples ($n = 1,267$) from 40 bighorn sheep populations in California, Idaho, Nevada, Oregon, Utah, and Washington and 47 domestic sheep flocks ($n = 2,508$ samples) in 13 states across the United States (USDA Aphis 2015).

^c Samples ($n = 1,589$) from 42 bighorn sheep populations in California, Idaho, Nevada, Oregon, Utah, and Washington and 37 domestic sheep flocks ($n = 323$ samples) across the United States (USDA Aphis 2015).

^d Parham et al. (2006), Cassirer et al. (2017).

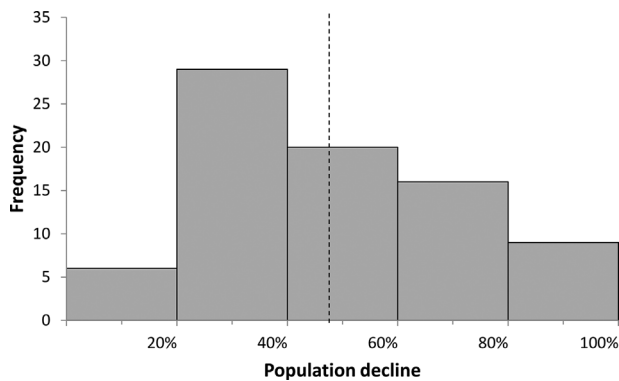


Figure 1. Population declines reported after pneumonia events in bighorn sheep populations in Alberta and British Columbia, Canada; and Idaho, Montana, Nebraska, Nevada, North Dakota, Oregon, Utah, and Washington, USA, 1978–2016. Dashed line represents median mortality of 48% in 82 pneumonia events. Data provided by state and provincial agencies and the Western Association of Fish and Wildlife Agencies Wild Sheep Working Group.

metapopulation of south-central Nevada, USA; and in the southern Nevada metapopulation (Fig. 2B), likely reflect a multiplier effect on a single spillover event when carrier bighorn sheep spread the pathogen across neighboring populations over time.

Multiple strains of *M. ovipneumoniae* observed within a single bighorn sheep population (Fig. 2B) often represent sequential pathogen invasion events. When a new strain is introduced into a population with ongoing infection, it may

replace the existing strain or eventually fade out. Retrospective analysis in the intensively sampled Hells Canyon metapopulation demonstrated a pattern of sequential spillovers and strain replacement or fadeout (Cassirer et al. 2017). Additional data and genomic analyses will be useful for confirming relationships among strains within and between populations and for more rigorous modeling of the ancestral phylogeny and transmission dynamics.

Pathogen Persistence

In 6 states (i.e., California, Idaho, Nevada, Oregon, Utah, and Washington), 63% of 155 populations where infection status is known, have been exposed to *M. ovipneumoniae*, including most native (never extirpated) herds (Fig. 2A). Exposure, as determined by the presence of *M. ovipneumoniae*-specific antibodies, indicates that at least some members of the population have been infected during their lifetime. Exposure does not confirm ongoing shedding, but infection is often maintained in exposed populations by (generally) asymptomatic carriers (Plowright et al. 2016, Cassirer et al. 2017).

Persistently infected populations have a high likelihood of prolonged periods of disease in juveniles and occasionally adults. High rates of pneumonia-induced lamb mortality (20–100%) between 4 and 14 weeks of age are common and reduce recruitment, limiting population growth or causing declines when combined with other mortality factors (Ryder et al. 1992, Enk et al. 2001, Smith et al. 2014, Smith et al. 2015). Some populations rebound (Coggins and Matthews

