# Bighorn sheep pneumonia: Sorting out the cause of a polymicrobial disease

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## ARTICLE INFO

## ABSTRACT

Pneumonia of bighorn sheep (*Ovis canadensis*) is a dramatic disease of high morbidity and mortality first described more than 80 years ago. The etiology of the disease has been debated since its initial discovery, and at various times lungworms, *Mannheimia haemolytica* and other Pasteurellaceae, and *Mycoplasma ovipneumoniae* have been proposed as primary causal agents. A multi-factorial "respiratory disease complex" has also been proposed as confirmation of causation has eluded investigators. In this paper we review the evidence for each of the candidate primary agents with regard to causal criteria including strength of association, temporality, plausibility, experimental evidence, and analogy. While we find some degree of biological plausibility for all agents and strong experimental evidence for *M. haemolytica*, we demonstrate that of the alternatives considered, *M. ovipneumoniae* is the best supported by all criteria and is therefore the most parsimonious explanation for the disease. The strong but somewhat controversial experimental evidence implicating disease transmission from domestic sheep is consistent with this finding. Based on epidemiologic and microbiologic data, we propose that healthy bighorn sheep populations are naïve to *M. ovipneumoniae*, and that its introduction to susceptible bighorn sheep populations results in epizootic polymicrobial bacterial pneumonia often followed by chronic infection in recovered adults. If this hypothesized model is correct, efforts to control this disease by development or application of vectored vaccines to Pasteurellaceae are unlikely to provide significant benefits, whereas efforts to ensure segregation of healthy bighorn sheep populations from *M. ovipneumoniae*-infected reservoir hosts are crucial to prevention of new disease epizootics. It may also be possible to develop *M. ovipneumoniae* vaccines or other management strategies that could reduce the impact of this devastating disease in bighorn sheep.

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## 1. Introduction

Philosophers of science have long debated the process of causal inference, coming to a current consensus following the work of Karl Popper and others that proof of hypothesis is essentially unattainable, and that it is instead hypothesis falsification that drives scientific progress (Popper,

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1959). The cause of a disease has been defined as an event, condition, or characteristic that plays an essential role in producing the disease and, following Popper, the causal effect of any single factor can only be understood in relationship to conceivable alternatives (Rothman, 1986). Bighorn sheep pneumonia exemplifies the difficulty of causal inference even in the case of a dramatic infectious disease characterized by high morbidity and mortality, and the cause(s) of this disease have been subject to decades of debate and controversy. In this paper, we compare the evidence for several candidate causal microbial agents that have been proposed for epizootic pneumonia of bighorn sheep, including lungworms, Pasteurellaceae (especially *Mannheimia haemolytica*), and *Mycoplasma ovipneumoniae*, using widely accepted criteria for causality of disease, including strength of association, temporal relationships, biological plausibility, experimental evidence and analogy (Rothman, 1986).

### 1.1. Background

Bighorn sheep vanished from much of their historic range in North America during westward expansion in the early 20th century (Dice, 1919; Grinnell, 1928; Buechner, 1960). The precipitous decline in numbers, from 1.5–2 million in the 19th century to 15–18,000 in the United States by 1960 (Buechner, 1960) was not a unique phenomenon, as many other wildlife species' populations were similarly devastated during this era. However, the complete extirpation of bighorn sheep from much of their range, the slow rate of recovery despite intensive management efforts, and the recent listing of several U.S. populations as federally endangered (USFWS, 1998, 2000) sets them apart from most other North American ungulates.

