SARCOPTIC MANGE IN BLACK BEARS (*URSUS AMERICANUS*)

by

KEVIN D. NIEDRINGHAUS

(Under the Direction of Michael J. Yabsley)

ABSTRACT

There have been increasing reports of black bears (*Ursus americanus*) with severe skin disease across multiple states in the Eastern and mid-Western United States over the last three decades. The cause of these lesions in the majority of cases was determined to be sarcoptic mange due to the detection of *Sarcoptes scabiei* mites observed in skin scrapes. The emergence of this disease in black bears warranted investigating several basic epidemiological questions. To start, an extensive literature review was performed that described the natural history of *S. scabiei* including the history of the disease and taxonomy and life cycle of the mite, among other topics. The review also provided a comprehensive list of North American wildlife species that have been reported with sarcoptic mange, and finally summarizes what we know about this disease in four commonly-affected North American carnivore hosts: wolves (*Canis lupus*), coyotes (*Canis latrans*), red foxes (*Vulpes Vulpes)* and black bears. In the first research section, I attempted to determine the geographic extent and number of cases of sarcoptic mange in black bears. The second study attempted to determine if exposure to one of several pathogens commonly infecting black bears was a potential risk factor for clinical mange. The third study used a serological approach to determine the extent of exposure in bears without clinical disease to gain a better appreciation for which populations of bears are exposed to mites, and which populations may be at risk of disease in the future. The fourth study determined the ability of mites to survive off the

live host and used these data to speculate on the role of indirect transmission of mites between black bears, a host species that is generally considered to be solitary. In addition to the utility of these studies in advancing our understanding of sarcoptic mange in wildlife, many of these studies can also be used to drive management decisions or lay the groundwork for future research of this disease in bears.

INDEX WORDS: Mange, *Sarcoptes scabiei*, wildlife health, serology, *Ursus americanus*, Pennsylvania, ELISA, co-infection

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DEDICATION

This dissertation is dedicated to my son, Francis. One day, I hope you benefit from this work more than anyone.

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CHAPTER 1

INTRODUCTION AND A REVIEW OF SARCOPTIC MANGE IN NORTH AMERICAN WILDLIFE[1]

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ABSTRACT

The “itch mite” or “mange mite”, *Sarcoptes scabiei,* causes scabies in humans and sarcoptic mange in domestic and free-ranging animals. This mite has a wide host range due to its ability to adapt to new hosts and has been spread across the globe presumably through human expansion. While disease caused by *S. scabiei* has been very well-studied in humans and domestic animals, there are still numerous gaps in our understanding of this pathogen in free-ranging wildlife. The literature on sarcoptic mange in North American wildlife is particularly limited, which may be due to the relatively limited number of clinically-affected species and lack of severe population impacts seen in other continents. This review article provides a summary of the current knowledge of mange in wildlife, with a focus on the most common clinically-affected species in North America including red foxes (*Vulpes vulpes*), gray wolves (*Canis lupus*), coyotes (*Canis latrans*), and American black bears (*Ursus americanus*).

INTRODUCTION

1: Introduction

Sarcoptic mange is a common, widespread disease of domestic and wild mammals (Currier et al., 2011). The causative agent is *Sarcoptes scabiei*, a microscopic mite that infests the skin of its host by burrowing into the epidermis (Fuller, 2013). It is an acarid that belongs to the order Sarcoptiformes, which includes other mites of veterinary importance such as *Psoroptes, Knemicodoptes,* and *Notoedres,* among others. In humans, *S. scabiei* causes disease known as scabies, and in animals the disease is referred to as sarcoptic mange (McCarthy et al., 2004). While not proven, one theory suggests that *S. scabiei* originated as a pathogen of humans with animals serving as aberrant spillover hosts. In this theory, the observed variability in host

adaptations of *S. scabiei* is likely the result of continuous interbreeding of the different strains that affect humans and animals (Fain, 1978, 1991).

In general, the lesions most commonly associated with sarcoptic mange include alopecia, hyperkeratosis, and erythema often accompanied by intense pruritus. Thick skin crusting and fissuring often occur, and many animals die from emaciation or secondary infections with bacteria or yeast (Fischer et al., 2003; Radi, 2004; Oleaga et al., 2008; Nakagawa et al., 2009). Mange epizootics have been reported in a variety of host species worldwide. These events are often associated with high morbidity and mortality in wildlife populations, including Cantabrian chamois (*Rupicapra pyrenaica parava*) in Spain, red foxes (*Vulpes vulpes*) in Fennoscandia, and wombats (*Lasiorhinus* sp. and *Vombatus ursinus*) in Australia (Fernández-Moran et al. 1997; Pence and Ueckermann, 2002).

Scabies in humans has been recognized since biblical times and was one of the first human diseases with a known etiology. Various treatments in animals, using olive oil, lupine, wine, tar, or grease, were described in Europe and the Middle East between the 1st and 16th centuries. The term *scabies* may have been first used by the Roman physician Celsus, but this is not widely accepted. The etiology of mange was not determined to be a parasite until the 17th century by Bonomo. He and other colleagues made large advances on the biology of *S. scabiei* by describing the two sexes and replication by sexual reproduction. Linnaeus was the first to formally describe and name the mite – as *Acarus humanus subcutaneous* in man and *Acarus exulcerans* in animals. The rediscovered mite was renamed by Renucci in 1834 to *Acarus scabiei* from a human in Paris. For additional information, multiple reviews on the history of scabies and mange have been published (Friedman, 1934; Roncalli, 1987; Currier et al., 2011).

Sarcoptic mange is a well-documented and researched disease of wildlife in Europe, Australia, Africa, and Asia (Zumpt and Ledger, 1973; Mörner, 1992; Kraabol et al., 2015; Fraser et al., 2016; Old et al., 2018). Although sarcoptic mange is a common cause of disease in select wildlife species in North America, similar published reports or reviews are lacking. Herein, we review the natural history of *S. scabiei*, including morphology, diagnostics, and research on wildlife species in North America. Research from wildlife outside of North America or in humans is addressed where it can be related to the disease in North American wildlife.

BODY OF TEXT

2. *Sarcoptes scabiei*

2.1. Phylogeny and classification

Sarcoptes scabiei (Linnaeus, 1758) is in the superorder Acariformes and order Sarcoptiformes. It is within the superfamily Sarcoptoidea, and family Sarcoptidae. Sarcoptidae contains three subfamilies including Sarcoptinae which consists of four genera, including *Sarcoptes* (Desch, 2001; Zhang, 2013). It has been suggested that *S. scabiei* is a single heterogenous species that exhibits a high degree of host specificity but has some level of cross-infectivity (Stone et al., 1972; Pence et al. 1975; Fain, 1978; Arlian et al., 1984b; Zahler et al., 1999). Traditionally, variant forms of *S. scabiei* have been identified based on the host species from which they were detected (e.g. *Sarcoptes scabiei* var. *canis, Sarcoptes scabiei* var. *suis,* etc.) and inability to cause pronounced clinical disease in taxonomically distinct hosts (Fain, 1968; Ruiz et al. 1977; Fain, 1978; Arlian et al. 1984b; Arlian et al. 1988b; Arlian et al. 1989). However, few morphological differences are seen among mites found on different host species (Fain, 1968; Fain, 1978). Rather, it is believed that the differences between these variants, which define their host preference, are physiologic and/or genetic (Pence et al., 1975). Other than

human variants being distinct from the 'animal' clade, genetic studies conducted to date have not been able to consistently distinguish between different host variants using common gene targets for mites including internal transcribed spacer (ITS) region-2 (ITS-2) and cytochrome oxidase 1 (COI) (Zahler et al., 1999; Berrilli et al. 2002; Skerratt et al., 2002; Gu and Yang, 2008; Gu and Yang, 2009; Peltier et al. 2017).

In contrast, consistent clustering in geographic or host specificity can still be obtained using microsatellites and mitochondrial DNA as markers, which shows uncertainty for the usefulness of ITS-2 as a gene for *S. scabiei* phylogenetic analyses (Zahler et al., 1999; Walton et al., 2004; Soglia et al., 2007; Alasaad et al., 2009; Rasero et al., 2010; Gakuya et al. 2011). There is potential for microsatellites and mitochondrial DNA to have value, but there is little consistency in which microsatellites or targets are chosen inhibiting the use of comparing large datasets. The *Sarcoptes*-World Molecular Network was created to improve methods of *Sarcoptes* detection as well as provide a central location for comparing phylogenetic data (Alasaad et al., 2011). A formal consensus on the taxonomy based on morphological and genetic features has not been made other than to suggest that all *Sarcoptes scabiei* variants are the same genetically diverse species (Fraser et al., 2016).

2.2. Life cycle

The life cycle of *S. scabiei* consists of five stages: egg, larva, protonymph, tritonymph, and adult (Fig. 1) (Fain, 1968; Arlian and Vyszenski-Moher, 1988). Adults create tunnels through the superficial layer of host skin in part accomplished by cutting mouthpieces and hooks on the legs (Fig. 2A) (Arlian and Vyszenski-Moher, 1988). Little is known about the secreted substances the mite may use to help aid in this tunneling process (Arlian et al., 1984a). Penetration into the epidermis must be achieved for infestation and disease manifestation to

occur (Arlian, 1989). Most tunnels track through the stratum corneum of the epidermis; however, mites can penetrate the stratum granulosum and stratum spinosum in both humans and animals (Video 1) (Morrison et al., 1982; Levi et al., 2012). Mites are able to penetrate the skin within 30 minutes of contact (Arlian et al., 1984a; Arlian and Vyszenski-Moher, 1988).

Adult females will lay approximately three to four eggs per day, and it is estimated that one mite can produce over 50 eggs during its four to six week life expectancy (Arlian and Morgan, 2017). Based on studies using a rabbit model, the larvae hatch from eggs between 50 and 53 hours, larvae molt to protonymphs 3-4 days later, and protonymphs to tritonymphs and tritonymphs to adult were both 2-3 days thereafter (Arlian and Vyszenski-Moher, 1988). There is likely significant variation in the duration of each life stage based on temperature, humidity, host, and observation methods, but much of this variation and importance of different factors are poorly understood (Arlian and Morgan, 2017). Larvae, nymphs, and adult males can also be found in these tunnels ingesting host cells and lymph. The entire life cycle from egg to adult takes approximately two weeks, and all life stages can be found on the same individual host (Arlian and Vyszenski-Moher, 1988).

2.3. Morphology

Detailed morphological features were initially described by Fain in 1968. Overall, the *S. scabiei* idiosoma is dorsally convex and ventrally flattened. All four pairs of limbs of the mite are short and stout with the anterior two pairs of limbs extending out beyond the margin of the idiosoma while the posterior two pairs of limbs do not in adults. The tarsi of the anterior two legs have two blade-like claws as well as stalked empodium with distal pads, and the tibiotarsi of the posterior legs have one or two blade-like claws depending on whether the mite is male or female. Extending from the tarsi are long, unsegmented pedicels with bell-like caruncles. These

are found on the anterior two pairs of legs in females and on all four pairs of legs in males. Females have long setae extending from their posterior two pairs of legs (Fain, 1968; Pence et al., 1975; Colloff and Spieksma, 1992; Wall and Shearer, 2001).

Cytologically, *S. scabiei* is uniquely identified by its characteristic club-like setae on the posterior end of its dorsal idiosoma and by the tooth-like cuticular denticles/spines of the females in the mid-dorsal region of the idiosoma. Both sexes have claws on the terminal segments of all legs as well as have a terminal anus. Transverse, ridged, dorsal striations are present on the idiosoma. These morphologic characteristics distinguish *S. scabiei* from other sarcoptiform mites found on select mammalian hosts such as *Notoedres* spp. (dorsal anus), *Psoroptes* spp. (smooth body, jointed leg stalks, and teardrop-shaped), *Trixacarus caviae* (adult females approximately 200 microns shorter in length), *Ursicoptes* spp. (ovoid to elongated idiosoma), and *Chorioptes* spp. (short pedicels) (Bornstein et al., 2001; Wall and Shearer, 2001; Yunker et al., 1980). *Demodex* spp. is another mite commonly associated with clinical disease in numerous wild and domestic mammals, but they have a distinct 'cigar-shaped' morphology (Elston and Elston, 2014).

2.4 Transmission

Transmission of *S. scabiei*, to any host, occurs via direct and/or indirect contact (i.e. shared environments or fomites) (Smith, 1986; Arlian et al., 1988a; Arlian et al., 1989). The importance of each mechanism of transmission likely varies between hosts based on a variety of factors, including host susceptibility and behavior, mite strain, and environmental conditions. Direct contact transmission is often the primary means of transmission in humans (Otero et al., 2004; Chosidow, 2006). In wildlife, the mechanisms of transmission are likely variable and include both direct transmission in social species as well as indirect transmission in more solitary

species, but our understanding of mechanisms of transmission in many wildlife species is lacking (Dominguez et al., 2008; Devenish-Nelson et al., 2014; Almberg et al., 2015; Ezenwa et al., 2016). Vertical transmission between adults and offspring has also been reported and occurs after birth (Cargill and Dobson, 1979a, b; Arends et al., 1990; Fthenakis et al. 2001). Numerous field-based molecular and experimental studies on the transmission of mites between similar and different hosts, including between animals and humans, have suggested that infestivity and severe disease occurred most commonly when mites were shared between similar hosts rather than between distantly related hosts (Smith and Claypool, 1967; Thomsett, 1968; Samuel, 1981; Arlian et al., 1984b; Arlian et al., 1988b; Bornstein, 1991; Mitra et al., 1995).

An important factor influencing the efficiency of indirect transmission is mite survival in the environment. Temperature, humidity, and possibly mite strain are important factors that can affect the ability of mites to survive off of the host, with survival being shortest at temperatures less than 0˚C and above 45˚C and at lower relative humidity (less than 25%); mites survived longest at cool (between 4 and 10˚C) but not freezing temperatures and high (97%) relative humidity **(**Arlian et al., 1984a; Arlian et al., 1989; Niedringhaus et al. 2019a). In the environment, mites use multiple cues to seek out new hosts, including temperature and odor (Arlian et al., 1984c). Additionally, it was shown that mites are likely only able to penetrate the skin and cause subsequent disease between one half to two thirds of its survival time in the environment (Arlian et al., 1984a; Arlian et al., 1989). Simulation models showed that San Juan Kit foxes (*Vulpes macrotis mutica*) likely transmit mites indirectly between family groups using dens rather than direct contact (Montecino-Latorre et al., 2019). Additionally, indirect transmission through shared dens is likely the most dominant mechanism of mite transmission among wombats as well as possibly within and between carnivore species in Europe (Kolodziej-

Sobocinska et al. 2014; Martin et al. 2019). Evidence of indirect transmission and data showing mite survival off of the live host suggest that scenarios when animals share space, including artificial feeding sites, may contribute to mite transmission (Süld et al. 2014; Niedringhaus et al. 2019a).

3. Sarcoptic mange

3.1 Clinical signs and pathology

The incubation period (i.e. period from exposure to the development of observable signs or lesions) is dependent on host and the quantity of mite exposure. Experimentally, incubation period has ranged from 6 days in domestic dogs to 30 days in other species (Stone et al., 1972; Mörner and Christensson, 1984; Bornstein, 1991; Bornstein and Zakrisson, 1993a; Bornstein et al., 1995). The most common clinical signs and gross lesions in all hosts include pruritus, erythema, hyperkeratosis, seborrhea, and alopecia (Bornstein and Zakrisson, 1993a; Bornstein et al., 1995; Leon-Vizcaino et al., 1999; Aujla et al., 2000). However, these signs can result in at least two unique manifestations of mange: 'ordinary' mange characterized by predominately alopecia (in haired mammals) with relatively few mites present, and 'crusted mange' that results in severe hyperkeratosis and serocelluar crusts and is associated with a large mite burden (Pence and Ueckermann, 2002; Fraser et al. 2018a). These presentations in humans are often known as 'classical' scabies and 'Norwegian' or 'crusted' scabies, respectively (Arlian et al. 2004).

The progression of lesions is largely consistent among experimental infections of dogs, pigs, rabbits, and foxes. The first observable lesions include seborrhea and erythema, followed by crusting and alopecia several days thereafter (Stone et al., 1972; Samuel, 1981; Bornstein et al., 1995; Nimmervoll et al., 2013). The lesions radiate from the site of infection until hyperkeratosis occurs (Little et al., 1998b). As the disease progresses, similar lesions begin to

appear on other parts of the body including the limbs (Stone et al., 1972; Pence et al., 1983; Mörner and Christensson, 1984; Bornstein et al., 1995). As the immune response progresses, pruritus increases while mite burden decreases. Subsequent chronic lesions include skin thickening, lichenification, loss of nutritional condition, secondary bacterial or yeast infections of the skin, and in some cases the animal may become septic (Bornstein et al., 1995). The intense pruritus results in a dramatic increase in the number and severity of self-inflicted lesions created by the host from licking and scratching at its skin (Samuel, 1981). Thus, many of the lesions seen in later infestations are due to the manifestation of the hypersensitivity response rather than the mites themselves (Pence and Ueckermann, 2002). Nimmervoll et al. (2013) suggested that in foxes, lesions start as focal skin disease and either progress to a severe hyperkeratosis with generalized skin lesions or switch to an alopecic/healing form (Fig. 2B). The end stages of the disease often show animals with reduced appetite, dehydration, and poor physical condition (Bornstein et al., 1995; Samuel, 1981; Martin et al. 2018). Several organisms have been associated with secondary infections in cases of sarcoptic mange including *Malassezia pachydermatis* and *Pelodera strongyloides* although their role in lesions present is largely unknown (Salkin et al., 1980; Fitzgerald et al., 2008; Peltier et al., 2018).

Sarcoptes mites produce a variety of antigenic material (e.g. eggshells, molted skins, dead mites, and mite feces) as they penetrate and burrow through the skin of the host (Arlian et al., 1985; Morgan et al., 2016). The type of immune response is largely dependent on the immune status of the host and if the host can induce an appropriate hypersensitivity response (Pence and Ueckermann, 2002). Some highly susceptible species (e.g. red foxes) develop a hypersensitivity response to this material, the most common of which is the Type 1 (i.e. immediate response) (Little et al., 1998b; Tarigan and Huntley, 2005). A Type 4 (i.e. delayed

response), where many T-lymphocytes accumulate in the dermis, has been reported in humans, domestic dogs, and pigs and in conjunction with a Type I reaction (Sheahan, 1975; Davis and Moon, 1990; Bornstein and Zakrisson, 1993b; Skerratt, 2003; Elder et al., 2006). The Type I hypersensitivity primarily manifests as hyperplasia of mast cells and eosinophils with associated increases in these cell types on blood cell counts (Little et al., 1998b).