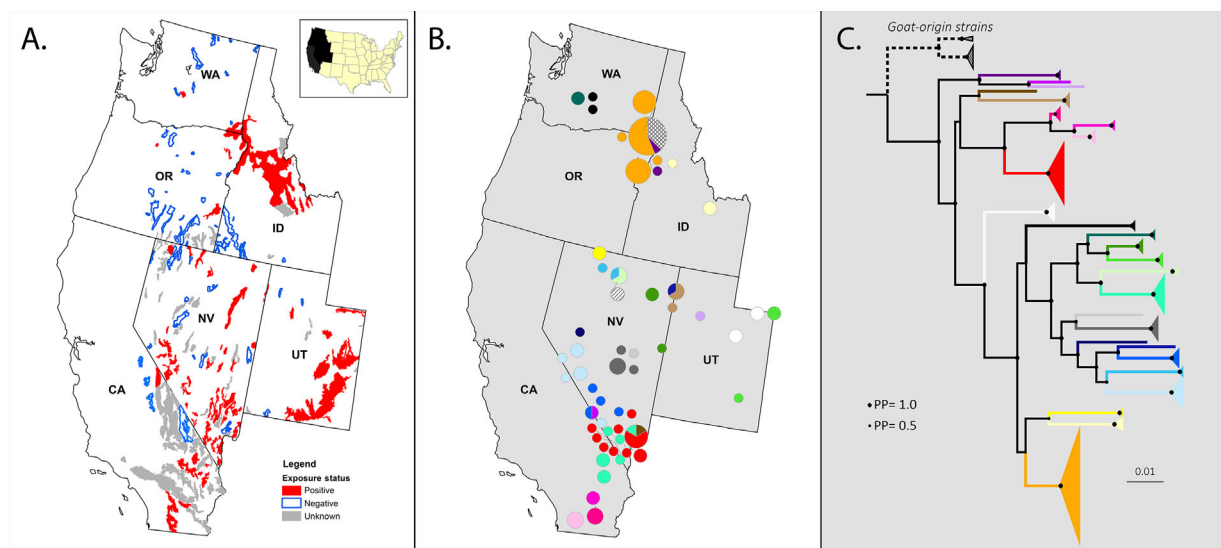


Figure 2. Exposure status and strain types of *Mycoplasma ovipneumoniae* detected in bighorn sheep populations in Washington, Oregon, Idaho, Utah, California, and Nevada, USA. A) Exposure of bighorn sheep populations to *M. ovipneumoniae*, 1999–2016. We assigned exposure based on results of blood serum samples ($n \geq 10$ from each population) submitted to the Washington Animal Disease and Diagnostic Laboratory for *M. ovipneumoniae*-specific serum antibody testing. Populations were classified as positive if antibodies were detected in at least one sample. Populations were classified as negative if no antibodies were detected from ≥ 15 samples. B) Spatial distribution of 28 *M. ovipneumoniae* genotypes (strains) obtained from bighorn sheep, 1984–2016. Each strain type is identified by a different color (domestic sheep origin, $n = 26$) or hatching (domestic goat origin, $n = 2$). Strains of the same color represent well-supported monophyletic clusters (posterior probability, PP > 0.95) with 99.7% to 100% sequence identity (as in panel C). In general, strains that are shades of the same colors are more closely related than strains of different colors. Pie charts indicate the proportional composition of strain types found at a given location over the entire time period of sampling. Chart size is relative to sample size. C) Bayesian majority rule consensus phylogeny of *M. ovipneumoniae* strains derived from bighorn sheep, with colors corresponding to strains shown in panel B. We based phylogenetic analyses on multilocus sequence typing data from 4 genetic loci (16S, IGS, *rpoB*, *gyrB*). Node support is reported as PP, with circle size relative to value (only PP > 0.60 shown). Scale bar indicates genetic distance in units of nucleotide substitutions per site. Dashed line represents the *M. ovipneumoniae* lineage derived from domestic goats.

1992, Jorgenson et al. 1997), but in others there is no trend towards recovery for decades (Manlove et al. 2016). In these cases, the demographic costs of pathogen persistence can outweigh the effects of the initial epizootic. Persistently infected populations also pose a disease risk for adjacent herds and, if they are used as source stock for translocations, moving carriers can inadvertently spread infection over long distances.

