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Invited Review

A review of neosporosis and pathologic findings of *Neospora caninum* infection in wildlife

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ABSTRACT

Neospora caninum is an apicomplexan parasite that is the etiologic agent of neosporosis, a devastating infectious disease regarded as a major cause of reproductive loss in cattle and neuromuscular disease in dogs worldwide. This protozoan pathogen is maintained in the environment by a heteroxenous life cycle that involves a definitive canid host and a wide range of intermediate hosts. In recent years, a number of wildlife species have been investigated for their possible involvement in the *N. caninum* life cycle and many have been implicated as intermediate hosts. However, in many instances these studies have utilized serological and molecular techniques to detect infection in clinically normal animals, and investigation of possible associated morbidity, mortality, and pathology has been neglected. As such, the occurrence and importance of *Neospora*-associated disease in wildlife species are unknown. In order to improve our understanding of the significance of *N. caninum* infection in nondomestic species, the present review provides an up-to-date summary of clinical neosporosis and *N. caninum*-associated pathologic lesions in naturally and experimentally infected wildlife species. We provide a list of all free-ranging and captive wildlife species identified with *N. caninum* infection to date using currently available diagnostic tools. The advantages and disadvantages of diagnostic methods in wildlife are addressed in order to recommend optimal diagnosis of confirming *N. caninum* infection and neosporosis in nondomestic species. Although current data would suggest that *N. caninum* infection does not adversely impact wildlife populations, there is a need for greater international uniformity in the diagnosis of *N. caninum* infection and neosporosis in nondomestic species in order to assess the true consequences of parasite infection.

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1. Introduction

Neospora caninum (Apicomplexa: Coccidia), the etiologic agent of the polysystemic disease neosporosis, is an obligate intracellular tissue cyst-forming coccidian parasite of the phylum Apicomplexa (Dubey et al., 2007; Dubey and Schares, 2011). *Neospora caninum* shares many morphologic and biologic features with its close relative *Toxoplasma gondii* (Dubey et al., 2002, 2007; Dubey and Schares, 2011). Prior to its initial recognition in Norwegian dogs in 1984 (Bjerkas et al., 1984) and consequential classification as a distinct species in 1988 (Dubey et al., 1988), many *N. caninum* infections were misdiagnosed as toxoplasmosis (Dubey et al., 2002; Dubey and Schares, 2011). Key differences were subsequently identified that distinguish the two parasites with regard to their natural host range, antigenicity, virulence factors, and pathogenesis (for reviews, see Dubey and Lindsay, 1996; Dubey et al., 2002; Dubey et al., 2007). Differences between *N. caninum* and *T. gondii* have also been described using comparative genomics and transcriptomics analyses (Reid et al., 2012). In the past two decades *N. caninum* has been extensively investigated due to its importance as a veterinary pathogen. As a result of these studies, it is now known that *N. caninum* has a global distribution and causes severe neuromuscular disease in dogs, and abortion and neonatal mortality in cattle, resulting in devastating economic losses to the beef and dairy industries (Dubey et al., 2007; Dubey and Schares, 2011; Reichel et al., 2013).

Less is known about the epizootiology and impact of this parasite in wildlife (reviewed by Gondim, 2006; Dubey et al., 2007; Dubey and Schares, 2011; Almeria, 2013). Most studies of *N. caninum* infection in wildlife species report on the prevalence of infection using serologic and/or molecular diagnostic assays in asymptomatic animals. While helpful in documenting evidence of exposure to the pathogen amongst wildlife species, these studies do not provide insight into the nature of the host–pathogen interactions in these potential intermediate hosts. In some instances, these analyses are also limited by the uncertainty regarding the sensitivity and specificity of the assays used.

This review provides a critical analysis of clinical neosporosis and related pathologic findings in free-ranging and captive wildlife species for which postmortem analyses of gross and microscopic lesions have been described. Building upon the current literature, this paper aims to improve our knowledge of the host–pathogen interactions in wildlife by (1) reviewing the prevalence of clinical neosporosis as an outcome of infection with *N. caninum* in nondomestic species and the factors that predispose to pathologic sequelae, (2) examining our current understanding of the impact of *N. caninum* infection on wildlife populations, and (3) formulating best practice guidelines for documenting *N. caninum* infection and neosporosis in wildlife. *Neospora caninum* seroprevalence and molecular diagnostic studies in nondomestic species have been well reviewed (Gondim, 2006; Dubey et al., 2007; Dubey and Schares, 2011; Almeria, 2013) and, unless specifically associated with pathology or clinical disease, the details of these reviews will not be reiterated here.

2. Life cycle and transmission: domestic and sylvatic cycles

Neospora caninum is characterized by a complex facultative heteroxenous life cycle that involves a definitive canid host in which sexual replication occurs, and a range of intermediate hosts in which asexual replication takes place (Dubey and Lindsay, 1996; Dubey et al., 2006, 2007; Dubey and Schares, 2011). To date, the only confirmed definitive hosts of *N. caninum* are members of the *Canis* genus, including domestic and wild dogs (*Canis familiaris*) (McAllister et al., 1998), coyotes (*Canis latrans*) (Gondim et al., 2004b), gray wolves (*Canis lupus lupus*) (Dubey et al., 2011), and dingoes (*Canis lupus dingo*) (King et al., 2010). Cattle are the most common intermediate host of *N. caninum;* however, in recent years infection has been reported in many warm-blooded vertebrate species – some with the potential to serve as intermediate hosts in domestic and sylvatic transmission cycles (Gondim, 2006; Dubey et al., 2007; Dubey and Schares, 2011; Almeria, 2013). *Neospora caninum* is not considered to be zoonotic despite some serologic evidence of human exposure, particularly in immunocompromised populations (Tranas et al., 1999; Lobato et al., 2006; Barratt et al., 2010).

The *N. caninum* life cycle is characterized by three known infectious life stages: sporozoites within sporulated oocysts, rapidly dividing tachyzoites, and slowly proliferating bradyzoites within tissue cysts (Dubey et al., 2006). Light microscopic and ultrastructural morphology of these stages have been well described, with the notable exception of sporulated oocysts for which ultrastructural description is still lacking (Dubey and Lindsay, 1996; Speer et al., 1999; Dubey et al., 2002, 2006; Dubey, 2003). Oocysts are the environmentally resistant form of the parasite. They are presumably generated by sexual replication in the intestinal epithelial cells of