3.2 Diagnostic testing and monitoring

While clinical signs can be suggestive of mange, confirming the disease in individual animals requires one of the following techniques: histology/cytology to identify mites and describe the associated pathology, detection of antibodies in the serum, and/or molecular techniques (Angelone-Alasaad et al., 2015). Sarcoptic mange can grossly appear similar to other skin diseases, and identification of mites, typically by skin scrape or biopsy, is necessary to make an accurate diagnosis in both humans and animals (Curtis, 2012; Hill and Steinberg, 1993). In addition, mange can be caused by different species, even genera, of mites in individual host species so morphologic or molecular identification of mites is important. For example, mange in black bears (*Ursus americanus*) can be caused by *S. scabiei*, *Ursicoptes americanus*, and *Demodex ursi* (Yunker et al. 1980; Desch, 2009; Peltier et al. 2018). While skin scrapes are the most commonly used method for diagnosing mange, variation in mite burden and host response between species may result in inconsistencies for this diagnostic approach (Little et al., 1998b; Fraser et al., 2018; Peltier et al., 2018). For example, in canids, the mite burden is generally low even in severely affected animals and consequently cytology may not be effective at detecting mites in these hosts (Hill and Steinberg, 1993; Samuel, 1981). In other species (e.g. pigs, humans, and bears) mite burdens are higher with similar or less severe clinical signs, resulting in

higher success of detection of mites via cytology (Davis and Moon, 1990; Walton and Currie, 2007; Peltier et al. 2018).

Characteristic histological lesions, including eosinophilic or lymphocytic dermatitis, acanthosis, and severe parakeratotic hyperkeratosis can help support a diagnosis of mange. While seeing cross-sections of arthropods within the epidermis is often diagnostic for this disease, identifying mite species on histology can be problematic in hosts that may be infested by multiple species (Pence et al., 1983; Nimmervoll et al., 2013; Salvadori et al., 2016; Peltier et al., 2018). Conventional and real-time polymerase chain reaction targeting the 16S ribosomal RNA, rRNA, ITS-2, and/or COI genes, as well as microsatellites, has been successfully utilized to identify *S. scabiei* DNA from skin scrapings in numerous animal species and humans (Walton et al., 1997; Fukuyama et al., 2010; Angelone-Alasaad et al., 2015; Peltier et al., 2017). To reduce the requirement of capturing wildlife for testing, an assay to detect *Notoedres* spp. in the feces of bobcats was created, but similar techniques for the detection of *S. scabiei* in bears was unsuccessful at mite detection (Stephenson et al., 2013; Peltier et al., 2018). PCR may be more a sensitive technique than cytology in cases where there is a low mite burden, such as in dogs and foxes; histology may also provide evidence of infestation but is considered less specific (Nimmervoll et al., 2013; Cypher et al., 2017). More recently, a loop-mediated isothermal amplification (LAMP) assay was developed to rapidly diagnose mange (Fraser et al. 2018b).

Several approaches can be used to investigate mange and mite exposure in populations. Serological tests can be useful to determine previous exposure to *S. scabiei*, but may not differentiate past exposure with current clinical disease. Similarly, its usefulness for individuals can be limited due to unknown time of initial exposure, possible differences in individual immune responses, and unknown applicability for commercially available assays for use in

wildlife species. An enzyme-linked immunosorbent serologic assay (ELISA) has been developed for use in dogs and pigs for the detection of antibodies against *S. scabiei*. This and similar assays have been evaluated in many other wild and domestic animal taxa with variable results (e.g., Bornstein and Zakrisson, 1993a; Bornstein et al., 1996; Bornstein et al., 2006; Haas et al., 2015; Fuchs et al. 2016; Raez-Bravo et al., 2016; Peltier et al., 2018). More recent techniques reported to diagnose sarcoptic mange in wildlife include a dot-ELISA for use in rabbits and has shown to be a simple, quick, and convenient way to accurately diagnose the disease (Zhang et al., 2013). An indirect ELISA, as well as a Western blot assay, has been used on lung extract and pleural fluid from animals that died prior to blood collection, allowing testing to be performed on animals that may not have died as recently or when serum is unavailable (Jakubek et al., 2012). Serology can be complicated by cross-reactivity, particularly in wildlife, due to infestation by closely-related mite species (Arlian et al., 2015; Arlian et al. 2017).

Additional methods to monitor the prevalence, distribution, and consequences of mange in wild populations have been investigated. Detector dogs have been trained to find animals with sarcoptic mange in an attempt to detect cases and control the disease in populations of Alpine chamois (*Rupicapra rupicapra rupicapra*) and Alpine ibex (*Capra ibex*) (Alasaad et al., 2012b). Radio-collaring affected animals can show the impacts of mange on multiple individuals, including evidence of a drastic reduction in home-range sizes of affected raccoon dogs (*Nyctereutes procyonoides*; Süld et al. 2017). Camera traps have been used to monitor mange distribution in wildlife. This technique has become popular because it likely reduces the bias of clinically-ill animals being more likely to be shot or caught (Carricondo-Sanchez et al., 2017). Camera traps have been used to estimate prevalence of sarcoptic mange in coyotes (*Canis latrans*), feral swine, and white-tailed deer (*Odocoileus virginianus*), but only severe cases of

mange were consistently diagnosed, and mild cases often went undetected (Brewster et al., 2017). Camera traps have also been used to monitor mange in raccoon dogs in Japan, wolves (*Canis lupus*) in Italy and Spain, and bare-nosed wombats (*Vombatus ursinus*) in Australia (Oleaga et al., 2011; Borchard et al., 2012; Galaverni et al., 2012; Saito and Sonoda, 2017). Thermal imaging for tele-diagnosis and physiological consequences of mange in Spanish ibex and gray wolves were also explored (Arenas et al., 2002; Cross et al. 2016). However, imaging techniques are sensitive but lack specificity as this approach cannot distinguish between mange and other causes of skin disease or alopecia nor determine the species of mite potentially involved.

3.3 Management and Treatment

There are several approaches that have been used to manage sarcoptic mange in free-ranging wildlife, and each approach has advantages and disadvantages. Wildlife managers can attempt to reduce the likelihood of transmission of *S. scabiei* between hosts by reducing unnatural contacts between individuals (including minimizing artificial feeding), by maintaining biosecurity when trapping, handling, or transporting diseased wildlife, emphasizing prevention of a novel pathogen introduction, or by treatment and rehabilitation of individual animals (Wobeser, 2002; Sorensen et al., 2014; Van Wick & Hashem, 2019). Additionally, transmission studies show a lack of evidence for density-dependent transmission, although it is likely context-dependent (i.e., more density-dependent in some systems and frequency-dependent in others;Devenish-Nelson et al. 2014). There is little research on methods and efficacy of managing mange in free-ranging wildlife without treatment. Hunting animals or reducing densities alone may not halt the disease spread because animals may move more into newly-created territories (Lindstrom and Mörner, 1985). Dogs able to find carcasses and live animals

affected with mange allows removal or treatment of those individuals as means to prevent additional transmission of the parasite and more accurate monitoring of the population effects of mange, but this technique would not be feasible in many susceptible hosts (Alasaad et al., 2012b).

Additionally, one should consider whether attempted management of an endemic disease in a population that is considered healthy from a conservation standpoint should be pursued. If management of sarcoptic mange in wildlife is being considered, the actions should be tailored to the biology of the host affected. For example, if dens or burrows are a significant source of transmission in some canids or wombats, the approach would be different compared to bears where dens are unlikely to be a source of infestation (Martin et al. 2017; Montecino-Latorre et al. 2019; Niedringhaus et al. 2019a).

Managing mange in domestic species typically involves preventive treatments or the use of approved drugs for treatment of clinical cases by a veterinarian. Numerous publications regarding various treatment regimens have been published for sarcoptic mange in livestock and companion domestic animals including cats, goats, dogs, pigs, and alpacas (Ibrahim and Abusamra, 1987; Jacobson et al., 1999; Wagner and Wendlberger, 2000; Curtis, 2004; Malik et al., 2006; Twomey et al., 2009; Becskei et al., 2016; Beugnet et al., 2016; Romero et al., 2016). However, there is limited information regarding the approved use of any of these treatments for use in free-ranging wildlife.

Treatment of mange in free-ranging wildlife is controversial, but has been conducted for a variety of reasons, including animal welfare concerns, threatened or endangered species, or for research purposes. Rowe and others (2019) recently provided a review on treatment of sarcoptic mange in wildlife and noted that most studies have been performed in Australia, Africa, and

Europe. Based on their review, ivermectin applied subcutaneously for multiple doses between 200 and 400 µg/kg was the most successful and common treatment approach used in these studies, but fluralaner, amitraz, and phoxim were successfully used in some studies. Overall success of treatment was often influenced by severity of disease and number of dosages with greater number of doses given often associated with treatment success (Leon-Vizcaino et al. 2001; Munang'Andu et al. 2010). Additionally, supportive care with the use of fluids and antibiotics also improved the treatment success in captive raccoon dogs (Kido et al. 2014). Two studies that showed a failure of resolution of clinical signs were from moderately to severely-affected animals as well as from single-application of ivermectin and topical selamectin (Newman et al. 2002; Speight et al. 2003).

The authors of the review (Rowe et al. 2019) also acknowledged the lack of randomized control trials as well as minimal post-treatment monitoring of wildlife species to determine treatment efficacy and possible re-infection. Their broad recommendations included treating only mild to moderately-affected animals and removing severely-affected individuals from the population. When deciding if treatment is appropriate, factors must be considered including possible side effects of the drugs, severity of disease, if multiple doses are required and can be delivered, the ability to provide supportive care, ability to monitor or data suggesting post-treatment success, Animal Medicinal Drug Use Clarification (AMDUCA) and withdrawal time compliance in animals that may enter the food chain, potential for development of drug resistance, determining if the animal is truly cleared of infection or becomes a subclinical carrier, and if the animal is being translocated to a mange-free area (Currie et al., 2004; Terada et al., 2010; Rowe et al. 2019). In several instances involving species of special concern, studies have shown treatment can lead to population recovery (Mörner, 1992; Goltsman et al. 1996; Leon-

Vizcaino et al. 2001; Cypher et al. 2017). However in most scenarios, it may be more important to ask the question 'is treatment warranted' rather than 'which treatment is warranted.'

4. Mange in North American Wildlife

4.1. Host range

Globally, it is estimated that *S. scabiei* affects more than 100 species of mammals representing a wide variety of taxa including canids, ungulates, marsupials, felids, suids, rodents, and primates. In North America, the number of free-ranging species reported to develop clinical sarcoptic mange is less than in other continents, and canids are the hosts primarily affected, particularly at the population-level (Fig. 3). Sarcoptic mange in other continents more commonly affects other taxa including cervids, bovids, felids, rodents, and mustelids, and canids are the primary hosts affected by mange (Bornstein et al., 2001). For example, in Europe, sarcoptic mange is considered one of the most common causes of mortality in chamois and Spanish ibex, but also affects numerous other bovids, cervids, mustelids, and felids, many of which also occur but not have not been reported in North America (Mörner, 1992; Rossi et al., 1995; Fernandez-Moran et al., 1997; Ryser-Degiorgis et al., 2002; Kolodziej-Sobocinska et al. 2014). A wide variety of species have been reported to develop clinical disease in Africa including giraffes, gorillas, lions, and cheetahs, among other many cervids (Zumpt and Ledger, 1973; Mwanzia et al., 1995; Graczyk et al., 2001; Alasaad et al., 2012a), and Australian wildlife that are affected are primarily wombats, wallabies, and dingoes (Fraser et al., 2016; Skerratt et al., 1998). This contrasts with North America where sarcoptic mange in cervids and bovids is rare, but rather these taxa tend to develop mange due to *Chorioptes* or *Psoroptes* while felids develop mange due to *Notoedres cati* (Bates, 1999; Nemeth et al. 2014; Foley et al. 2016). A summary of the species documented to be infested by *S. scabiei* in North America is described in

Table 1. In some reports, morphological features specific to *S. scabiei* were not thoroughly described, and there is possibility of mis-identification. Astorga et al. (2018) also provide a map showing the distribution of hosts in North America documented to have sarcoptic mange.

Early reports of epizootics in North American wildlife include outbreaks in red foxes in Ohio and Wisconsin (Olive and Riley, 1948; Trainer and Hale, 1969). The mite was likely introduced into Montana, USA and Alberta, Canada through the intentional use of the mite to control coyote and wolf populations (Knowles, 1909; Pence et al., 1983). In Montana, this 'experiment' was sanctioned by the state government and involved the State Veterinarian inoculating 200 wolves and coyotes in various counties in Montana; later, coyotes with suspected mange were reported in Wyoming, but it is unclear if the spread was related to the initial introduction (Knowles, 1909). Since then, mange has been observed in wild canids across the country and is considered endemic in many of these species (Almberg et al., 2012; Bornstein et al., 2001; Chronert et al., 2007; Kamler and Gipson, 2002; Little et al., 1998a).

In North America, populations of red fox, coyotes, and gray wolves appear to experience epizootics every thirty to forty-five years (Pence and Windberg, 1994). Mild cases of mange have been recently reported in Texas in white-tailed deer but are presumed to not be contributing to morbidity or mortality (Brewster et al., 2017). There are several examples of sarcoptic mange in novel hosts in the North America. The federally endangered kit fox (*Vulpes macrotis mutica*) has increased mortality in an urban, high-density population in Bakersfield, California (Cypher et al., 2017; Rudd et al. 2019). The case fatality rate in this population may be as high as 100%.

4.2 Foxes

Red foxes are one of the most widespread canid species globally and are highly susceptible to sarcoptic mange (Little et al., 1998a). The majority of research on mange in red

foxes has occurred in Europe, where the disease has affected this species since the late 1600s (Friedman, 1934). The red fox population in Bristol, United Kingdom (UK) is arguably the most studied fox population in the world, largely as a result of ongoing mange dynamics research in this group (Baker et al., 2000; Soulsbury et al., 2007). Several examples of severe red fox population impacts have been reported after the *S. scabiei* introduction or acute outbreaks, including the likely extinction of red foxes from a Danish island and severe population declines in Bristol, UK (Mörner, 1992; Henriksen et al., 1993; Lindstrom et al., 1994).

In North America, reports of mange in red foxes are often sporadic, isolated, and rarely associated with recognized severe population impacts. These reports are primarily limited to the eastern United States (Gosselink et al., 2007; Little et al., 1998a; Olive and Riley, 1948; Pryor, 1956; Storm et al., 1976; Trainer and Hale, 1969). In some of these studies, small declines in red fox numbers were reported after acute mange outbreaks, but there was also evidence of recovery of some affected individuals (Storm et al., 1976; Trainer and Hale, 1969).

Red foxes in urban settings in North America, similar to other continents, were more likely to develop disease and die from mange compared to rural populations, which may be influenced by exposure difference or detection bias (Gosselink et al., 2007; Soulsbury et al., 2007). Behavioral changes were reported in red foxes including a decline in activity, loss of fear of humans, and lower likelihood of dispersal (Trainer and Hale, 1969; Storm et al., 1976). Mortality can occur as quickly as 3-4 months following infection (Stone et al., 1972). Foxes with mange also generally are in worse nutritional condition compared to foxes without mange, and they lose more mass compared to affected coyotes and wolves (Trainer and Hale, 1969; Todd et al., 1981; Pence et al., 1983; Pence and Windberg, 1994; Newman et al., 2002; Davidson

et al., 2008). In one study in the UK, foxes with mange survived one fifth as long as foxes without mange (Newman et al., 2002).

There are data to suggest that host-parasite adaptation can occur. Serologic testing of red fox in Norway showed that the ratio of seropositive-mange negative foxes to seropositive-mange positive foxes increased significantly ten years following the initial outbreak confirming that either the fox or the parasite had adapted and fewer clinical cases were observed as a result (Davidson et al., 2008). This adaptation likely has or is occurring in North American foxes, but no studies have been performed in this continent. Interestingly, clinical sarcoptic mange is extremely rare in gray foxes (*Urocyon cinereoargenteus*) despite this species being sympatric with red fox throughout much of the United States (Pryor, 1956; Davidson et al., 1992a; Davidson et al., 1992b; Stone et al., 1982). There are no known reports of mange in swift foxes (*Vulpes velox*), the reason for which is unknown.

4.3 Coyotes

Coyotes with sarcoptic mange have been reported in Alberta, Canada and Montana, USA since the early 1900's, southern Texas in the 1920s, and in the mid-western United States since the 1950's (Pence et al., 1983; Trainer and Hale, 1969). The expansion of sarcoptic mange in coyotes is possibly associated with the expanding populations of the host (Hody and Kays, 2018). Most of the recent publications regarding mange in coyotes in North America centered around urban populations in Edmonton, Canada and several outbreaks in southern Texas between 1975 and 1995. However, isolated reports or small epizootics of mange in coyotes have been reported in multiple areas of North America, including up to 25% of coyotes in British Columbia showing signs of mange (Cowan, 1951; Trainer and Hale, 1969; Stone et al., 1972;

Grinder and Krausman, 2001; Kamler and Gipson, 2002; Chronert et al., 2007). Mange has likely occurred in most areas where coyotes exist in North America.

Several studies have looked at behavior changes in coyotes with mange. Coyotes with mange showed less avoidance of residential areas, particularly during the day, and preferred resource sites with anthropogenic food and bedding sources compared to individuals without mange (Murray and St Clair, 2017). In one study, coyotes with mange were more likely to use residential habitat prior to mange-induced mortality, particularly in the winter (Wilson, 2012). Coyotes with skin disease presumed to be from mange were more likely to access urban compost piles, had larger home ranges, and were more active during the day compared to clinically normal animals (Murray et al., 2015b; Murray et al., 2016). Other studies have shown that no differences in home range between coyotes with or without mange (Kamler and Gipson, 2002; Chronert et al., 2007). Similarly, coyotes with mange were not observed changing their home ranges between years (Chronert et al., 2007). Urban coyotes were more likely to have mange, be in poor physical condition, and were more likely to show conflict-prone behavior compared to rural coyotes (Murray et al., 2015a). Studies in other areas have shown that coyotes with mange stayed closer to carrion food sources than coyotes without mange, and carrion food sources made up a larger percentage of diet in coyotes with mange (Todd et al., 1981). Severely affected individuals were shown to be listless and lacked appropriate fear of humans (Trainer and Hale, 1969). During mange outbreaks, coyotes were less likely to reproduce compared to years with less mange (Pence et al., 1983).