Chronically infected populations occasionally experience years with no evidence of disease in juveniles or adults. In approximately 20% of years following all-age disease epizootics in Hells Canyon, lamb survival was high and similar to that observed in unexposed populations (Cassirer et al. 2013). These sporadic disease fadeouts may be due to a delay or failure of *M. ovipneumoniae* transmission to susceptible lambs, as opposed to local pathogen extirpation, because pneumonia epizootics recur in subsequent years. A single or even several years with apparently healthy rates of lamb survival is not necessarily a harbinger of pathogen fadeout and population recovery (Manlove et al. 2016).

Social behavior likely plays an important role in determining the patterns of pneumonia epizootics and disease fadeout. Males are more likely to be directly associated with spillover and spread within and across populations during all-age outbreaks simply because they have larger home ranges and make more long distance movements (DeCesare and Pletscher 2006, O'Brien et al. 2014, Borg et al. 2016). However, dam-lamb and lamb-lamb interactions may be the most important routes of transmission in persistently infected populations (Manlove et al. 2017). Population substructure seems to protect some nursery groups from pathogens (Manlove et al. 2014) perhaps because no carrier dams are present. However, substructuring also might decouple contact rates and associated pathogen transmission from population size. If contact rates remain high as populations decline, transmission may never drop below the threshold required for pathogen extinction. This form of frequency-dependent transmission is common in social animals, and allows disease to persist at low population sizes. This can ultimately lead to host extirpation especially when combined with other stochastic events affecting small populations (de Castro and Bolker 2005).

MONITORING POPULATIONS FOR INFECTION AND DISEASE

All-age pneumonia epizootics are usually readily detected by observations of sick and dying sheep where populations are being actively monitored or are easily observed. However, low mortality outbreaks and epizootics in small and remote populations may be overlooked and underreported. Bighorn sheep also die from other diseases and not all sheep with clinical signs of respiratory disease (for example coughing) have pneumonia. Necropsy and laboratory testing are recommended when animals die from unknown causes, or when pneumonia is suspected. Pneumonia epizootics should be considered as a plausible cause when there is a sudden decline in a bighorn sheep population, particularly if followed by low recruitment.

Outside of all-age outbreaks, juvenile survival, particularly during the first 4 months of life, is the best demographic indicator of health status in bighorn sheep populations. Poor survival to weaning, (~4 months of age; Festa-Bianchet 1988), is the most sensitive signal of pneumonia-induced mortality in lambs. In Hells Canyon, there was a 100% probability of pneumonia being detected when survival to weaning was <50% (Cassirer et al. 2013, Manlove et al. 2016; Fig. 3A); however, this relationship might differ in areas with higher rates of non-disease-related neonatal mortality. Recruitment of juveniles as yearlings and population trend are less clear and specific metrics for classification of health status. Although most populations are stable or decline slowly during periods of persistent infection, pneumonia also might be present when lamb:female ratios at 9–12 months (recruitment) are ≤ 0.30 (Fig. 3A), even if populations are stable or slightly increasing (Fig. 3B, Table S7 available online in Supporting Information).

Diagnostic testing procedures for respiratory disease are continually changing as technology advances and knowledge of the disease and disease agents evolve. Comprehensive testing guidelines for wild sheep produced by the Western Association of Fish and Wildlife Agencies Wildlife Health Committee (2015) provide a good recent overview for a broad array of pathogens. Sampling for *M. ovipneumoniae* should be a part of any bighorn sheep health surveillance protocol and can also be used to monitor potential sources of domestic spillover. The most efficient diagnostic strategies for detection vary by host species and by infection stage. In acute infection (e.g., during all-age or lamb pneumonia epizootics in bighorn sheep, or in 8–16-week-old domestic lambs or kids in an enzootic flock), *M. ovipneumoniae* can be detected by PCR tests in a high proportion of animals' nasal swabs or pneumonic lung tissues. Infection status of domestic sheep and goat flocks is also best determined by PCR tests on nasal swabs. Given the high *M. ovipneumoniae* shedding prevalence in domestic sheep flocks (median 0.56; Table 1), PCR testing on swab samples from 10 adults should be sufficient (99% probability, binomial test) to detect whether *M. ovipneumoniae* is present. Repeated sampling is recommended to confirm negative status. In contrast, determining the exposure status of chronically infected bighorn sheep herds is most efficiently done by testing for serum antibodies, given the relatively high seroprevalence (median 0.67) and lower PCR prevalence in wild sheep (Table 1). Blood serum samples from 15 animals are generally adequate to determine exposure status if prevalence is ≥ 0.25 (99% probability, binomial test). If no antibodies are detected, the population can be considered unexposed, unless samples are collected recently after transmission, prior to immune response development. Nasal swabs from ≥ 18 animals should be adequate (85% probability) to detect shedding by PCR in bighorn sheep populations with *M. ovipneumoniae* prevalence of ≥ 0.10 . Larger sample sizes may be required to account for non-detection error associated with field sampling and diagnostic testing (Walsh et al. 2016). Strain-type can be identified in PCR-positive samples. Nasal or sinus swabs can also be collected from