As with other species of wildlife, market hunting and competition with livestock for forage contributed to the decline of bighorn sheep (Spencer, 1943; Buechner, 1960). However, an unusual correlation between the introduction of domestic sheep (*Ovis aries*) and the rapid disappearance of bighorn sheep was noted by early investigators (Grinnell, 1928; Schillenger, 1937; Marsh, 1938). Pneumonia was recognized as an important cause of the decline by the turn of the 20th century, and remains the most significant disease impeding recovery (Rush, 1927; Buechner, 1960; Gross et al., 2000; Cassirer and Sinclair, 2007). Pneumonia outbreaks in previously healthy bighorn sheep populations typically affect all ages of animals, result in 30–90% mortality, and are nearly always followed by at least several years of annual pneumonia outbreaks restricted to lambs that dramatically reduce population growth (Spraker et al., 1984; Ryder et al., 1992; Cassirer et al., 1996; George et al., 2008). Sporadic or continuous pneumonia events can persist in both adults and lambs in interconnected populations for many years, limiting population growth at best and potentially leading to extinction at worst (Cassirer and Sinclair, 2007).

Pathologic descriptions of bighorn sheep pneumonia were first provided in the first half of the 20th century (Rush, 1927; Marsh, 1938). Rush described a chronic pneumonia and noted lung adhesions, pus, "dark ulcers" and "a white strip around the edge of the lobes" in sheep necropsied in an all-age pneumonia outbreak that killed about 75% of the population on a portion of the Sun River game range in Montana in 1925. Marsh described a chronic pneumonia associated with lungworms (*Protostrongylus stilesi*), *Corynebacterium* (now *Trueperella*) *pyogenes* and *Pasteurella* spp. in winter pneumonia mortalities on the Sun River game range and Glacier and Yellowstone National Parks in the 1920s and 1930s, and an acute bacterial pneumonia associated with *Pasteurella* spp. and *T. pyogenes* in a high mortality summer pneumonia event affecting 2- to 3-month-old lambs at the National Bison Range. A similar variety of pathologies and agents continues to be observed in bighorn sheep pneumonia cases. More recently, additional lesions including rhinitis, otitis media, sinusitis, tracheitis, pleuritis, bronchiolar hyperplasia, and bronchiectasis have been associated with this disease (Cassirer and Sinclair, 2007; Besser et al., 2008). *M. ovipneumoniae* and respiratory viruses, especially parainfluenza-3 and respiratory syncytial virus, have also been added to list of potential pathogens (Aune et al., 1998; Weiser et al., 2003; Rudolph et al., 2007; Besser et al., 2008).

While there has been a lack of clarity surrounding the pathogens associated with bighorn sheep pneumonia, experimental trials commingling bighorn and domestic sheep have had very clear results: nearly all bighorn sheep (88 of 90, 98%) commingled with domestic sheep in 11 published studies conducted between 1979 and 2009 died of pneumonia, while the domestic sheep remained healthy, as summarized in Besser et al. (2012a). In marked contrast, most (52 of 56, 93%) bighorn sheep survived similar commingling with non-ovine ungulates, including cattle, horses, deer, elk and llamas, also summarized in Besser et al. (2012a). Therefore, candidate agents enzootic in domestic sheep have been and remain a logical focus of etiologic investigations of bighorn sheep pneumonia.

The epidemiology of emerging diseases in wildlife is often unclear and causative agents are often elusive (McCallum and Dobson, 1995; Laurance et al., 1996). However, pneumonia in bighorn sheep is particularly unusual in that during nearly a century of investigation and despite the occurrence of disease outbreaks with dramatically high morbidity and mortality, no specific pathogen has been strongly or consistently associated with the disease. This rather confusing situation further led to development of the concept of a respiratory disease complex lacking a single causal agent and due instead to environmental or physiological stressors predisposing animals to invasion of the lungs with a combination of agents (Spraker et al., 1984; Rudolph et al., 2007). However, little evidence has been found for a correlative or causal relationship of physiological (Kraabel and Miller, 1997; Goldstein et al., 2005) or environmental stressors (Monello et al., 2001) and pneumonia in bighorn sheep. Thus a long history of conflicting and changing ideas about etiology and epidemiology and a lack of systematic examination of the evidence for causality have produced significant roadblocks to understanding and managing pneumonia in bighorn sheep.