Pence and Windberg described two epizootics of mange in coyotes in southern Texas (Pence and Windberg, 1994; Pence et al., 1983). At the peak of the epizootic in the early 1980s and 1990s, as many as 60 and 80% of coyotes in southern Texas had mange, respectively,

depending on the year (Pence et al., 1983; Pence and Windberg, 1994). Despite over 70% mortality occurring in one study, no long-term population impacts were apparent (Pence and Windberg, 1994). Variation likely occurs however, as the percentage of coyotes with mange at the peak of an epizootic in another study was 32% (Kamler and Gipson, 2002). These studies hypothesized that the outbreaks were cyclical and were caused by a virulent strain of the mites enhanced by a high coyote density and social behaviors, although no genetic analyses were performed on the mites. Kamler and Gipson (2002) followed a clinically-normal male coyote that mated with a female coyote with mange. The male never developed any signs of mange, suggesting some animals are exposed but do not develop observable disease (Kamler and Gipson, 2002). A study of urban coyotes in Chicago, Illinois (USA) showed that mange was endemic in the population and did not affect annual survival rates (Wilson, 2012).

In multiple studies, the number of cases of healing/resolving mange in coyotes was low suggesting either high mortality in severely affected animals that are not recovered or that coyotes are less susceptible to severe disease compared to red foxes (Todd et al., 1981; Pence et al., 1983). However, multiple cases of coyotes with mange that survive have been reported, and mild disease can likely occur in this species (Pence and Windberg, 1994; Chronert et al., 2007). Coyotes could also be exposed to mites without infestation becoming established, further complicating estimations of mortality rate. Mange-specific mortality varied across studies but was as high as 55% in one study in South Dakota (Pence et al., 1983; Chronert et al., 2007). Other studies have suggested that mange in coyotes was highest when population numbers were high and were immediately followed by sharp declines suggesting a density-dependent relationship (Gier et al. 1978; Todd et al. 1981). However, this relationship was not shown by

Pence and others (1983). Adult male coyotes appear to be more likely to have mange than other age-sex categories (Todd et al., 1981; Pence et al., 1983).

4.4 Wolves

Mange has been reported in gray wolves, Mexican wolves (*C. lupus baileyi*), and red wolves in North America since as early as 1889 but was likely present before this time (Todd et al., 1981; Jimenez et al., 2010). In Alberta, Canada during the 1970s, mange in gray wolves varied greatly between regions and years, and mange was implicated as limiting population growth during this time period (Gunson, 1992). Additionally, both wolves and coyotes had a higher prevalence of mange than red foxes which are considered the most commonly and severely affected. Sarcoptic mange was reported in wolves in the Midwestern USA in the 1990s and in the northern Rocky Mountains in the early 2000s (Jimenez et al., 2010).

Sarcoptic mange was first reported in wolves in Yellowstone National Park (YNP) in January 2007 (Smith and Almberg, 2007). Almberg et al. (2012) reported that mange spread outward following the initial introduction in YNP with highest risk of infection in packs closest to the index pack. Mange was reportedly highest in Yellowstone wolves during the winter months and dipped in the summer (Almberg et al., 2015). Additionally, pack size did not appear to be a risk factor for development of sarcoptic mange (rather, pack size appeared protective), but prevalence within a pack did seem to positively influence risk of transmission. In one study, no support was found for age, sex, or coat color as a risk factor for disease, and being previously infested was not associated with reduced risk of future infestations, which contrasts with data from Iberian wolves (*C. lupus signatus*) in Spain where yearlings were least likely to be diseased compared to adults and pups (Oleaga et al., 2011; Almberg et al., 2015). In another study, wolf pups had a higher prevalence of mange in years where overall mange in the entire population

was reduced (Todd et al., 1981). In Alberta, peaks of sarcoptic mange in wolves followed peaks of mange in coyotes by one year (Todd et al., 1981).

With social species, transmission is thought to occur more frequently within the group rather than between different groups as reported in the Yellowstone National Park wolf packs (Almberg et al., 2012). The overall spatial spread of the disease is consistent with pack to pack spread rather than repeated spillover events from outside of YNP. However, the spread of mange appeared to be highly variable within individual packs with some consistently presenting with low prevalence and severity while others suffered from rapid spread and high severity (Almberg et al., 2012). Coyotes also confirmed to have mange in wolf habitats possibly contributed to spreading the pathogen directly or indirectly (Jimenez et al., 2010).

Changes in wolf behavior have been observed after the development of clinical disease potentially due to the increased metabolic demands associated with infestation and thermoregulation due to hair loss (Shelly and Gehring, 2002). Wolves became weak and withdrew from the pack, stayed in areas of lower elevation and less snow, sought out shelter in rural areas near humans, and scavenged carcasses rather than wasting energy hunting (Jimenez et al., 2010). Gray wolves with sarcoptic mange and subsequent hair loss have been shown to have a reduced ability to maintain appropriate thermoregulation. These physiologic changes result in an increased energy demand in clinically-affected wolves and results in wolves compensating by reducing their movement or only moving during warmer times of the day (Cross et al., 2016). One report of wolves using porcupine dens in Wisconsin suggests that in extreme situations, animals with severe mange will seek out abnormal den sites (Wydeven et al., 2003). Wolves with clinical disease were reportedly more likely to consume carrion than hunt for live prey compared to clinically-normal animals, and wolves being tracked also reduced their movements

after severe disease developed (Shelly and Gehring, 2002). Similar to coyotes, wolves had significantly less body fat and kidney fat if affected with *S. scabiei* affected with mange compared to wolves without mange although to a lesser extent (Todd et al., 1981). Wolves and coyotes with mange had between 4 and 22% less body mass compared to animals without mange based on the severity of the disease (Todd et al., 1981).

Multiple studies have shown that pup recruitment was significantly reduced when mange was prevalent in a wolf population (Todd et al., 1981; Jimenez et al., 2010). Mange was also implicated as being a potential cause for pack dissolution and negative growth rates in pack size (Almberg et al., 2012). The risk of mortality from mange decreased as the size of the pack increased, particularly if the pack-mates were mange-free, and as the elk-to-wolf ratio increased. Solitary animals with mange were at higher risk of mortality than those in a pack, and that a large pack size resulted in higher survival of wolves with mange (Almberg et al., 2015). The overall mange-associated mortality in North American wolves is unknown but estimates range between 27 and 34% in the midwestern USA but is estimated at 5.6% in Swedish wolves (Jimenez et al., 2010; Fuchs et al., 2016).

It was noted that not all wolves infested died from the disease or its secondary affects, as survivability depended on disease severity and seasonal variation. Though many individual wolves died from mange or mange-related complications, only a few wolf packs in a few specific areas of Wyoming and Montana were affected (Jimenez et al., 2010). Wolves in Sweden in southern populations are more likely to have antibodies to *S. scabiei*, which may be related to their smaller territories in southern latitudes, as was observed in YNP in the USA, and the higher densities of red foxes (Almberg et al., 2012; Fuchs et al., 2016). Packs of gray wolves in Sweden show that individual animals with clinical disease are often in contact with clinically-

normal animals without antibodies to *S. scabiei*, which suggests unknown factors contribute to disease development in some individuals or in some packs (Fuchs et al., 2016). However, several packs in close approximation to those with active mange remained mange-free, and similarly packs a larger distance from those with mange ultimately developed the disease, possibly from infested lone dispersers (Almberg et al., 2012). One study also showed that juveniles are more likely to be clinically-affected than older adults similar to other species such as red foxes (Todd et al., 1981; Pence et al., 1983; Newman et al., 2002). Currently the northern mountain range wolf population continues to increase annually despite the spread of mange in the population (Jimenez et al, 2010).

4.5 Bears

Historically, American black bears were not considered a typical host for *S. scabiei*, and mange was rarely reported in North America (Bornstein et al., 2001). A study describing three bears with sarcoptic mange in Michigan was the first report in 1984, and another isolated case was reported in Michigan in 2008 co-infected with the nematode *Pelodera strongyloides* (Schmitt et al., 1987; Fitzgerald et al., 2008). Numerous bears in New Mexico were observed to have dermatitis and hair loss but the cause of these lesions was not determined and was not associated with severe morbidity or mortality (Costello et al., 2006). Beginning in the early 1990s, sarcoptic mange began to be more frequently detected in black bears in Pennsylvania (Sommerer, 2014). Since then, the disease has expanded outward into New York, West Virginia, Virginia, and Maryland, and is a regular cause of morbidity and mortality in this region (Niedringhaus et al. 2019b)**.**

The emergence of sarcoptic mange in bears is new relative to other species, and limited research on mange in bears has been performed. While urban areas are often associated with

mange in other hosts, particularly canids, there was no association with impervious land cover and the likelihood of clinical mange in black bears (Gosselink et al., 2007; Soulsbury et al., 2007; Sommerer, 2014; Murray et al., 2015b). Genetic studies on the mites from bears in Pennsylvania and surrounding states indicated there are several haplotypes circulating in bears in the affected region, but a unique bear-specific genotype was not identified, although only two gene targets were investigated (Peltier et al., 2017). When diagnosing clinical mange in bears, skin scrapes appeared to be the most sensitive method for mite detection and identification, as previously mentioned, likely due to the high numbers of mites on bears compared to some other hosts (Peltier et al., 2018). Bears, unlike many other mange-susceptible hosts, are not a social species for much of the year, and transmission dynamics and outbreak epidemiology between individual bears are likely different compared to other hosts. Additional research in this system will help our understanding of mite adaptability, transmission, and host susceptibility. There are no known reports of sarcoptic mange in polar bears (*Ursus maritimus*) or grizzly bears (*Ursus arctos*) to the authors' knowledge.

5. Conclusions

The severity of sarcoptic mange on wildlife populations is highly variable but has potential to cause severe impacts in naïve and susceptible populations. *Sarcoptes scabiei* has an unprecedented ability to cause disease in a wide host range involving taxa from five orders of mammals from North America. The continued expansion of hosts reported to develop this disease warrants continued research to better understand host susceptibility and disease epidemiology. Specifically, advances in modelling techniques that better quantify mange impacts on wildlife populations in North America, similar to what has been suggested for bare-nosed wombats in Australia, can provide valuable data on potential population effects,

particularly since the impact on many species is likely under-appreciated due to general lack of surveillance (Beeton et al. 2019). Expanding hosts for *S. scabiei* could result in a similar expansion of the parasite and potential spillover into aberrant hosts. Additionally, anthropogenic effects on the environment, including climate change, increased contact with humans, domestic animals, and wild animals, and changes in environmental health may all contribute to mange outbreaks and host susceptibility. Decisions regarding mange management in wildlife populations requires a thorough evaluation of the risks and benefits of each management option while considering that taking no action may sometimes be the most appropriate. Factors that should be considered in any potential management decision include individual animal welfare, the conservation status of the species affected, and responsible treatment protocols.

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Table 1. Published host records and selected geographic records for *Sarcoptes scabiei* in free-ranging North American wildlife

Host	State/Province	Source
Canidae		
Kit fox (*Vulpes macrotis mutica*)	California, USA	(Cypher et al., 2017)
Gray wolf (*Canis lupus*)	Alberta, Canada	(Gunson, 1992)
	Multiple States, USA	(Wydeven et al. 1995)
	Wisconsin, USA	(Wydeven et al. 2003)
	Montana/Wyoming, USA	(Jimenez et al. 2010)
	Multiple States, USA	(Almberg et al. 2012)
	Alaska, USA	(Cross et al. 2016)
Coyote (*Canis latrans*)	Wisconsin, USA	(Trainer and Hale, 1969)
	Alberta, Canada	(Todd et al. 1981)
	Louisiana/Texas, USA	(Pence et al. 1981)
	Oklahoma/Wyoming/ Kansas, USA	(Morrison et al. 1982)
	Arizona, USA	(Grinder and Krausman, 2001)
	Kansas, USA	(Kamler and Gipson, 2002)
	South Dakota, USA	(Chronert et al. 2007)

	Illinois, USA	(Wilson, 2012)
Red wolf (*Canis rufus*)	Louisiana, USA	(Pence et al., 1981)
Mexican wolf (*Canis lupus baileyi*)	Arizona, USA	Jimenez et al. 2010
Red fox (*Vulpes vulpes*)	Ohio, USA	(Olive and Riley, 1948)
	Pennsylvania, USA	(Pryor, 1956)
	Wisconsin, USA	(Trainer and Hale, 1969)
	New York	(Stone, 1974)
	Various states, USA	(Storm et al. 1976)
	New Brunswick/Nova Scotia, Canada	(Smith, 1978)
	Various states, USA	(Little et al. 1998a)
	Alberta, Canada	(Vanderkop and Lowes, 1992)
	Virginia, USA	(Kelly and Sleeman, 2003)
	Illinois, USA	(Gosselink et al. 2007)
Gray fox (*Urocyon cinereoargenteus*)	New York, USA	(Stone et al., 1982)
	Pennsylvania, USA	(Pryor, 1956)
Cervidae		
White-tailed deer (*Odocoileus virginianus*)	Texas, USA	(Brewster et al., 2017)

Ursidae		
American black bear (*Ursus americanus*)	Michigan, USA	(Schmitt et al., 1987)
	Pennsylvania, USA	(Peltier et al. 2017)
	Virginia, USA	(Van Wick and Hashem, 2019)
Procyonidae		
Raccoon (*Procyon lotor*)	Michigan, USA	(Fitzgerald et al., 2004)
Mustelidae		
Fisher (*Martes pennanti*)	Maine, USA	(O'Meara et al., 1960)
Suidae		
Feral swine (*Sus scrofa*)	Various southeastern states, USA	(Smith et al., 1982)
Erethizontidae		
North American porcupine (*Erethizon dorsatum*)	Maine, USA	(Payne and O'Meara, 1958)
	Pennsylvania, USA	(Peltier et al. 2017)
Sciuridae		

Fox squirrel (*Sciurus niger*)	Michigan, USA	(Fitzgerald et al., 2004)
Leporidae		
Swamp rabbit (*Sylvilagus aquaticus*)	North Carolina, USA	(Stringer et al., 1969)
Muridae		
House mouse (*Mus musculus*)	New York, USA	(Meierhenry and Clausen, 1977)
Bovidae		
Bighorn sheep (*Ovis canadensis canadensis*)	Western Canada	(Cowan, 1951)

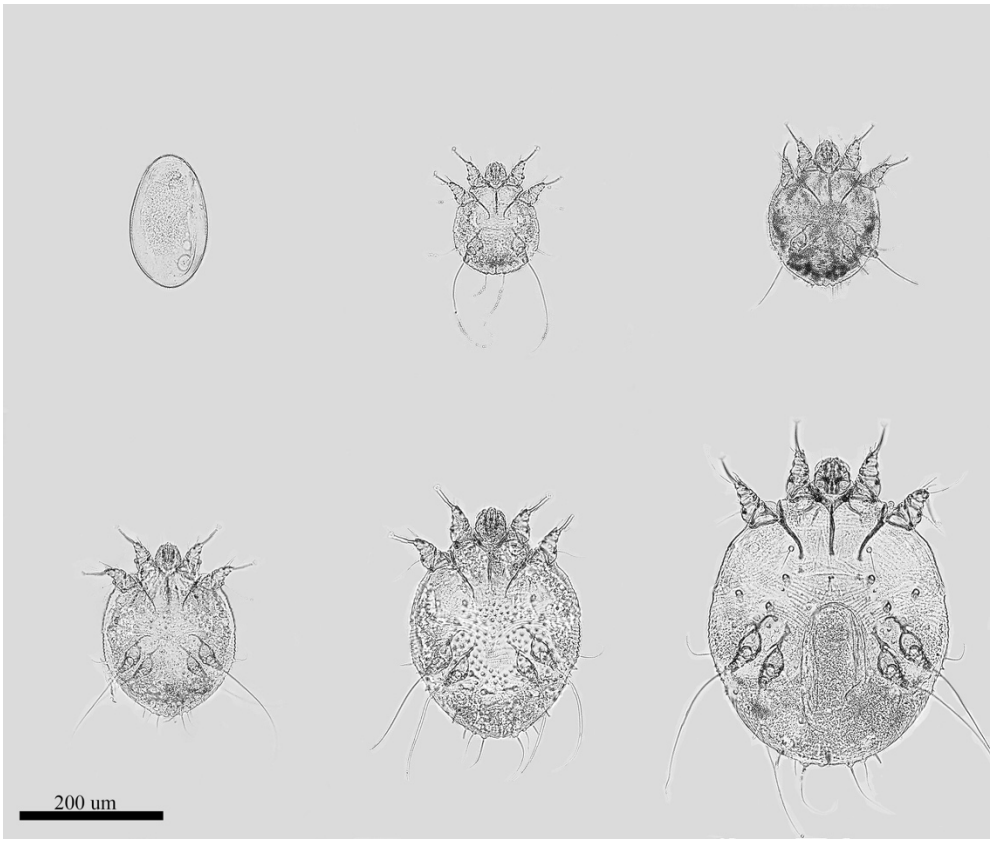

Fig. 1: Life stages of *S. scabiei.* Top left: Egg; Top middle: Larva; Top right: Protonymph; Bottom left: Tritonymph; Bottom middle: Adult Male; Bottom right: Adult Female

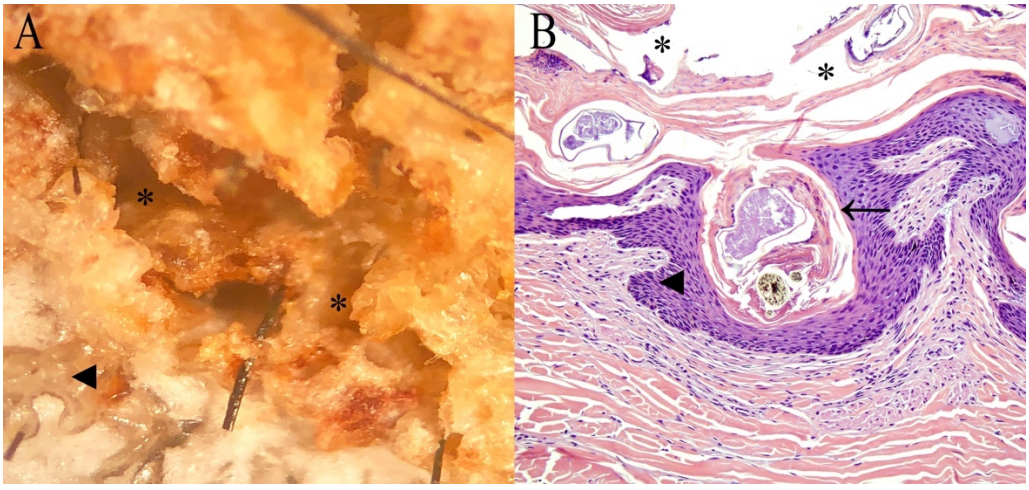

Fig. 2: Microscopic lesions of a bear with sarcoptic mange. (A) Close-up view of hyperkeratotic and crusted skin showing a mite tunnel. (B) Histological section with cross-section of *S. scabiei*

within the epidermis. (Asterisks: mite tunnels; arrowheads: epidermis; arrow pointing to *S. scabiei*).