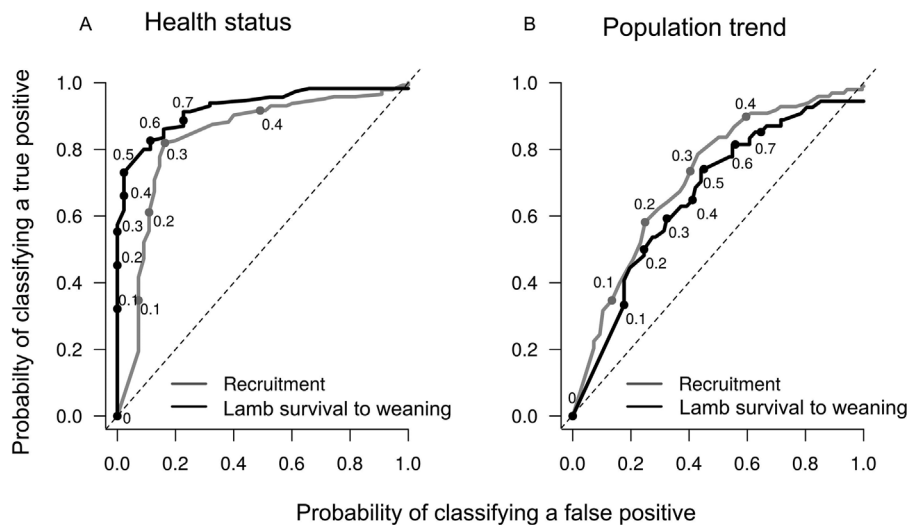


Figure 3. Receiver operating characteristic (ROC) curves identifying optimal lamb survival to weaning (black) and recruitment lamb:female ratios (gray) cut-off values for correctly classifying A) presence of pneumonia and B) declining population trend in bighorn sheep populations in Hells Canyon, Idaho, Oregon, and Washington, USA, 1997–2015 (Manlove et al. 2016). The y axis indicates sensitivity and the x axis indicates inverse specificity of lamb survival and recruitment values. A perfect predictor would have a value of 1 on the y axis and 0 on the x axis for a score of 1 AUC (area under curve). The dashed line represents values with no ability to predict categories (0.50 AUC). A) Lamb survival to weaning (AUC = 0.93) was an excellent predictor of health status and performed better than recruitment (AUC = 0.84). B) Recruitment (AUC = 0.72) was a better predictor of population trend than juvenile survival to weaning (AUC = 0.66). Optimal cut-off values for assigning presence of pneumonia were juvenile survival to weaning of <0.60 (84% accuracy) or recruitment of <0.30 lambs:female (82% accuracy). The optimal cut-off value for classifying populations as declining was recruitment of <0.20 lambs:female (69% accuracy).

fresh or frozen dead animals including heads of hunter-harvested bighorn sheep. Formalin-fixed paraffin-embedded pneumonic lung tissue blocks routinely archived by most diagnostic laboratories for histopathology also provide a DNA source for investigating historical presence and strain types of *M. ovipneumoniae* and other pathogens.