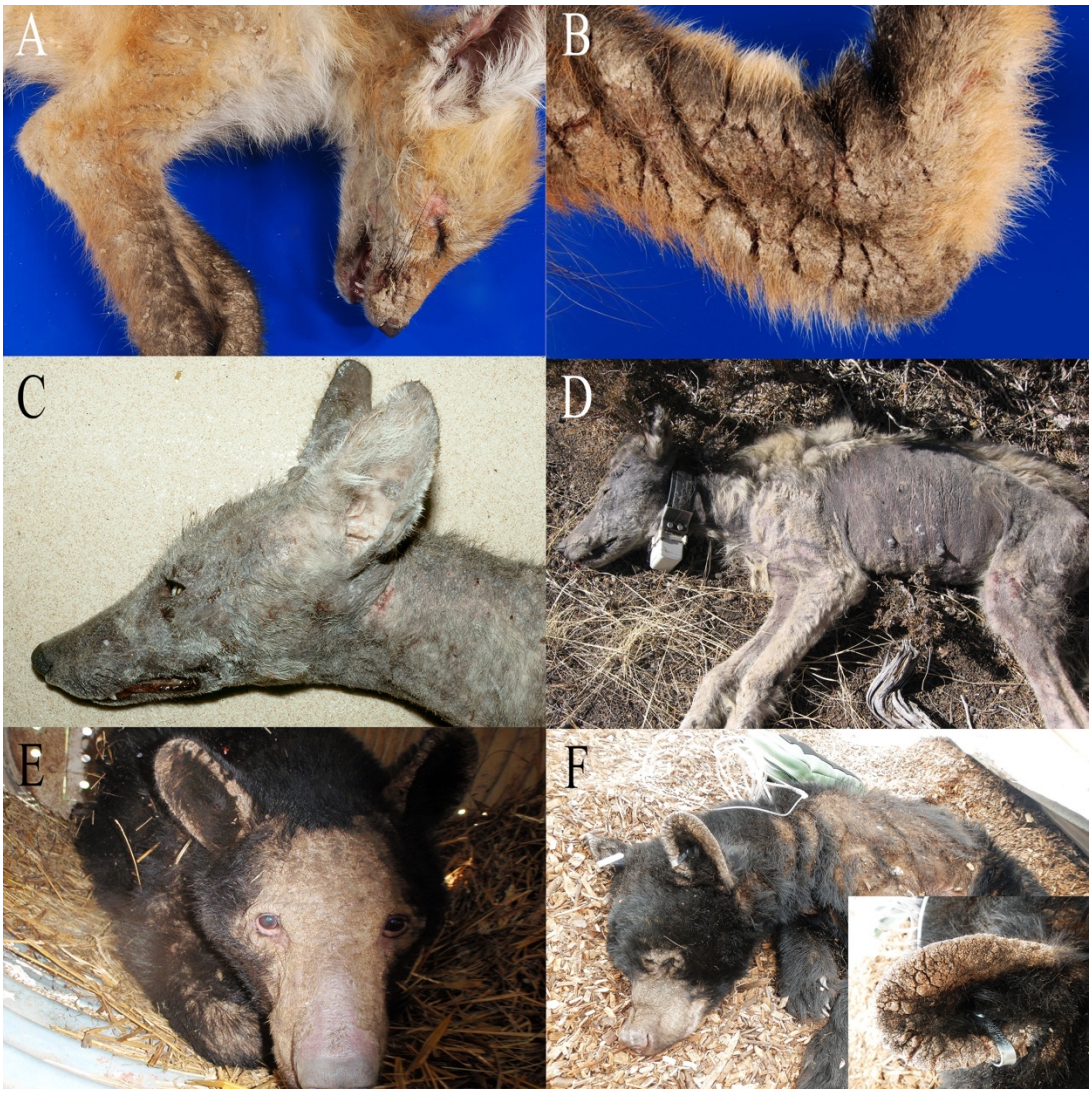

Fig. 3: North American mammals with clinical sarcoptic mange. (A) Red fox with lesions on the face. (B) The same red fox showing a close up of the hyperkeratosis fissures in the skin. (C) Coyote with alopecia on the head and neck. (D) Gray wolf showing alopecia on the head, flanks, and hind limbs (Photo credit Yellowstone Wolf Project/National Park Service). (E) Black bear in a culvert trap showing severe alopecia and skin thickening on the face, ears, and forelimb. (F)

Black bear showing additional crusting and alopecia on the ears, flank, and muzzle; inset: close-up of hyperkeratotic and crusted skin.

CHAPTER 2

EMERGENCE AND EXPANSION OF SARCOPTIC MANGE IN AMERICAN BLACK BEARS (*URSUS AMERICANUS)* IN THE EASTERN UNITED STATES[2]

[2]Niedringhaus KD, Brown JD, Ternent M, Childress W, Gettings JR, Yabsley MJ. Accepted by Veterinary Parasitology: Regional Studies and Reports. (doi:10.1016/j.vprsr.2019.100303). Reprinted here with permission of publisher.

ABSTRACT

Mange was historically rare in American black bears (*Ursus americanus*). Since the 1990s, however, sarcoptic mange has become more widespread in black bears with hundreds of reports in 2018 from eight states. This emerging disease has potential implications regarding human and animal health and on future black bear management.

BODY OF TEXT

Sarcoptes scabiei is a zoonotic mite that affects hundreds of species globally (Pence and Ueckermann, 2002). The disease is referred to as scabies in people and sarcoptic mange in domestic and wild animals. Mange in animals is often clinically similar to Norwegian or crusted scabies in people and is characterized by severe skin lesions, secondary bacterial and fungal infections, emaciation, and often mortality (Pence and Ueckermann, 2002; Nakagawa et al. 2009; Nimmervoll et al. 2013). Many wildlife populations have endemic sarcoptic mange, but epidemics can cause severe population declines, particularly when mites are introduced into naïve populations or hosts (Henriksen et al. 1993; Martin et al. 2010).

Sarcoptic mange was previously considered to be rare in American black bears (*Ursus americanus*). The disease was observed sporadically in the Midwestern and eastern United States between the 1980s and early 2000s (Schmitt et al. 1987; Fitzgerald et al. 2008). However, more recently, reports of sarcoptic mange in bears have become common and widespread, particularly in the mid-Atlantic states (Peltier et al. 2017; Peltier et al. 2018). The objective of this study was to determine the frequency and distribution of sarcoptic mange in American black bears in the USA.

Between August and October of 2018, we surveyed bear or furbearer biologists or technicians and/or wildlife health personnel from 40 state wildlife agencies with a known

resident black bear population to determine if, when, and where suspected (skin disease in an area with confirmed sarcoptic mange) or confirmed cases (skin disease associated with mite identification) of sarcoptic mange in bears have occurred. These reports included those already published in the literature as well as from the clinical case database of the Southeastern Cooperative Wildlife Disease Study (SCWDS). The distribution and frequency of sarcoptic mange reports by decade are in Fig. 1.

In Pennsylvania, the first documented case of sarcoptic mange was in 1991 in Indiana County in an adult male black bear. A year later, three more bears were reported with the disease in Indiana and adjacent Clearfield County. Over the subsequent 27 years, sarcoptic mange was reported in 55 out of 67 counties in Pennsylvania, and the number of cases continues to increase. In 2018, the number of suspected or confirmed cases reported in Pennsylvania was 277, which is a 296% increase from 2008 (70 cases).

More recently, states surrounding Pennsylvania reported sarcoptic mange in bears. In New York, the disease was first confirmed in 2011 in Herkimer County, and now the disease occurs in 17 counties. West Virginia and Virginia also confirmed mange in bears near the Pennsylvania border in 2003 and 2012, respectively. Despite a high bear population, sarcoptic mange has not yet been confirmed in New Jersey or northeastern Pennsylvania, including the Poconos, to the best of our knowledge. Arkansas and Oklahoma confirmed their first cases of sarcoptic mange in black bears in 2018.

Sarcoptic mange has not been formally reported or confirmed in bears in Tennessee, Kentucky, or any other state due east of Arkansas, south of Virginia, or west of Oklahoma. This large gap between the mid-Atlantic area, the Great Lakes region, and Arkansas/Oklahoma suggests that these are novel foci. In a previous genetic study, samples from the northeastern

USA suggested that multiple strains of mites are circulating in black bears based on *cox1* sequences; additional genetic analyses from mites in these new regions or with other genetic markers/techniques may provide additional insights into disease expansion (Peltier et al. 2017).

The cause for the emergence and expansion of sarcoptic mange in black bears is unknown. The American black bear range overlaps with many other mammalian hosts that are commonly affected by sarcoptic mange, including red fox (*Vulpes vulpes*) and coyotes (*Canis latrans*); while the host-switch and emergence of this disease in bears is likely due from spillover from a canid or other wildlife host, it is presumed that inter-bear transmission is occurring in highly-impacted areas (Astorga et al. 2018). It is unknown if infestation consistently causes clinical disease or if some bears are predisposed to overt mange as has been suggested with notoedric mange in wild felids associated with exposure to anticoagulant rodenticides (Riley et al. 2010). Additionally, it is unclear if potentially bear-adapted mites are found across the eastern USA (either subclinically or clinically but have not been found/reported) or are only found in areas with reported clinical disease.

The relatively slow rate of mange expansion in this host in the northeastern USA may be a result of the generally solitary nature of bears, which is different than many other social species commonly affected with mange such as wolves (*Canis lupus*) and coyotes (Almberg et al. 2015). Mites are likely transmitted through direct and indirect contact with other infected bears, and we do not currently know how the mite is maintained in bear populations compared to canids. The radiating pattern of disease expansion suggests that mites themselves or an unidentified co-infection or risk factor is spreading, but additional studies are needed. Many state wildlife agencies have also reported increasing bear populations since the 1980s, including Pennsylvania, Michigan, and Arkansas, among others (Hristienko and McDonald, 2007). The increasing bear

populations in these states suggests a potential role of bear density in disease emergence or pathogen transmission; however, it is unclear why there are fewer cases in Michigan, Arkansas, and other states with increasing bear populations compared to Pennsylvania. The apparent increase in mange may be a true increase in prevalence, a constant prevalence in an increasing host population, or both.

There are several implications for the emergence of this new disease system. As the disease continues to spread across the eastern United States, additional bear populations may be at risk. If bears with outward mange become more common, it may have additional implications for wildlife management agencies including changes in hunters' or tourists' attitudes towards bears.

Bears are another host species, along with other domestic and wild animals, that can be infected with mange. Domestic animal owners, including farmers and pet owners, and humans, including hunters and wildlife management personnel, should take precautionary measures to limit contact with animals with mange or their environments.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.vprsr.2019.100303.

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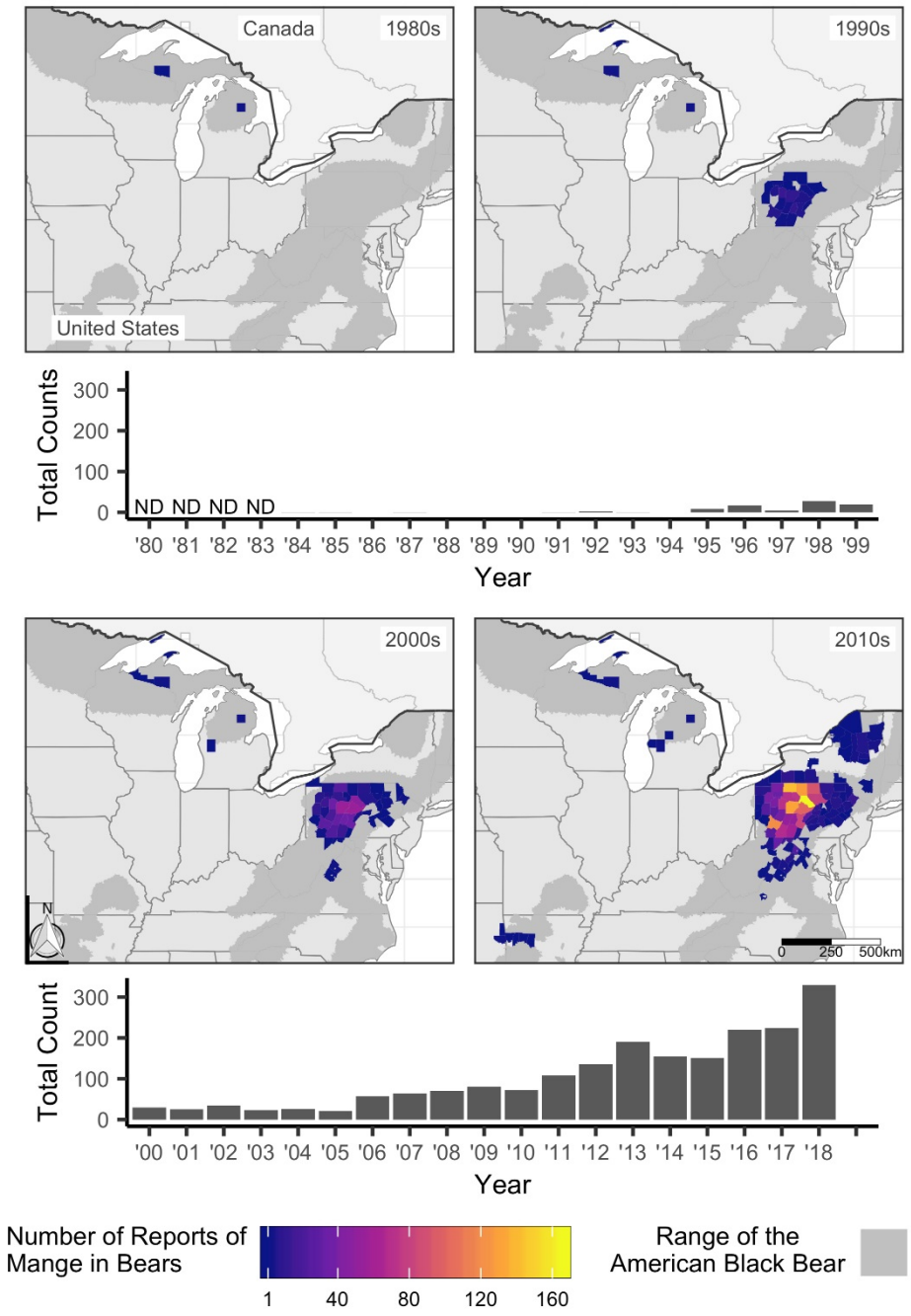

Fig. 2.1. The spatial and temporal distribution of cumulative reported or confirmed cases of sarcoptic mange in black bears from 1980 to 2018 in the United States as obtained from a survey of the state agencies. ND=no data.

CHAPTER 3

EXPOSURE TO MULTIPLE PATHOGENS IN AMERICAN BLACK BEARS (*URSUS AMERICANUS*) IN PENNSYLVANIA, USA IS NOT ASSOCIATED WITH SARCOPTIC MANGE[3]

[3]Niedringhaus KD, Brown JD, Ternent M, Cleveland CA, Yabsley MJ. To be submitted to Veterinary Sciences.

ABSTRACT

Infectious diseases, particularly of wildlife, are intrinsically linked to human and domestic animal health. Reports of sarcoptic mange in black bears (*Ursus americanus*) are increasing, particularly in multiple Mid-Atlantic and Northeastern states. While the reason for this increase is unknown, mange in other species has been associated with immunosuppression from multiple causes. Serum from bears across Pennsylvania were collected during 2014-2018 to determine the seroprevalence of five pathogens important for animal and/or human health: canine distemper virus (CDV), canine parvovirus (CPV), canine adenovirus-1 (CAV), *Toxoplasma gondii*, and *Trichinella* sp. from 50 bears with sarcoptic mange and 287 bears that were clinically normal. Several of these pathogens, particularly canine distemper virus, is associated with immunosuppression in other hosts. In addition to describing the seroprevalence and relating these findings to data from other regions, statistics were performed to determine if antibodies to any of these pathogens were associated with the development of mange in bears. The overall seroprevalence to these pathogens was as follows: CDV 7.1% (17/240), CPV 16% (15/94), CAV 7.9% (6/87), *T. gondii* 64.9% (194/299), and *Trichinella* sp. 3.2% (7/222). While there was no association with mange and antibodies to these pathogens, infection with one or more of these pathogens has implications for bears, other wildlife, domestic animal, and human health. Additional research regarding potential risk factors for mange development in bears, characterization of infection or disease with these pathogens, and potential consequences of infection are also warranted.

INTRODUCTION

Infectious diseases in wildlife are increasingly recognized as being linked to human and domestic animal health. The emergence and expansion of multiple diseases in wild animals,

including chytridiomycosis, white nose syndrome, and chronic wasting disease, among others, can have significant welfare, economic, and conservation implications for companion animals, livestock, and other free-ranging wildlife (Fisher et al. 2012, Miller et al. 2013, Gortázar et al. 2014, Viana et al. 2015). Additionally, some of the most important emerging pathogens in humans are believed to have originated from wild animals (Jones et al. 2008). As a result, it is increasingly important to continually monitor and study the presence of diseases and pathogens in free-ranging species. American black bears (*Ursus americanus*) are one of several wildlife species with an expanding population in many states in the Eastern United States, and this expansion potentially affects the interface between this species and humans and domestic animals (Hristienko and MacDonald, 2007; Hassell et al. 2017).

Sarcoptic mange, caused by the astigmatid mite *Sarcoptes scabiei*, is an important disease of wildlife and domestic animals, as well as in humans where the disease is known as scabies (Arlian and Morgan 2017). In humans, a severe form of scabies, known as crusted or Norwegian scabies, results in severe, typically non-pruritic hyperkeratosis and is considered to occur in patients that have a compromised immune system due to co-infections with immunosuppressive pathogens or a result of immunosuppressive therapy (Roberts et al. 2005). The less severe form of scabies, known as classical scabies has many presentations but typically results in localized or regional rash that is intensely pruritic (McCarthy et al. 2004). Variation in disease severity between individuals is likely multifactorial and involves the interaction of various risk factors including strain of mite involved, presence of toxins, co-infections, and host immune status (Healey and Gaafar 1977, Roberts et al. 2005, Riley et al. 2007, Camkerten et al. 2009, Oleaga et al. 2015, Singla et al. 2015). Demodectic mange in white-tailed deer (*Odocoileus virginianus*) is

another example of a wildlife species developing mange presumably due to host immunosuppression from a variety of causes (Nemeth et al., 2013).

Sarcoptic mange is an emerging disease in American black bears and is now commonly reported in the Northeastern and Mid-Atlantic United States, particularly in Pennsylvania (Niedringhaus et al. 2019). The cause of the increasing incidence and geographical expansion of this disease in bears over the last 30 years is unknown and is likely multifactorial (Peltier et al. 2017, Peltier et al. 2018). In addition to *S. scabiei,* black bears are commonly infected by a wide diversity of bacterial and viral pathogens and other parasites (Cook and Pelton 1978, Crum et al. 1978; Dies 1979, Clover et al. 1989, Chomel et al. 1995, Dunbar et al. 1998, Farajollahi et al. 2003, Yabsley et al. 2009, Bourne et al. 2010, Leydet and Liang 2013, Stephenson et al. 2015, Westmoreland et al. 2016). Infection and subsequent seroconversion from many of these pathogens is common, but clinical disease due to infectious pathogens, other than from *S. scabiei,* is considered rare in free-ranging black bears (Bourne et al. 2010, Keel et al. 2018). However, clinical disease from canine distemper virus (CDV), *Toxoplasma gondii,* and canine adenovirus-1 (CAV) in free-ranging bears has only recently been reported which corresponds with a significant increase in prevalence and distribution of clinical sarcoptic mange in bears in Pennsylvania (Cottrell et al. 2013, Huffman and Roscoe 2014, Knowles et al. 2018; Niedringhaus et al., 2019).

The objectives of this paper are 1) to provide serologic data on five common pathogens (CDV, CAV-1, canine parvovirus; CPV, *T. gondii*, and *Trichinella* sp.) from black bears from Pennsylvania, USA; 2) compare the results with selected previous serology studies in black bears throughout the USA and Canada; and 3) to compare the presence of antibodies of these pathogens between bears that are clinically normal from those that have sarcoptic mange. We

hypothesize that the recent detection of clinical CDV, which is known to cause immunosuppression in other wildlife species, in bears in Pennsylvania is associated with an increased incidence of sarcoptic mange (Williams, 2001).

MATERIALS AND METHODS

Between 2014-2016, serum was collected from adult and yearling bears during den checks of radio-collared sows (February and March) and during routine trapping associated with the ongoing bear population monitoring efforts in Pennsylvania. Blood was collected in serum separator tubes and kept cool in the field. Samples were centrifuged at the end of the day and serum was stored at -20 °C until testing was performed. If there was skin disease suggestive of sarcoptic mange (Figure 1), deep skin scrapes were collected into 70% ethanol and later examined microscopically to determine the presence of *S. scabiei* based on morphological criteria (Mullen and O'Connor, 2019) (Figure 2). All procedures complied with the University of Georgia's Institutional Animal Care and Use Committee (IACUC; A2013-10-016 and A2015-05-13).

To determine the presence of antibodies to CAV-1 and parvovirus, serum neutralization and hemagglutination inhibition assays, respectively, were performed by the Athens Veterinary Diagnostic Laboratories in Athens, GA, USA as described (Appel et al. 1973; Carmichael et al. 1980). Antibodies to CDV were detected using a serum neutralization assay as described (Appel and Robson 1973). Antibodies to *T. gondii* and *Trichinella* sp. were detected using a modified agglutination test and enzyme-linked immunosorbent assay (SafePath Laboratories, Carlsbad, CA, USA), respectively, at the United States Department of Agriculture Animal Parasitic Disease Laboratory (Dubey and Desmonts 1987). Seropositive criteria were based on the

following titers: CAV-1 and CDV ≥ 4, CPV ≥ 10, and *T. gondii* ≥ 25. Criteria for *Trichinella* sp. included a corrected optical density value of > 0.30.

To obtain other studies for comparison, a literature search was performed using all combinations of key words "black bear" and "*ursus americanus*" as well as "canine distemper", "parvovirus", "toxoplasma", "trichinella", and "adenovirus" using Google scholar and Pubmed search engines. Chi-squared tests were performed to compare the proportion of bears with antibodies to each pathogen between those with clinical mange and those that were clinically normal with alpha = 0.05. Statistical analyses were performed using R, Version 3.0.1 (RCoreTeam 2017).

RESULTS

Serum samples from 337 bears were included in this study, including 50 samples from bears with confirmed sarcoptic mange and 287 samples from bears with no evidence of mange (although not all bears were tested for all five pathogens due to limited sample availability for certain individuals). Antibody prevalence for each pathogen are summarized in Table 1. Of the five pathogens included, prevalence of *T. gondii* was highest (172/267, 66.4%) followed by CPV (15/94, 16%) whereas antibodies to *Trichinella* sp. and CAV-1 were relatively uncommon being found in 7/188 (3.7%) and 2/41 (4.9%) of bears, respectively. Antibodies against CPV, CAV-1, and *T. gondii* were detected at a higher, but insignificant, prevalence in bears with mange (19.6%, 8.7%, and 68.8%, respectively) compared to those without mange (16.0%, 6.9%, 64.9%). Antibodies to *Trichinella* and CDV were only slightly more common in non-mange bears (3.7% and 7.2%, respectively) compared to mange bears (0% and 6.5%, respectively). Table 2 shows the seroprevalence of the five tested pathogens in black bears from other studies.

DISCUSSION

The potential role of co-infections in the development of sarcoptic mange is incompletely understood in any animal host or in humans (Astorga et al. 2018). In this study, the presence of antibodies to several common pathogens in bears was not associated with sarcoptic mange. Of the pathogens investigated, CDV is the pathogen most frequently associated with immunosuppression and secondary bacterial and parasitic infections in wildlife hosts (Williams 2001). The lack of association between CDV and mange in this study may be the result of bears being inherently susceptible to clinical disease after *S. scabiei* infestation regardless of immune status. Prevalence to CDV in black bears varied across previous studies and ranged from 0% in Alaska to over 30% in Maryland, USA (Bronson et al. 2014). The seroprevalence of CDV in Pennsylvania bears in this study is within this range and is consistent between with results in bears in other regions that are not experiencing increased reports of sarcoptic mange.

The other four pathogens investigated are not commonly considered to cause significant immunosuppression in wildlife hosts. The lack of association, regardless of directionality, may reflect a true lack of association, the result of a relatively small sample size, or the antibody responses of these pathogens being altered as a result of mange. The seroprevalence of CPV and CAV-1 in this study is similar to that described from bears in Maryland during a similar time period (Bronson et al. 2014) as well as from bears from Florida in the 1990s (Dunbar et al. 1998). Since bears are commonly exposed to these pathogens and clinical disease has not been reported from CPV infection in bears in Pennsylvania, it is presumed that these pathogens are unlikely to be a significant health concern for bears in this region, but the ability of bears to amplify or shed these pathogens is unknown. It is plausible the geographical expansion of black bears in the eastern US could result in increased contact with domestic animals resulting in

higher frequency of transmission of these pathogens (as well as *S. scabiei*) with bears. Additionally, it is unknown whether antibodies to CPV detected in this study were from presumed CPV-2 or from other closely-related parvoviruses.

Clinical disease due to CDV, CAV-1, and *T. gondii,* in free-ranging bears has only recently been reported (Cottrell et al. 2013, Huffman and Roscoe 2014, Knowles et al. 2018). The first published clinical case of canine distemper in a black bear was from a yearling in Pennsylvania in 2011. This animal displayed clinical signs and had lesions consistent with canine distemper in other species (Cottrell et al. 2013). In addition, two other previously unpublished cases of canine distemper have been recently detected in Pennsylvania (Justin Brown, personal communication). One case involved a cub that was found dead in a den with a clinically normal sow in 2015. This cub had a bronchointerstitial pneumonia with rare syncytia and intracytoplasmic inclusion bodies consistent with CDV, and CDV was detected in the lung by fluorescent antibody testing. The second case was suspected based on inclusion bodies in the brain but was not confirmed via additional testing.

Disease from CAV-1 infection was reported in multiple captive black bears as well as in a free-ranging brown bear in Alaska (Pursell et al. 1983, Collins et al. 1984, Whetstone et al. 1988, Knowles et al. 2018). In addition to clinical disease, the seroprevalence of CAV may be increasing in bears across North America. There is evidence that CAV-1 has been endemic in Alaska for 40 years or more and that seroprevalence, as well as brown bear cub mortality, is increasing in this region (Zarnke et al. 1989; Chomel et al. 1998; Ramey et al. 2019). As a result, and due to the important implications of this pathogen on the health of domestic dogs, it is important to continue to monitor for changes in CAV seroprevalence in bears (both clinically and subclinically).

The published case of toxoplasmosis in a black bear was from New Jersey and involved a cub with multi-organ necrosis associated with *T. gondii* (Huffman and Roscoe 2014). No known clinical disease has occurred due to canine or feline parvovirus or *Trichinella* sp. infection despite the detection of antibodies from many prior years (Barker and Parrish 2001, Dick and Pozio 2001, Bourne et al. 2010, Keel et al. 2018). Despite widespread seroconversion of bears in Pennsylvania to *T. gondii,* there was no evidence of infectious being a risk factor for mange. While the seroprevalence in this study is less than previous studies from bears in Pennsylvania, the overall trend appears to be increasing seroprevalence in bears from other populations over time as well as a higher seroprevalence in bears in eastern North America compared to western North America, but more research and statistical analyses on this subject are warranted. Additionally, variations in seroprevalence may be reflected in variability of the assay used as well as the age of the bear as seroprevalence appears to increase in black bears in Pennsylvania with age (Briscoe et al. 1993; Dubey et al. 1995). Emerging seroprevalence and first case report of mortality from *T. gondii* warrants heightened surveillance of this pathogen due to wildlife and domestic animal implications (Huffman and Roscoe 2014).

The assays and titers used as diagnostic cutoffs, when described, varied between many studies further complicating comparisons between regions and over time. Assays for CDV included one or a combination of ELISAs and indirect fluorescent antibody assays as well as serum neutralizations; cutoff values from serum neutralization ranging from 1 in a study from Alaska (Chomel et al. 1998) to 12 in the Northwest Territories, Canada (Johnson et al. 2013). Indirect fluorescent antibody assays were used for CPV in a study from California (Stephenson et al. 2015), and positive cutoff titers for studies also hemagglutination inhibition assays, similar to this study, ranged from 20 in all other studies to 10 in the current study. Serum neutralization

assays were used exclusively for CAV-1, and while most studies used a cutoff titer of ≥4, one study used ≥10 as positive, possibly resulting in a lower seroprevalence (Mortenson 1998). The assays used to detect antibodies to *T. gondii* included modified hemagglutination tests, latex agglutination tests, indirect hemagglutination assay, and Sabin-Feldman dye tests. When modified agglutination tests, as used in this study, were employed, the diagnostic cutoffs ranged from 16 in a study in the Appalachian Mountains, USA (Cox et al. 2017) to 64 in Florida (Dunbar et al. 1998). The assays for *Trichinella* sp. included the latex particle test, inhibition agglutination assay, as well as ELISA as for this study. Corrected optical densities considered positive were most often 0.3 in other studies as well as the current study.

This study also emphasizes that bears in Pennsylvania were commonly exposed to three zoonotic parasites: *S. scabiei, T. gondii,* and *Trichinella* sp. While there is only anecdotal evidence suggesting mild classical scabies can occur in humans handling bears with clinical sarcoptic mange (Ternent, personal communication), reports of transmission and subsequent disease have been reported in humans after contracting mites from other animal hosts (Chakrabarti et al. 1981a, Chakrabarti et al. 1981b, Mitra et al. 1995, Heukelbach and Feldmeier 2006). Consumption of bear meat has been suggested as a rare cause of toxoplasmosis in humans, and consumption of bear meat is currently considered to be the greatest risk of trichinellosis in humans (Dubey 2000, Tenter et al. 2000, Wilson et al. 2015). Appropriately cooking bear meat to kill these two parasites is the best way to mitigate risks (Clausen et al. 1996, Nutter et al. 1998, Hill and Dubey 2013).

To our knowledge, this study is the first to investigate seroprevalence to common bear pathogens in Pennsylvania including CDV, CAV-1, and CPV as well as the first to explore the potential role of co-infections in an emerging disease (sarcoptic mange) in black bears.

Additional studies are warranted to further explore the emergence of sarcoptic mange in black bears in the Northeastern United States and any potential risk factors within the affected populations. Understanding the mechanisms of transmission, variation in host immune responses, and overall *S. scabiei* exposure can help our understanding of this emerging disease.

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Table 1 | Comparison of the seroprevalence of five pathogens in black bears from Pennsylvania between groups of bears with confirmed sarcoptic mange and clinically normal bears.

Pathogen	Mange No. pos/tested (%)	Non-Mange No. pos/tested (%)	Total No. pos/tested (%)	X^{2a}	p
CDV	2/31 (6.5)	15/209 (7.2)	17/240 (7.1)	0.0216	0.883
CPV	9/46 (19.6)	6/48 (12.5)	15/94 (16.0)	0.8743	0.350
CAV	4/46 (8.7)	2/41 (4.9)	6/87 (6.9)	0.4920	0.483
T. gondii	22/32 (68.8)	172/267 (66.4)	194/299 (64.9)	0.2352	0.628
Trichinella spp.	0/32 (0)	7/188 (3.7)	7/220 (3.2)	1.2	0.267

CDV=Canine distemper virus; CPV=canine parvovirus; CAV=canine adenovirus

[a]Chi-squared test: estimation of the difference between the expected and observed values.

Table 2 | Previous studies showing the seroprevalence of select pathogens infecting free-ranging black bears in North America compared to the current study.

Pathogen and Years Sampled	Number positive/No. tested (%)	Location	Reference
CDV			
N/A	0/47 (0)	Great Smoky Mt. NP, USA	Cook and Pelton 1978
1988-1991	0/76 (0%)	Alaska, USA	Chomel et al. 1998
1993-1997	8/165 (4.8%)	Northwestern States, USA	Mortenson 1998
1993-1995	5/66 (8%)	Florida, USA	Dunbar et al. 1998
1994-2001	1/38 (3%)	Banff NP and BC, Canada	Philippa et al. 2004
1999-2011	25/82 (30.5%)	Maryland, USA	Bronson et al. 2014
2001- 2003	24/157 (15.3%)	California, USA	Stephenson et al. 2015
2002-2010	2/6 (33%)	Northwest Territories, Canada	Johnson et al. 2013
2014-2016	17/240 (7.1%)	Pennsylvania, USA	Current Study
PV			
1988-1991	0/76 (0%)	Alaska, USA	Chomel et al. 1998
1993-1995	10/62 (16%)	Florida, USA	Dunbar et al. 1998
1999-2011	10/82 (12.2%)	Maryland, USA	Bronson et al. 2014
2001- 2003	1/157 (0.6%)	California, USA	Stephenson et al. 2015
2002-2010	0/14 (0%)	Northwest Territories, Canada	Johnson et al. 2013
2014-2016	15/94 (16%)	Pennsylvania, USA	Current Study
CAV			
1984	1/33 (3%)	Washington, USA	Foreyt et al. 1986
1988-1991	3/76 (4%)	Alaska, USA	Chomel et al. 1998
1993-1995	4/66 (6%)	Florida, USA	Dunbar et al. 1998
1993-1997	3/165 (1.8%)	Northwestern States, USA	Mortenson 1998

1994-2001	8/38 (8%)	Banff/British Columbia, Canada	Philippa et al. 2004
1999-2011	7/82 (8.5%)	Maryland, USA	Bronson et al. 2014
2014-2016	6/86 (6.9%)	Pennsylvania, USA	Current Study
T. gondii			
N/A	40/149 (27%)	California, USA	Ruppanner et al. 1982
N/A	132/328 (40.2%)	New Jersey, USA	Kinyon 2004
N/A	1/3 (33%)	Ontario, Canada	Quinn et al. 1976
1971-1977	23/303 (8%)	Idaho, USA	Binninger et al. 1980
1971-1974	7/16 (43.8%)	Ontario, Canada	Tizard et al. 1976
1976-1996	62/143 (43%)	Alaska, USA	Zarnke et al. 2000
1988-1991	6/40 (15%)	Alaska, USA	Chomel et al. 1995
1989-1992	532/665 (80%)	Pennsylvania, USA	Briscoe et al. 1993
1993	22/28 (78.6%)	Pennsylvania, USA	Dubey et al. 1995
1993-1995	37/66 (56%)	Florida, USA	Dunbar et al. 1998
1993-1997	89/198 (45%)	Northwestern States, USA	Mortenson 1998
1994-2001	5/38 (13%)	Banff NP and BC, Canada	Philippa et al. 2004
1996-1997	120/143 (84%)	North Carolina, USA	Nutter et al. 1998
1999-2011	70/82 (85.4%)	Maryland, USA	Bronson et al. 2014
2001- 2003	67/239 (28%)	California, USA	Stephenson et al. 2015
2002-2010	2/16 (12.5%)	Northwest Territories, Canada	Johnson et al. 2013
2004-2006	13/29 (44.8%)	Florida, USA	Chambers et al. 2012
2012-2013	33/53 (62%)	Central Appalachia, USA	Cox et al. 2017
2014-2016	194/299 (64.9%)	Pennsylvania, USA	Current Study
***Trichinella* spp.**			
N/A	18/141(13%)	California, USA	Ruppanner et al. 1982
1971-1977	16/122 (13%)	Idaho, USA	Binninger et al. 1980
1988-1991	11/76 (14.5%)	Alaska, USA	Chomel et al. 1998
1993-1997	2/103 (1.9%)	Oregon, USA	Mortenson et al. 2014
1996-1997	0/79 (0%)	North Carolina, USA	Nutter et al. 1998
2001- 2003	6/80 (7.5%)	California, USA	Stephenson et al. 2015
2014-2016	7/220 (3.2%)	Pennsylvania, USA	Current Study

CDV=Canine distemper virus; PV=parvovirus; CAV=canine adenovirus

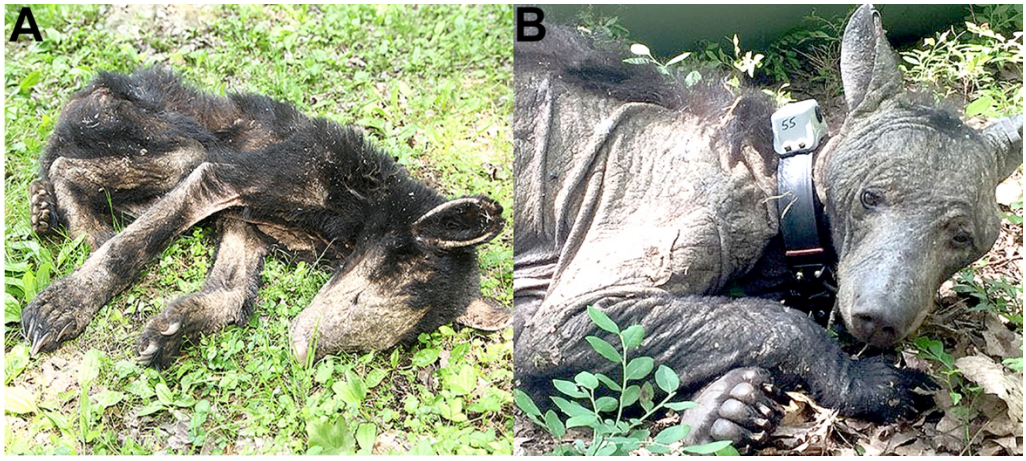

Figure 1 | Black bears with mange. **(A)** Young black bear with clinical sarcoptic mange; note severe emaciation and patchy hair loss. **(B)** Collared sow with severe alopecia as a result of sarcoptic mange.