MANAGEMENT OF PNEUMONIA IN BIGHORN SHEEP

Wildlife managers and veterinarians have tried many techniques for controlling and mitigating respiratory disease in wild sheep populations, including administering antibiotics (Coggins 1988, Rudolph et al. 2007, McAdoo et al. 2010), vaccination (Cassirer et al. 2001, Sirochman et al. 2012), mineral supplementation (Coggins 2006, Sirochman et al. 2012), anthelmintic treatment (Miller et al. 2000, Goldstein et al. 2005), selective culling (Edwards et al. 2010, Bernatowicz et al. 2016, Ramsey et al. 2016), partial or complete depopulation (Cassirer et al. 1996, McFarlane and Aoude 2010, Bernatowicz et al. 2016), augmentation, and limiting population size and dispersal. The variety of methods employed, and the lack of clear successes, partially reflects past uncertainty over the causative agents and biological processes involved. The *ad hoc* nature of some of the treatments also limits broader inference. More rigorous testing of a broad ensemble of approaches for management is needed to account for the inherent challenges and variability associated with managing disease in free-ranging wildlife.

Large-scale pathogen eradication is rarely seen as a realistic goal (Klepac et al. 2013), particularly in the presence of a reservoir host, and indeed is not considered a viable option for wild sheep respiratory disease. Instead, more practical

management objectives include controlling the spatial extent or prevalence of the pathogen, facilitating natural pathogen extinction, or reducing the demographic costs of infection (Wobeser 2002, Joseph et al. 2013). Attempts to manage bighorn sheep pneumonia fall broadly into 2 categories: 1) strategies that directly aim to reduce exposure and transmission such as preventing spillover, treatment with antibiotics, vaccination, targeted culling of shedders, reducing population size or density, and population eradication; and 2) strategies that aim to increase individual resistance or herd resilience, including improving nutritional condition, increasing genetic diversity, managing co-infection, or increasing or modifying spatial structuring. Some approaches (such as vaccination or density reduction) could conceivably have application in both categories.

Preventing exposure, theoretically and in practice, offers the most direct and effective method for disease control. Managing transmission is a component of disease prevention strategies for most zoonoses and other spillover diseases (Ebinger et al. 2011, Viana et al. 2014) including test and cull for brucellosis, oral vaccination for rabies, and reduction of deer density for tuberculosis (Rupprecht et al. 1986, Schmitt et al. 2002, Slate et al. 2005, Schumaker et al. 2012). However, managing transmission can be a long-term and costly endeavor. Promoting individual resistance and population resilience has theoretical and empirical support in a number of systems. In general, managing populations to maximize their individual- or herd-level resilience makes good sense (Stephen 2014). Whether increased resistance and resilience can offset the costs of an exotic pathogen like *M. ovipneumoniae*, which generally produces high mortality rates in non-adapted but otherwise robust hosts, remains to

be seen. Below, we discuss past performance and future potential of these management strategies in combating bighorn sheep pneumonia.

Preventing Spillover and Pathogen Invasion

State and federal natural resource agencies have widely instituted policies to prevent pathogen spillover by encouraging or requiring spatial separation between wild sheep and domestic sheep and goats (Western Association of Fish and Wildlife Agencies Wild Sheep Working Group 2012, Bureau of Land Management 2016). Federal and state policies are informed by models, such as the USDA Forest Service's Bighorn Sheep Risk of Contact Tool (Woolever et al. 2015), which incorporate bighorn sheep space use, habitat preferences, foray probabilities, and demographics (Clifford et al. 2009, Cahn et al. 2011, Carpenter et al. 2014, O'Brien et al. 2014) to identify geographic locations with high risk of domestic-wild sheep contact. These models allow comparison of proposed management alternatives and assessment of population-level consequences for bighorn sheep. Resulting actions may take the form of closing or retiring public grazing allotments, altering their timing of use, trucking rather than trailing sheep between pastures, or changing grazing classification from domestic sheep or goats to other livestock (USDA Forest Service 2010, Bureau of Land Management 2017).