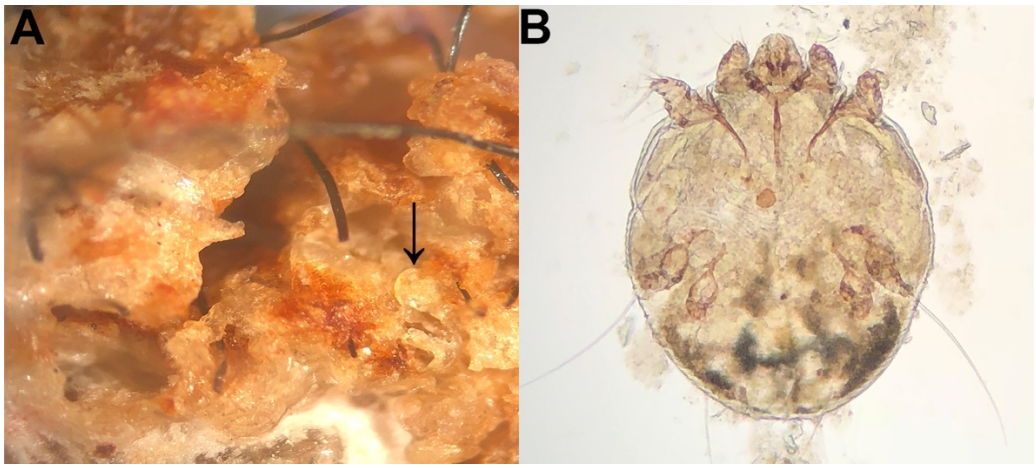

Figure 2 | Microscopic views of *S. scabiei.* **(A)** Severe hyperkeratosis in the epidermis associated with round mites (arrow). **(B)** High-magnification image of an adult, female *S. scabiei* mite; this species can be differentiated from other mites on bears by its round shape and short legs.

CHAPTER 4

SEROLOGY AS A TOOL TO INVESTIGATE SARCOPTIC MANGE IN BLACK BEARS (*URSUS AMERICANUS*)[4]

[4]Niedringhaus KD, Brown JD, Ternent M, Peltier SK, Van Wick P, Yabsley MJ. Submitted to the Journal of Wildlife Diseases on April 2, 2019.

ABSTRACT

Black bears have historically been considered an uncommon host for sarcoptic mange. However, over the last twenty-five years, sarcoptic mange has been increasingly reported in black bears in the northeastern USA. Syndromic monitoring is the most common surveillance approach for mange in bears, and these reports have provided important data on the distribution of this disease. To date, tools to monitor exposure to the causative mite, *Sarcoptes scabiei,* in bear populations have not been thoroughly evaluated under field conditions. In this study, a commercially-available ELISA, designed to detect antibodies against *S. scabiei* in dogs, was validated for use in black bears with a maximum combined sensitivity and specificity of 95.6% and 96.6%, respectively. To further examine the performance of this assay, serial serum samples from black bears with confirmed sarcoptic mange were collected post-treatment to determine the persistence of detectable antibody response with the ELISA. Antibodies in bears waned to below the limit of detection between four and fourteen weeks suggesting that serology studies may under-estimate the number of exposed bears after antibodies have waned. State-wide serosurveys in Pennsylvania from hunter-harvested bears over two years showed a significant difference in seroprevalence between regions with high mange (mean seroprevalence 6.7% with a range of 6.6 and 6.8%) and low mange (no seropositive bears were detected). Within Pennsylvania, these data indicate that the geographic distribution of exposure to *S. scabiei*, based on serologic testing, generally reflects the distribution of overt disease, as determined by syndromic surveillance. Collectively, these results indicate the evaluated ELISA is an effective tool for monitoring *S. scabiei* exposure in bear populations and provides the framework for additional studies regarding mange epidemiology in bears.

INTRODUCTION

Sarcoptes scabiei is a genetically diverse species of mite that can cause severe skin disease in a wide variety of taxa (Zahler et al. 1999; Bornstein et al. 2001). Introductions of this mite into susceptible, naïve populations have resulted in swift and widespread mortality on multiple continents (Lindström et al. 1994; Gortázar et al. 2007; Fraser et al. 2016). In other scenarios, including the recent emergence of sarcoptic mange in American black bears (*Ursus americanus*), the disease may take decades to spread across the landscape (Niedringhaus et al. 2019; *submitted*). Sarcoptic mange has been confirmed in black bears in Pennsylvania since 1991. The disease is not diffusely present throughout Pennsylvania; rather the geographic distribution is a relatively demarcated focus that expanded outward from the central part of the state slowly over the last three decades (Sommerer, 2014). In addition, increases in mange cases may be an artifact of an expanding black bear population (Peltier et al. 2017; Niedringhaus et al. 2019 *submitted*).

Many states, including Pennsylvania, use syndromic monitoring for mange in bear populations where animals with clinical disease consistent with mange are collated in a centralized database. Currently, tools for systematically monitoring *S. scabiei* infection at the population level are lacking. Serologic surveys would provide valuable data on the distribution of exposure to *S. scabiei* and may suggest more widespread exposure of the mite than may be missed due to syndromic monitoring alone. For sarcoptic mange, numerous serological assays have been developed and utilized across a wide range of taxa. These assays have been used to diagnose mange in individual animals as well as in research settings to study antibody response dynamics, pathogen surveillance, timing of initial exposure prior to clinical disease emergence, and disease outbreak resolution in populations (Little et al. 1998; Davidson et al. 2008; Oleaga et

al. 2008; Oleaga et al. 2011; Millán et al. 2012). Many of these assays were designed for use in domestic animals, including dogs, pigs, and rabbits and have been utilized in numerous closely-related wildlife taxa (Davidson et al. 2008; Casais et al. 2015; Haas et al. 2015; Ráez-Bravo et al. 2016). A recent study indicated the potential of a commercially-available indirect ELISA for detecting *S. scabiei* antibodies in black bears, but test accuracy and validity were not thoroughly evaluated (Peltier et al. 2018).

Major obstacles for performing large-scale wildlife disease surveillance studies include the lack of data on test performance and understanding of antibody persistence in wildlife species prior to field application (Stallknecht, 2007). This study aims to address these obstacles by addressing the following: 1) quantifying test accuracy of the aforementioned ELISA kit to detect antibodies against *S. scabiei* in black bears; 2) quantifying the persistence of antibodies against *S. scabiei* over time to estimate the window of antibody detection in a bear after mite exposure; and 3) determine if there is widespread exposure to *S. scabiei* in bears across Pennsylvania, USA. These data will also provide insight regarding susceptibility of individual bears after mite exposure as well as provide evidence of the usefulness of this assay in future population-level exposure studies.

MATERIALS AND METHODS

Antibody test

The serology kit used in this study was designed to detect IgG antibodies to *S. scabiei* var *canis* in dogs (SARCOPTES-ELISA 2001® DOG, AFOSA, GmbH, Germany). The assay was performed according to the manufacturer's instructions. The manufacturer-supplied canine control sera were used to validate each test run. For test accuracy calculations, bears with overt

mange cytologically confirmed to be associated with *S. scabiei* were grouped as true-positive, and clinically normal, seronegative cubs born to seronegative sows were categorized as true-negatives. The optical density (OD) cut-off point to obtain maximum combined sensitivity and specificity was determined using the 'OptimalCutPoints' package, and sensitivity, specificity, and area under a receiver operating curve (ROC) was estimated using the 'ROCR' package in R statistical software version 3.4.1 (Sing et al. 2005; Lopez-Raton et al. 2014; R core Team, 2017). The OD was read at 450nm ten minutes after the addition of the substrate solution.

Diagnostic cut-off analyses

Blood samples were collected from bears via venipuncture, as previously described (Peltier et al. 2018), from bears during den checks between February and March of 2014-2017 or opportunistically from mange suspect diagnostic cases throughout the year. Samples were collected from bears of multiple ages including 6-11-week-old, clinically-normal cubs and their sows and from yearling and adult bears with and without evidence of mange. In a previous study, skin scrapes were determined to be the best method of mite detection in clinically-affected bears and was used as the gold standard for test accuracy calculations (true positives) (Peltier et al. 2018). After blood collection, the samples were centrifuged to separate serum from cell layer and transferred to plastic cryovials prior to shipment to the Southeastern Cooperative Wildlife Disease Study (SCWDS) in Athens, GA, for testing.

In conjunction with the manufacturer-supplied canine control positive and negative sera to confirm test-run validity, sera from seronegative cubs born to seronegative sows were used as negative controls and sera from seropositive bears with confirmed sarcoptic mange were used as positive controls. Testing on these field samples was performed as previously described

according to the manufacturer's instructions. The corrected OD (OD sample-OD bear negative control) and test result (corrected OD x 100 / OD bear positive control – OD bear negative control) were calculated for each sample. Test result values greater than 10 were considered positive and less than 10 considered negative. The test result of '10' cutoff was used to include all results between 10 and 15 as positive rather than 'inconclusive' as suggested by the manufacturer. This was done to increase sensitivity but also due to the consistently lower corrected OD values in true positive bears compared to positive canine control samples. All sampling protocols were approved by the University of Georgia's Institutional Animal Care and Use Committee (IACUC; A2013-10-016 and A2015-05-13).

Antibody persistence

To determine persistence of antibodies, serum samples were obtained from seven bears with lesions consistent with mange that were admitted to the Wildlife Center of Virginia between 2016 and 2018. On admission, each bear was immobilized with approximately 2-3mg/kg ketamine (KetaVed®, VEDCO, Inc., St. Joseph, Missouri, USA) and 0.02-0.04mg/kg medetomidine (Medetomidine HCl, ZooPharm, Laramie, Wyoming, USA) via pole syringe. Drug dosages varied based on each bear's level of debilitation. Once anesthetized, skin scrapes were performed on areas with skin crusts and examined microscopically to confirm the presence of *S. scabiei* based on mite morphology. Blood was collected from the femoral artery or vein and sorted into purple and red-top tubes for a complete blood count and biochemistry analysis, respectively. An additional sample was collected in a red-top tube and stored in a -18°C (0°F) freezer until antibody analysis was performed. Each bear was treated with either 0.4mg/kg ivermectin (ProMectin® Injection, VEDCO, Inc., St. Joseph, Missouri, USA) SQ or 25mg/kg fluralaner (Bravecto®, Merck, Madison, New Jersey, USA) PO (Van Wick and Hashem 2019).

Each subsequent time the animal was immobilized for treatment or clinical evaluation, additional serum samples were taken. The timeframe of each immobilization varied on a case-by-case basis. After resolution of clinical signs and the rehabilitation process was completed, a final serum sample was obtained prior to release.

State-wide serosurvey

Since 1991, reports of confirmed or suspected cases of sarcoptic mange in black bears, including the township and county of origin, were recorded by the Pennsylvania Game Commission. This database was used to identify the number of confirmed or suspect mange cases for each township in Pennsylvania considered to have a resident bear population. These data were categorized as having no reports, one to five reports, or more than five reports of mange (Figure 1). Additionally, these data were used *a priori* to subjectively identify areas of Pennsylvania considered to have a high number of confirmed cases of sarcoptic mange ('high-mange area') as well as parts of the state with few reports of suspected but not confirmed cases ('low-mange' area) (Figure 1). A chi-squared test with alpha = 0.05 was used to determine if there was a difference in the seroprevalence between these high and low-mange areas.

Serum samples were collected from hunter-harvested black bears during the 2017 and 2018 Pennsylvania hunting seasons. Hunters are required to deliver their harvested bear to a check station within 24 hours of harvest. At the check station, bears were visually inspected to ensure they had no skin lesions consistent with mange, and demographic and spatial information was obtained from each bear. Blood samples were collected by scooping the sample out of the field-dressed body cavity. The blood sample was immediately transferred to a serum separator tube and centrifuged. Resulting serum samples were held at 4˚ C until they were shipped to SCWDS for testing (within days of collection).

RESULTS

Test accuracy

For assay validation, sera from 125 bears were obtained including 58 samples from presumed non-exposed cubs and clinically normal sows and 67 samples from bears with confirmed sarcoptic mange. Of the 67 mange-positive bears, 61 were seropositive (sensitivity of 91.0%), and all mange-negative cubs were seronegative (specificity of 100%). At corrected OD 0.028 using manufacturer-supplied canine positive and negative controls, the combined maximum sensitivity and specificity of the assay was 95.6% and 96.6%, respectively (Figure 2A). The area under the receiver operating curve (AUC) was 0.97 (95% CI 0.931, 1.008) (Figure 2B).

Antibody persistence

Serial serum samples from seven bears admitted to the WCV with confirmed sarcoptic mange were obtained as previously described. All seven bears were seropositive for *S. scabiei* upon admission and prior to first treatment and were seronegative by four, five, six, ten, twelve, and fourteen weeks after treatment (Figure 2C).

State-wide serosurvey

A total of 569 serum samples from clinically-normal black bears were obtained in 2017 and 2018. Of these, 283 were collected from high-mange areas (161 in 2017 and 122 in 2018) and 286 were collected from low-mange areas (189 in 2017 and 97 in 2018). The mean seroprevalence of bears with antibodies to *S. scabiei* in the high-mange area was 6.7% and ranged between 6.8% and 6.6% in 2017 and 2018, respectively. No bears were seropositive in

the low-mange area in either year, and there was a significant difference in seroprevalence between the high and low-mange areas ($p<0.0001$; $X^2=17.709$). Additionally, there were 437 reports of bears with confirmed or suspected sarcoptic mange in the high-mange area in 2017 and 2018, and 27 suspect mange cases in the low-mange area over the same time frame (Figure 1, Table 1).

DISCUSSION

This study shows that a commercially-available *S. scabiei* ELISA kit has potential field applications for wildlife and specifically for black bears. The use of serology in wildlife epidemiologic studies has many advantages, but there are factors that must be considered. First, most commercially-available assays were developed for domestic animals and are not validated for use in wildlife. Although some of these assays can be adapted for use in certain species, the lack of anti-IgG antibodies for many wildlife species, lack of appropriate controls, and possible genetic and/or antigen variation in the pathogen between host species and populations mean that some tests cannot be used and the results must be evaluated with caution (Gardner et al. 1996; Stallknecht, 2007; Arlian and Morgan 2017). Another consideration is the difficulty in acquiring high-quality serum samples. Our data suggest that samples collected from harvested bears are useful, allowing researchers to utilize check stations to collect adequate sample sizes for larger surveillance projects. Other studies have used variable-quality body fluids in autolyzed carcasses for the detection of antibodies against *S. scabiei* with good results (Bornstein et al. 2006; Jakubek et al. 2012).

The specific commercial kit used in this study has been used in other wildlife species. Although the assay is validated for domestic dogs, the combined maximum sensitivity (95.6%) and specificity (96.6%) of the assay in this study on black bears was similar to the

manufacturer's reported values in dogs (92.1% and 94.6%, respectively). These results were also similar to assay performance in red foxes (*Vulpes vulpes*) in Europe (sensitivity was 98.2% and specificity was 91.9%) (Nimmervoll et al. 2013). The increased sensitivity in foxes compared to bears is not surprising, as the kit was designed with anti-dog antibody conjugate and suggests that the conjugates used in the assay designed for dogs are more cross-reactive with red fox IgG compared to black bear IgG. Regardless, assay performance in bears was good, and the assay proved useful in understanding mange within bear populations in Pennsylvania.

The lack of antibodies detected in nine percent of clinically-affected animals in this study could be due to several factors including low IgG levels during the early stages of disease, chronic disease where the antibody class changed, or failure to develop an appropriate immune response as has been suggested in red foxes (Nimmervoll et al. 2013; Ráez-Bravo et al 2016; Astorga et al. 2018). Another reason for false negative results may include repeated freeze-thaw cycles of the samples, but samples in this study had very few freeze-thaw cycles (Arlian et al. 1994; Boadella and Gortázar 2011; Arlian & Morgan 2017). The detection of antibodies in clinically-normal animals may be the result of seroconversion from exposure of *S. scabiei* without the development of clinical disease or recovered clinical mange cases that have persistent antibodies as has been suggested in Iberian ibex (*Capra pyrenaica*) and Chamois (*Rupicapra* spp.) (Rambozzi et al. 2004; Sarasa et al. 2010). However, these studies used the labelled avidin-biotin detection system, which may have increased sensitivity compared to direct species-specific IgG detection used in this study. Another possibility for clinically normal animals to seroconvert is potential cross-reactivity with other pathogenic and non-pathogenic mite species (Bornstein 1995; Arlian & Morgan 2000; Millán et al. 2012). Black bears can also develop clinical disease of varying severity associated with *Demodex ursi* and *Ursicoptes*

americanus infestations, and while the assay is unlikely to cross-react with *D. ursi,* subclinical infections with *U. americanus* may result in cross-reaction and should be evaluated (Yunker et al. 1980; Bornstein et al. 1995; Foster et al. 1998).

This study did not examine the ability of antibodies to protect bears from re-infestation or development of clinical disease. Resistance to re-infestation has been reported in some species such as domestic dogs but not in red foxes (Arlian et al. 1994; Little et al. 1998). Collared bears in Pennsylvania have been noted to have mange repeated times (J. Brown, personnel communication). There is no evidence to suggest that bears would resist the development of clinical disease after initial resolution regardless of the presence or absence of antibodies. Since cell-mediated immunity is the predominate mechanism of protection, antibody detection is a useful measure of exposure from a diagnostic perspective but would not have value for indications of population immunity or protection (Arlian et al. 1994).

Antibody persistence is important to determine prior to field application because a rapid decline in detectable antibodies would result in an under-estimate of previous exposure. While the time until IgG detection after mite exposure could not be determined in this study due to unknown date of initial exposure, experimental studies in other animals have shown variation in the time to antibody detection which varied from 14 days in dogs, 28 days in wild boar and red fox, and 42 days in domestic pigs; however, differences in assay sensitivity and specific immunoglobulin class targeted likely affected these values (Bornstein and Zakrisson, 1993; Bornstein et al. 1995; Van Der Heijden et al. 2000; Haas et al. 2015). Additionally, a marked increase in antibody response time was noted in a second *S. scabiei* exposure in dogs suggesting repeated exposures may reduce the time to antibody detection (Bornstein and Zakrisson 1993). Considering seroconversion can occur by two weeks post-exposure in some species, our data

indicated a window for antibody detection is approximately four to 14 weeks in bears with potential false negative results occurring two to four weeks prior to lesion formation and after 14 weeks when antibodies have waned. This rapid seroreversion may have impacted our detected prevalence as most samples are collected during fall hunting seasons; therefore, bears exposed to mites in the spring or early summer may give false negative results by the time they are sampled.

No bears in the low-mange areas of Pennsylvania had detectable antibodies to *S. scabiei.* These negative data not only provide 'field validation' of the assay at the population level, it suggests that the sporadic bears with mild hair loss observed in this region may not be due to *S. scabiei* infestation. Most mange reports resulting from syndromic surveillance are not confirmed by cytology. Future instances of skin lesions in these regions without serologic evidence of mange should be examined to determine the cause of hair loss. Because sarcoptic mange is being reported more commonly in bears and possibly other hosts (e.g., San Joaquin kit foxes (*Vulpes macrotis mutica*) in the USA, use of serologic assays may provide additional insight on mange epidemiology in these hosts (Rudd et al. 2019; Niedringhaus et al. 2019; submitted). For example, previous studies have used serology data at the population level to answer questions regarding mange emergence and transmission. Four out of 327 (1.2%) clinically-normal red deer (*Cervus elaphus*) had antibodies to *S. scabiei* in a mange-affected area, which is lower than what we detected in black bears from an endemic region (Oleaga et al. 2008). The low prevalence of antibodies in clinically-normal red deer and black bears in these studies may reflect the high susceptibility of the hosts to development of clinical disease after infestation. Our study showed high concordance between the geographic distribution of exposure to *S. scabiei* and the occurrence of overt disease. Clinical mange may be associated with a co-stressor including co-infection with other pathogens or environmental toxin, immunosuppression due to various

causes, or other unknown factors (Riley et al. 2007; Astorga et al. 2018). Often it is unclear if the distribution of clinical mange correlates with the presence of mites or if mites are ubiquitous but clinical disease is only observed in association with the stressor. These data indicate that mange is a primary disease in bears and that the distribution of disease is associated with the presence of antibodies to *S. scabiei*, and presumably the mite.

A study in Sweden showed a similar difference in the spatial distribution of wolves with antibodies to *S. scabiei* and suggested that the populations with higher seroprevalence may be a result of increased habitat productivity and subsequent reduced home range size, and/or a higher regional red fox density (Fuchs et al. 2016). It is unclear if the presumed spatial association between seroprevalence and clinical disease in Pennsylvania bears is related to any of these factors. Unlike bears in our study, there was widespread exposure of wild boar (*Sus scrofa*) to *S. scabiei* in Switzerland even in areas without clinical disease suggesting extrinsic factors contribute to disease manifestation in some populations or individuals and not others (Haas et al. 2018). Serology testing in red foxes during an epizootic of sarcoptic mange in Norway was used to show that ten years after the initial epidemic started, there had been substantial host-parasite adaptation. The ratio of seropositive-mange negative to seropositive-mange positive foxes increased significantly confirming that either the fox or parasite had adapted, and fewer clinical cases were observed as a result (Davidson et al., 2008). Our study shows that similar long-term seroprevalence data could be obtained to determine if similar adaptation in high-mange areas will occur. Currently, it is unknown if naïve bear populations in other parts of North America are susceptible and may develop disease in the future, and additional studies to expand on mange epidemiology in bears in other regions are warranted.

This study describes a systematic approach that can be used to quantify infection in a

uniform manner over time and improve monitoring of mange in this species. This approach can also be used alone or in conjunction with syndromic surveillance to identify mange introduction into new areas. Finally, using the methods in this study can be useful to determine if mange is increasing in bears or is just a reflection of higher bear populations.

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Table 1: Seroprevalence of clinically normal black bears to *S. scabiei* and number of reports of clinical mange in high and low-mange areas in Pennsylvania, USA in 2017 and 2018.

	2017	**2018**	**Total**
Seroprevalence in high-mange area	11/161 (6.8%)	8/122 (6.6%)	19/283 (6.7%)
Seroprevalence in low-mange area	0/189 (0%)	0/97 (0%)	0/286 (0%)
Suspected or confirmed mange cases in high-mange area	160	277	437
Suspected mange cases in low-mange area	11	16	27

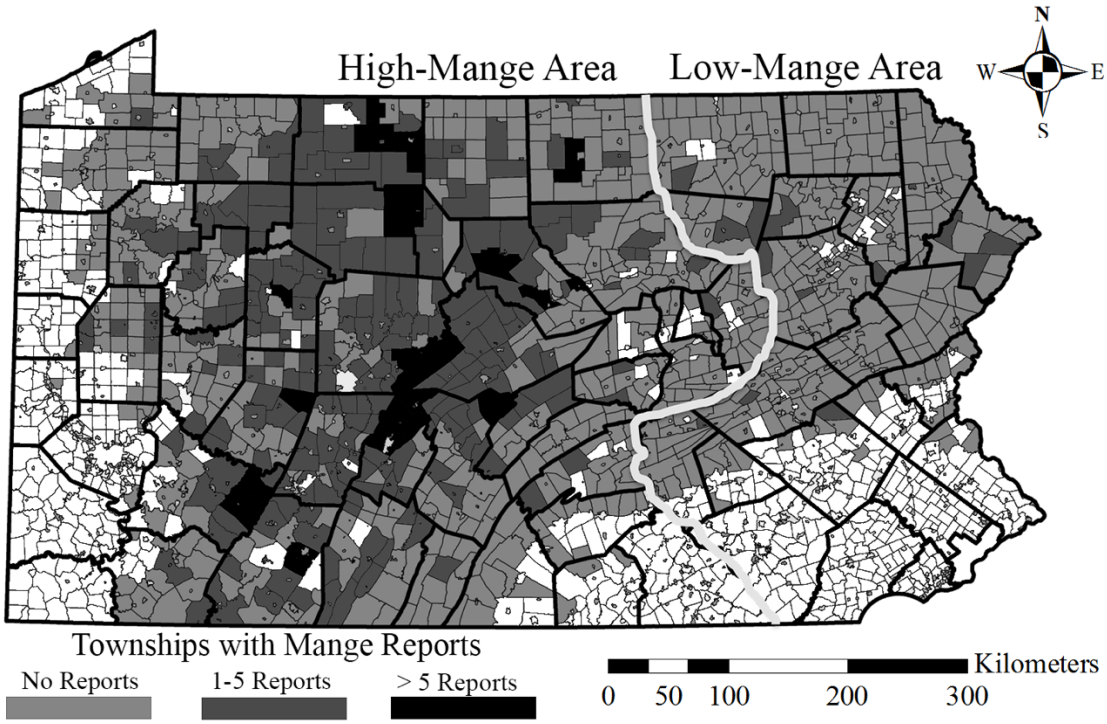

FIGURE 1. Map of Pennsylvania, USA, showing townships where at least one bear has been harvested since 1991. These townships were divided into those without any mange cases reported, with at least one suspected or confirmed mange case reported, and more than five suspected or confirmed cases reported. The vertical white line separates the 'high-mange' area in the west from the 'low-mange' area in the east. The white, unshaded townships are not considered to have a resident bear population.

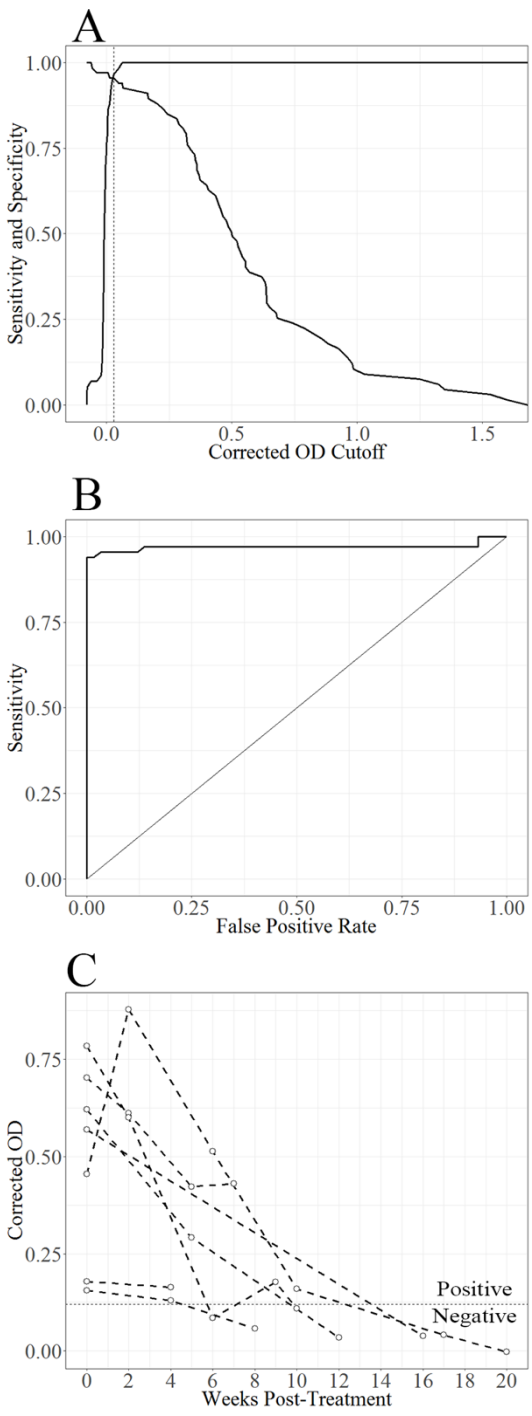

FIGURE 2. (A) The sensitivity and specificity of the ELISA when using clinically normal and clinically affected bear sera. At a corrected OD of 0.028 (vertical dashed line), the maximum combined sensitivity and specificity are 95.6 and 96.6%, respectively. (B) A receiver-operating

curve showing the false positive rate against sensitivity of the assay. The area under the curve (AUC) is 0.97. (C) Persistence of antibodies post-treatment of seven bears with confirmed sarcoptic mange. Open circles dictate individual samples tested. All bears were seropositive upon presentation prior to treatment. The test result was considered negative at a corrected OD value less than 0.12.

CHAPTER 5

EFFECTS OF TEMPERATURE ON THE SURVIVAL OF *SARCOPTES SCABIEI* OF BLACK BEAR (*URSUS AMERICANUS*) ORIGIN[5]

[5]Niedringhaus KD, Brown JD, Ternent MA, Peltier SK, Yabsley MJ. Submitted to Parasitology Research, October 12, 2018.

ABSTRACT

For two decades, the incidence and range of sarcoptic mange in black bears (*Ursus americanus*) in Pennsylvania has increased. The causative agent, *Sarcoptes scabiei,* can be directly or indirectly transmitted; therefore, data on environmental persistence is important for guiding management and public communications. The objective of this study was to determine the survival of *S. scabiei* at different temperatures. Full-section skin samples and superficial skin scrapes were collected from bears immediately after euthanasia due to severe mange. After ~24 hours on ice packs (shipment to lab), samples were placed in dishes at 0, 4, 18, or 30 ºC, and 60, 20, 12, and 25% relative humidity, respectively, and the percentage of mites alive, by life stage, was periodically determined. Humidity was recorded but not controlled. Temperature significantly affected mite survival, which was shortest at 0 ºC (mostly ≤ 4 hours) and longest at 4 ºC (up to 13 days). No mites survived beyond eight days at 18 ºC or six days at 30 ºC. Mites from full thickness skin sections survived significantly longer than those from superficial skin scrapes. Adults typically survived longer than nymphs and larvae except at 30 ºC where adults survived the shortest time. These data indicate that at cooler temperatures, *S. scabiei* can survive for days to over a week in the environment, especially if on host skin. However, these data also indicate that the environment is unlikely to be a long-term source of *S. scabiei* infection to bears, other wildlife, or domestic animals.

INTRODUCTION

The mite *Sarcoptes scabiei* is the causative agent of scabies in humans and mange in animals (Arlian 1989; Bornstein et al. 2001). In humans, the disease is most commonly seen in facilities where there are large numbers of people, in close proximity, allowing efficient mite transmission (e.g., nursing homes, prisons, hospitals, and schools), and the disease is most severe

in countries with limited health resources (Hengge et al. 2006; Romani et al. 2015). Dogs and pigs are the most commonly reported domestic species, but a wide range of other hosts have been reported (Fain 1978; Abu-Samra et al. 1981; Ibrahim and Abu-Samra 1987; Arends et al. 1990; Twomey et al. 2009).

Sarcoptic mange is also an important cause of disease in many wildlife species in North America including (but not limited to) red foxes (*Vulpes vulpes*), coyotes (*Canis latrans*), and, more recently, American black bears (*Ursus americanus*) (Pence and Ueckermann 2002; Peltier et al. 2018). While reports of sarcoptic mange have historically been rare in black bears, there has been an increase in the number of cases in certain parts of the United States, particularly in Pennsylvania. The cause of the increasing incidence of sarcoptic mange in black bears is currently unknown (Peltier et al. 2017). Transmission of mites between wildlife hosts likely involves both direct contact in more social species as well as indirect contact through the use of a shared environment, such as dens or burrows, as well as fomites (Skerratt et al. 1998; Almberg et al. 2015). Additionally, some strains of *S. scabiei* have shown host specificity (Samuel, 1981; Arlian et al. 1984b; Arlian et al. 1988). Transmission studies of mites between hosts generally indicate that mites have a higher degree of infestivity and cause more severe disease in hosts that are more closely related (Smith and Claypool 1967; Thomsett 1968; Samuel 1981; Arlian et al. 1984b; Arlian et al. 1988; Bornstein 1991; Mitra et al. 1995). There is little morphological and genetic difference between strains of mites from different wildlife hosts on a local scale (Arlian 1989; Peltier et al. 2017; Fraser et al. 2017). As a result, the mechanisms of mite transmission within and between wildlife systems, domestic animals, and humans are largely undefined.

Determining the survivability of black bear-origin *S. scabiei* mites in the environment is critical for understanding *S. scabiei* ecology in bears, managing risk factors for mite

transmission, and communicating with the general public in situations where bears with mange are encountered. The aim of this study was to characterize the survival of black bear-origin *S. scabiei* in the environment at different temperatures.

MATERIALS AND METHODS

Black bears with severe mange were euthanized by personnel of the Pennsylvania Game Commission following an agency standard operating procedure. All sample collection protocols were approved by the Institutional Animal Care and Use Committee at the University of Georgia (A2013-10-016 and A2015-05-13). Skin scrapes were examined immediately after the bear was euthanized to confirm the presence of large numbers of living mites. Within hours of euthanasia, multiple large sections of full-thickness skin were obtained from areas of affected skin based on the distribution of gross lesions and confirmation with cytology at the time of sampling. These large skin samples were placed into zip-lock bags and immediately shipped overnight to the Southeastern Cooperative Wildlife Disease Study (SCWDS) on ice packs. Samples were received at SCWDS within 24 hours of the bear being euthanized. Upon arrival, skin scrapes were examined again to determine that the mites were *S. scabiei* and that there was at least 95% survival of mites during shipment. Mites were determined to be alive based on visible movement within ten seconds of observation and no apparent desiccation or trauma to the mite's body, or idiosoma.

If the aforementioned criteria were met, the skin sections were randomly processed into two sample types, 2.5- x 2.5-cm full-thickness sections (meant to represent bear carcasses) and superficial skin scrapes (meant to represent superficial mites left behind in dens, traps, etc.). Approximately thirty samples of both scrapes and full thickness sections were obtained from each bear, and these were divided into eight groups. Skin scrapes were performed with sterile

scalpel blades and contained epidermal scales, crusts, and hair follicles. Scrapes and full-thickness sections were obtained from adjacent areas on the skin and covered similar dimensions. The four groups of skin sections and four groups of skin scrapes were placed in individual petri dishes and placed into incubators maintained at 0 ºC, 4 ºC, 18 ºC, and 30 ºC with 60%, 20%, 12%, and 25% relative humidity (RH), respectively. For 18 and 30 ºC groups, Fisherbrand™ Isotemp™ Biochemical Oxygen Demand Refrigerated Incubators were used, and standard household refrigerators and freezers were used for the 4 and 0 ºC groups. These temperatures were chosen because they reflect gaps from other published studies investigating *S. scabiei* survival as well as because of the range of seasonal temperatures in Pennsylvania. No individual sample was examined more than twice to reduce the influence of repeated heating and handling on mite survival. Relative humidities from each incubator were recorded but not controlled or manipulated. Both skin scrapes and skin sections at all temperature-humidity treatments were examined at 0, 4, 8, and 24 hrs, and daily thereafter until a sample had no live mites at two consecutive time points. Prior to examination, all skin scrapes and skin section samples were placed into the 30 ºC incubator for twenty minutes to allow mites to warm up and begin to move allowing for increased confidence in determining survival. The percentage of live mites, regardless of life stage, was determined at each time point relative to the number of live mites at time 0. Each sample was examined for approximately ten minutes from which at least 50% of the surface of the sample was examined resulting in an estimate of survival rather than complete count. Skin scrapes were performed on the full-thickness sections immediately before examination to better visualize the mites.