Other preventive management practices include capturing or culling escaped domestic sheep on bighorn sheep ranges and removing wild sheep observed near or commingling with domestics. Outreach efforts on private and public lands have encouraged landowner or public lands grazing permittee cooperation in double-fencing domestic sheep flocks in wild sheep habitat, using additional guard dogs, penning domestic sheep and goats at night, not turning sick sheep out to pasture, counting domestic sheep more frequently to better detect and gather strays, notifying local wildlife officials if wild sheep are observed near domestic sheep, and encouraging use of other best management practices (Western Association of Fish and Wildlife Agencies Wild Sheep Working Group 2012).

We are unaware of any formal evaluation of the success of existing separation strategies in preventing new outbreaks, though the regular appearance of new *M. ovipneumoniae* strains in bighorn sheep herds suggests there is room for improvement. Nevertheless, cross-species contact mitigation efforts almost certainly play a crucial role in reducing pathogen invasion. More work is needed to assess the strengths and weaknesses of existing approaches and to devise new and better strategies for managing both domestic and wild sheep to reduce transmission risk. Efforts are currently underway to investigate the feasibility of developing and maintaining *M. ovipneumoniae*-free domestic flocks, which could help reduce the significant risk of pathogen transmission from small domestic sheep and goat herds on private lands (Sells et al. 2015, Heinse et al. 2016, Cassirer et al. 2017).

Another paradigmatic approach to preventing pathogen introduction is reducing density of wild sheep populations. Associative studies (Monello et al. 2001, Sells et al. 2015)

report a positive relationship between wild sheep relative density (or population size) and risk of respiratory disease outbreaks. This relationship could mechanistically result from larger or higher density populations occupying a greater area and dispersing more widely or more often than smaller, lower density herds, with the consequence that increased density corresponds to increased contacts with neighboring domestic sheep or infected wild sheep herds (Monello et al. 2001). Evidence, however, for a density-dependent relationship in movements and dispersal in ungulates is limited and equivocal (Loison et al. 1999, Long et al. 2008) and pre-outbreak population sizes are often small (<50 to 200 animals) and do not differ from sizes of populations that remain healthy (Monello et al. 2001, Shannon et al. 2014).

Many reintroduced bighorn sheep populations experience robust or even exponential growth following initial establishment. When these populations are exposed to respiratory pathogens they often undergo die-offs followed by a prolonged period of low lamb recruitment, limiting recovery (Manlove et al. 2016). As a result, populations are often largest just prior to outbreaks, leading to a statistical, but not necessarily biological, association between population size and outbreak risk. The expected biological processes underlying a presumed density-dependent relationship are not evident, such as declining population growth rate or reduced juvenile recruitment (Jorgenson et al. 1997, Monello et al. 2001). Therefore, it is unknown whether reducing populations or keeping them small would actually mitigate risk, or whether disease outbreaks are simply associated with healthy, growing, and susceptible populations. Future work could pursue the underlying mechanisms directly and experimentally. Understanding the nature of observed associations of pneumonia and population size in bighorn sheep is needed to help minimize disease risk and maximize the number and distribution of wild sheep on the landscape.

Translocations have been widely and successfully used to increase the numbers, distribution, and genetic diversity of bighorn sheep populations (Singer et al. 2000a, Hogg et al. 2006, Olson et al. 2012). Translocations also present a clear risk for anthropogenically assisted pathogen introductions and opportunities for exposure at release sites (Cunningham 1996, Deem et al. 2001, Sainsbury and Vaughn-Higgins 2012, Aiello et al. 2014). Moving animals known to be positive for pneumonia pathogens into new ranges is risky (Western Association of Fish and Wildlife Agencies Wildlife Health Committee 2015). Mixing bighorn sheep from populations known to harbor pathogens with naïve animals, can and has, had poor results (Sandoval et al. 1987). Even if a pathogen is present in both source and recipient populations, immunity may not provide universal protection (Dassanayake et al. 2009, Cassirer et al. 2017). Most state, federal, and provincial agencies use health screenings to inform wild sheep translocation decisions. Careful matching of pathogen profiles, including relevant bacteria, viruses, and parasites in source, recipient, and adjacent bighorn sheep populations and selecting release sites with low risk of contact with domestic sheep and goats are important for translocation success. In practice, health surveys may be

conducted a year in advance at the herd level and with imperfect pathogen detection probabilities, resulting in uncertainty surrounding an individual's health status at the time of translocation. Furthermore, *M. ovipneumoniae* strain typing would not be expected to detect possible epitope variation resulting in immune escape, and health screenings are only as good as our knowledge of what to look for. Improved molecular-based approaches for detecting and describing pathogens and their associated virulence factors are needed. Development of rapid animal-side tests is in progress and, if successful, could also contribute to reducing disease risks posed by translocations.

Reducing Transmission During and Post-Epizootics

A number of agencies have attempted to manage active respiratory disease outbreaks. However, no management action, absent population eradication, has successfully stopped a pneumonia outbreak, and there is no evidence that any intervention has consistently reduced morbidity, mortality, or spread of disease. In part, this is due to the unplanned nature of outbreaks and the inability to randomly assign treatments and controls to matched populations to reliably test for an effect. Nevertheless, efforts to halt epizootics by administering antibiotic treatments (Sandoval et al. 1987, Coggins 1988, Rudolph et al. 2007, McAdoo et al. 2010), and by conducting random and selective culls (Cassirer et al. 1996, Edwards et al. 2010, Bernatowicz et al. 2016, Ramsey et al. 2016) have generally had mixed or negative results. In other wildlife species, depopulation has been successfully employed to prevent spread between populations, but culling zones or population segments to stop the spatial spread of epidemics have met with limited success (Wobeser 2002). Culling is rarely successful because by the time an epidemic is detectable, transmission is usually well under way; even if culling slows transmission, it is unlikely to stop it given imperfect detection of symptomatic animals, long infectious periods, ongoing contacts, and undetected animal movements within and between populations. Lack of success with antibiotics and vaccines administered during or after outbreaks may be a function of their low efficacy, targeting the wrong agent, or an inability to administer them appropriately in most free-ranging bighorn sheep populations.

Depopulation and reintroduction has occasionally been used in an attempt to manage small, particularly poorly performing herds struggling with persistent disease. Although this method may be effective when all members of the former herd are removed, significant effort is needed to ensure complete removal and that the ongoing risk of pathogen introduction is low. A current experimental management effort offering an alternative to depopulation of persistently affected populations exploits the relatively low shedding prevalence of *M. ovipneumoniae* in bighorn sheep by removing only chronic carrier females (Bernatowicz et al. 2016). The goal of this experiment is to stop the chain of transmission from dams to lambs and facilitate pathogen fade-out. If successful, this technique may be best applied to small, accessible populations, where extensive testing is

feasible, and the stochastic mortality of chronic carriers may bolster an active selective removal. In general, test-and-cull success hinges on test sensitivity, animal handling opportunity, pathogen prevalence, and the duration over which management is implemented. Targeted removal works best when a few individuals are responsible for most of the transmission (Lloyd-Smith et al. 2005, Streicker et al. 2013) and may require complete eradication of these carriers. For example, although test-and-cull efforts to control brucellosis in elk (*Cervus canadensis*) successfully met goals of reducing local prevalence (Scurlock et al. 2010, Schumaker et al. 2012) they never eradicated the disease, and upon the program's cessation, prevalence rapidly increased (Wyoming Game and Fish Department 2016). Test-and-cull strategies would ideally be timed to coincide with the lowest-possible pathogen prevalence and the highest levels of immunity, although we currently do not know when those minima and maxima occur.

Managing for Resistance and Resilience

Managing disease by maximizing individual resistance or population resilience has received renewed interest, particularly in the face of continuing challenges associated with direct control of transmission. Theoretical and empirical work across humans, domestic animals, and wildlife suggests that manipulating physiological condition, genetics, or co-infection can alter rates of morbidity and mortality and reduce infection intensity, which may in turn feedback on population-level dynamics (Beldomenico and Begon 2010). However, several studies have found that tradeoffs often exist between enhancing disease resistance and controlling transmission. For example, increasing food supply can minimize parasite-induced mortality (Pedersen and Greives 2008) but may also facilitate transmission (Becker et al. 2015), managing co-infections can reduce morbidity and mortality but can also accelerate pathogen spread (Ezenwa and Jolles 2015), and metapopulation structure can enhance disease spread while simultaneously allowing higher numbers of hosts to survive (Hess 1996, McCallum and Dobson 2002).