Additionally, at each examination time point, the number of live and dead mites were determined for adult, larval, and nymphal (combining protonymph and tritonymph) stages from

full-thickness sections (Fain 1968; Arlian 1989). Temperature and humidity were measured using commercial terrarium thermometers/hygrometer that were placed adjacent to the samples. A generalized linear mixed model was used to estimate the effects of skin sampling type and temperature on mite survival. Each individual bear was used as a random effect in the model, and temperature was used as a factored predictor variable to allow for non-linear relationships with temperature. Statistics and figures were performed using R Statistical software, and the mixed effect model was performed using the 'lme4' package (Bates et al. 2015; RCoreTeam 2017).

RESULTS

Skin samples from eleven bears were included in the study. The mean number of days survival of mites from each sample type and temperature-humidity treatment are summarized in Table 1. Mites in both skin scrapes and skin sections were inactivated after one freezing event, and no mites survived at freezing temperatures beyond eight hours. In only one trial did a small percentage of mites survive beyond four hours at 0 ºC (Fig 1). In temperatures above freezing, mite survival in skin sections and scrapes was inversely-related to temperature, with longest survival at 4 ºC and 20% RH and shortest at 30 ºC and 25% RH. Mites did not survive beyond six days at 30 ºC, eight days at 18 ºC, and 13 days at 4 ºC. The highest variation in survival was at 4 ºC with the minimum survival at five days and maximum survival at twelve days; the least variation between trials in survival above freezing was at 18 ºC with a range of four days to eight days.

Skin sample type significantly affected time to mite mortality ($X^2 = 15.91$; $p<0.0001$), and mite survival was on average 1.2 (sd 0.30) days longer in full-thickness sample sections than on skin scrapes across all temperatures. Temperature also significantly affected time to mortality

($X^2 = 418.49$; $p<0.0001$); mites survived an estimated 8.4, 5.4, and 3.8 (sd 0.42) days longer at 4 ºC, 18 ºC, and 30 ºC than 0 ºC regardless of skin sample type.

The maximum survival (days until 100% mortality) of different life stages of mites from full-thickness skin sections is shown in Figure 2. Within the 4 ºC and 18 ºC groups, adult mites survived the longest followed by nymphs with larvae surviving the shortest time. At 30 ºC, this trend was largely reversed with adults surviving the shortest time and larvae and nymphs surviving for nearly identical lengths of time. No differences in survival were noted among life stages at 0 ºC.

DISCUSSION

In this study we examined, for the first time, the survival of black bear-origin *S. scabiei* under different simulated environmental conditions and found differences in survival at different temperatures and between mites in skin sections and mites derived from skin scrapes. Similar to previous studies on the environmental survival of *S. scabiei* mites from other hosts, we found that mites survived longest at lower temperatures (above freezing; optimum of 10 and 13 ºC) and high RH (97 and 90%, although not controlled for in our study) (Cameron 1925; Mellanby 1942; Arlian et al. 1984a; Arlian et al. 1989). These conditions provided the best environment for survival with adult females surviving up to three weeks in these conditions when dog and/or human-strain mites from a rabbit host were examined (Arlian et al. 1984a; Arlian et al. 1989). The maximum mite survival in our experiment was observed at 4 ºC, suggesting that 4 to 10 ºC is likely the optimum temperature for mite survival. Mites in the Arlian studies also survived less than one day at 30 ºC, while at 30 ºC in our study, mites survived for up to six days in one trial and typically all died between two and five days (Arlian et al. 1984a; Arlian et al. 1989). The differences in these times is likely related to the humidity and possibly to the presence of

skin or skin crusts that may act as protection from these conditions or could provide a prolonged source of moisture that reduced desiccation in our study (Arlian et al. 1984a). In our study and previous studies (Mellanby et al. 1942; Arlian et al., 1984a; Arlian et al., 1989), mites very rarely survived freezing regardless of sample type. Temperature effects on general survival in our study was also generally similar to that in a fourth study, although RH was not recorded (Cameron 1925). Our study expands on the Mellanby et al. (1942) Arlian et al. (1984a) and Arlian et al., (1989) studies in two important ways. First, these data suggest that the presence of skin scrapes and, even more so, full sections of skin prolong survival of mites off of the live host compared to extracted mites without host hair or skin. Secondly, we included more replications (n=11) and noted a wider a range of survival times for each environmental condition, some of which were quite variable. There was also an important difference in this study compared to the two Arlian et al. (1984a, 1989) studies as mites from the previous studies were taken immediately off of the live host whereas in our study, mites were transported overnight to another laboratory, and duration of survivability may have been affected by this delay.

In this experimental trial and previous studies, only temperature and relative humidity were evaluated for impacts on mite survivability. However, it is important to note that other environmental factors likely contribute to mite survivability including exposure to ultraviolet light, status of clinical disease of the host prior to euthanasia, and the type of substrate underneath the animal, among others. Another limitation of this study was that infectiousness of mites was not determined. Ideally, the maximum time mites would be cable of re-infesting new hosts and ultimately the ability to cause disease in a new host would have been determined. This study did not take into account the ability of mites to seek a new host or to colonize, burrow, and breed after prolonged duration off of the host, all of which are required for the development of

clinical disease (Arlian et al. 1984a; Arlian et al. 1984c). It is estimated that mites retain their ability to penetrate host skin for less than half of the duration off of the host and may be even less if the mites were maintained in extreme environmental conditions (Arlian et al. 1984a; Arlian et al. 1988). When this is considered, the duration of potential risk of mite infestivity is likely even shorter than the times provided in this study allowing for an estimate of the maximum risk of additional transmission. The overestimation of risk for transmission provided in this study is important when making management decisions regarding the use of bear traps and communicating with the public on mite survival.

Collectively, these new data combined with previous studies indicate the environment is unlikely to be a reservoir or prolonged source of infestation for *S. scabiei*. However, it does show that the mite can persist off the host for a period of time, especially during cooler times of the year (e.g., spring and fall). Studies investigating the temperatures of dens of black bears at higher latitudes showed that den temperatures are often similar to the external environment suggesting that mites survive over winter on the host itself rather than in the den substrate (Folk et al. 1972; Rogers 1981). Unlike many canid species that are commonly infested with *S. scabiei* (coyotes, wolves, etc.), bears are not social animals for the majority of their lives, and this persistence in the environment allows for a "bridge" between animals that are unlikely to frequently be in direct contact (Almberg et al. 2015). This scenario is likely true for other solitary mammals affected by mange including wombats (Fraser et al. 1998; Martin et al. 2018). Due to their solitary nature, artificial scenarios where bears would come in close contact (such as baiting, wildlife feeding, or other food attractants) could promote the potential for transmission (Sorensen et al. 2014). However, mites are unlikely to survive in the environment during winter months in colder climates, and transfer to new hosts during this time likely occurs through direct

contact with infected bears. While fall and spring temperatures may support mite survival, transmission of mites between bears outside of hibernation possibly occurs most during the summer due to increased foraging activity and direct contact during mating; bear movement and subsequent direct or indirect contact may be minimized in extreme seasonal temperatures (Garshelis & Pelton 1980; Alt et al. 1980).

These data also are important for black bear management efforts. Black bears are frequently captured by state agencies for research or human-bear conflict mitigation, and during handling, equipment or capture sites that become contaminated with *S. scabiei* mites could serve as a risk for transmission to subsequent bears. Moreover, mite contamination of physical objects or locations where food attractants such as garbage dumpsters or bird feeders, regulated baiting during hunting seasons, or wildlife feeding by the public attracts multiple bears may also increase the risk of transmission. Consequently, these environmental survival data should be considered in the development of agency procedures for handling bears with mange, including establishing time periods for closing traps post-capture and possible environmental treatments. Knowledge of how freezing temperatures can kill mites may also be an effective management tool to disinfect equipment, clothing, or bear carcasses. Lastly, information on mite survival should be included in agency outreach materials to better inform the public about activities that may contribute to mange transmission.

Understanding the role of the environment in indirect transmission of mites between wildlife hosts is vital to understand and attempt to manage mange epizootics (Astorga et al. 2018; Martin et al. 2018). This study shows that the environment can potentially act as a source of indirect transmission of *S. scabiei* between hosts but is unlikely to be a reservoir for prolonged exposure. These data can be used to make informed decisions regarding the risk of transmission

via fomites or carcasses of animals with clinical mange depending on the season or environmental conditions. Additional studies involving environmentally safe and effective products to promote inactivation of mites that can be used in the field are warranted, as are studies determining the specific scenarios where mites are transmitted between animals.

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Table 1: Mean time (in days) until 100% mortality of mites across different temperatures or skin sample types.

Temperature (ºC)	**Skin Scrapes** Mean +/- St Dev.	**Full Thickness Sections** Mean +/- St. Dev.
0	0.29 +/- 0.08	0.38 +/- 0.27
4	7.25 +/- 1.89	8.75 +/- 2.34
18	4.67 +/- 0.63	5.75 +/- 1.25
30	3.06 +/- 1.84	4.50 +/- 1.67

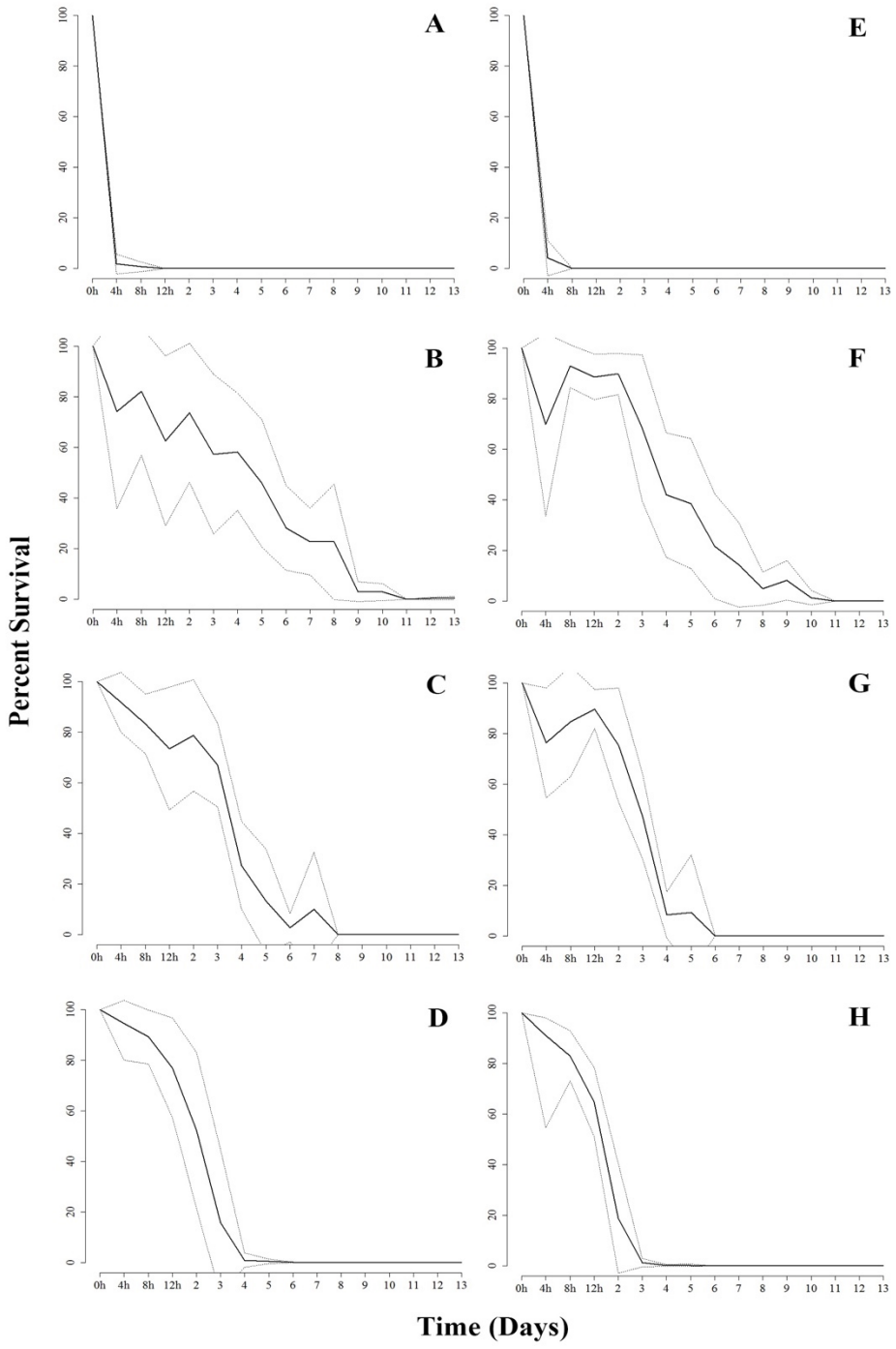

Fig 1: Average percent survival (solid lines) and standard deviation (dashed lines) in days of *Sarcoptes scabiei* mites from full section skin samples and skin scrapes from eleven bears kept at various environmental conditions. A-D: survival at 0 ºC, 4 ºC, 18 ºC, and 30 ºC from skin

scrapes, respectively; E-H: survival at 0 ºC, 4 ºC, 18 ºC, and 30 ºC from full-thickness skin sections, respectively.

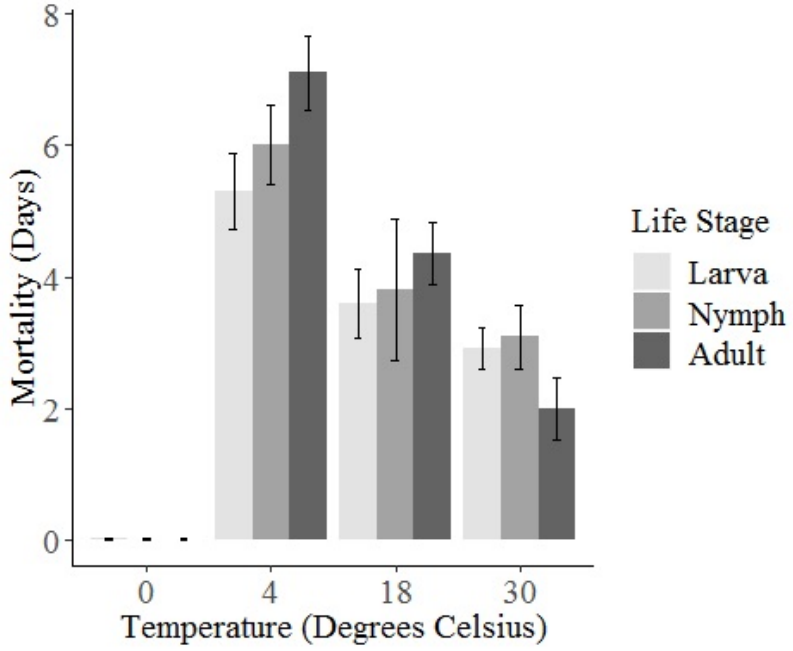

Fig 2: Maximum survival (days until 100% mortality) of *Sarcoptes scabiei* mites at different life stages and different temperatures from full-thickness skin sections.

CHAPTER 6

SUMMARY AND CONCLUSIONS

Sarcoptic mange is often being reported in novel hosts across the globe. The ability of this mite to adapt to new hosts emphasizes the need to continue to study this important parasite so that wildlife, domestic animal, and human health professionals can better manage this disease. In particular, the important role that *S. scabiei* has in affecting populations of many susceptible species, including several that are highly endangered, provides further evidence of why additional research of this pathogen will play an important role in future wildlife conservation practices.

In bears, there is no evidence to suggest that *S. scabiei* is associated with population-level effects. In fact, there appears to be a greater association between expanding bear populations and the presence of sarcoptic mange. While there are ongoing studies at other universities and agencies investigating the potential impact of this disease on individual and small populations of bears, only time will tell whether there will be any long-lasting population effects in this host.

It is important that future studies of this disease in bears determine whether high bear population density are associated with emergence of sarcoptic mange or only with mite transmission. It is likely that high bear populations contribute to increased transmission between individuals resulting in more mange cases being reported. However, the mechanisms involved in *S. scabiei* switching to bears, and all other novel hosts, are largely unknown. Additionally, it is unclear if the emergence of this disease in new areas is the result of multiple focal emerging events or due to spillover from other affected areas or expansion.

The original host(s) harboring mites that caused sarcoptic mange in the first bears in Pennsylvania are unknown, and additional molecular studies using modern techniques are currently being used in an attempt to determine the source host. Regardless of which host was the source of the recent emergence of this disease in black bears, there are populations of numerous species of wildlife in other continents that are impacted by sarcoptic mange, and many of these species are closely-related to both common and rare species in North America that have had few to no reports of sarcoptic mange. Many iconic North American species, including brown bears (*Ursus arctos*), polar bears (*Ursus maritimus*) lynx (*Lynx candensis*), mountain lions (*Puma concolor*), mountain goats (*Oreamnos americanus*), wolverines (*Gulo gulo*), American bison (*Bison bison*, mule deer (*Odocoileus hemionus*), or elk (*Cervus elaphus*) just to name a few, all may be at risk of developing sarcoptic mange in the future if additional host-colonization and mite adaptation occurs.

This dissertation describes a handful of studies that attempt not only to answer several fundamental questions about mange epidemiology in bears, but also provide data that could be useful for wildlife health personnel to manage this disease. This dissertation is only the beginning of the story of mange in bears and should provide the groundwork for additional studies of this disease in bears and all other wildlife species.