There are numerous examples of management actions intended to bolster individual resistance and overall population performance in struggling bighorn sheep populations but little systematic evaluation as to their efficacy. For example, there is no clear evidence of a causal relationship between nutritional condition and susceptibility to respiratory disease in bighorn sheep. Certainly the many experiments in captivity show that optimally provisioned bighorn sheep still succumb at high rates upon exposure to respiratory pathogens. Disease resistance may be correlated with genetic diversity (Luikart et al. 2008, Savage and Zamudio 2011) and researchers continue to seek evidence of host genetic resistance to respiratory disease, which might be expected in herds that are demographically successful even in the presence of long-term pathogen persistence but, to date, a genetic basis has not been found for the susceptibility of wild sheep to pneumonia (Gutierrez-Espeleta et al. 2001, Boyce et al. 2011). Currently, multi-jurisdictional efforts are

underway to collect data on animal condition, genetics, and pathogens to better understand their interactions with wild sheep health.

At the population level, maximizing resilience might include promoting large, widely distributed, genetically diverse metapopulations with spatial structuring and a range of behaviors (de Castro and Bolker 2005, Hess 1996). Indeed, there is some evidence that larger wild sheep populations may experience lower rates of mortality during pneumonia epizootics and are more able to recover than their smaller counterparts (Singer et al. 2001, Cassaigne et al. 2010). Furthermore, increasing population substructure may create asynchrony in transmission across groups of animals. Although this may not prevent epizootics and could actually increase pathogen persistence at the herd or metapopulation level (Grenfell and Harwood 1997, Swinton et al. 1998, Park et al. 2002), it might buffer against simultaneous population-wide epizootics and facilitate stochastic pathogen extinction from sub-herd or population segments (Cross et al. 2005). More work is needed to determine whether or not spatial structuring shields bighorn sheep populations from the worst outcomes of disease and how population structure might affect disease persistence. Current efforts are underway on a limited basis to expedite formation of metapopulation structure by assisted colonization of adjacent range. These manipulations may be most applicable to large, healthy populations.

MANAGEMENT IMPLICATIONS

The extensive costs of pathogen introduction and transmission observed across a wide range of habitats and populations indicate that preventing spillover is the most pressing immediate priority for management of pneumonia in bighorn sheep. Collaboration by wildlife and livestock managers on research and in practice is needed to develop more effective, sustainable approaches to reduce ongoing pathogen transmission from domestic small ruminants to wild sheep. Transmission risks posed by moving bighorn sheep to expand populations are also recognized and should be mitigated before translocations are conducted. In the absence of spillover, selection on the host and the pathogen may eventually lead to a less destructive relationship between wild sheep and the bacteria involved in pneumonia. However, considerable theory suggests that evolution toward increased resistance or reduced virulence is not always expected (Alizon et al. 2009, Osnas et al. 2015). Effective tools are needed to actively restore persistently infected stagnant or declining populations. A comprehensive examination of disease dynamics across populations to better understand how recovery occurs naturally would be useful to inform management of pneumonia in exposed populations.

In the long-term, agencies will need better strategies for the management of larger interconnected bighorn sheep populations for species viability. Engaging a diversity of perspectives in the wildlife, domestic animal, and health sciences through an inter- or trans-disciplinary process could provide new directions or refine existing approaches for management of healthy, resilient populations (Choi and Pak 2007, Allen-Scott et al. 2015). Natural

experiments and designed experiments conducted in an adaptive management framework can also accelerate learning about complex natural systems (Walters and Green 1997, Craig et al. 2012, Williams and Brown 2016). Inter-jurisdictional collaboration can greatly facilitate and, in many cases, is required for successful adaptive management. Replicated interventions with clear hypotheses, objectives, and defined expected outcomes accompanied by monitoring of treatments and controls could greatly advance understanding in the face of uncertainty and speed progress towards developing successful strategies for managing pneumonia in wild sheep.

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