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Review Article

Can Neosporosis Be a Threat to Human Health?

Razieh Hosseini[1*], Ali Hajimohammadi[2]

[1]Department of Veterinary Basic Sciences, SR.C., Islamic Azad University, Tehran, Iran
[2]Department of Clinical Sciences, School of Veterinary Medicine, Shiraz University, Shiraz, Iran

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***Corresponding author:**
Razieh Hosseini,
Emails:
razieh.hosseini@iau.ac.ir,
Hosseini_945@yahoo.com

Abstract

Introduction: *Neospora caninum* is an intracellular protozoan parasite that primarily affects domestic animals, notably dogs and cattle, but its presence in wildlife is increasing. This parasite is a significant cause of abortion in cattle and can lead to severe neurological disorders in dogs. The transmission dynamics of *N. caninum*, particularly from dogs to humans, have been a subject of considerable investigation. The implications of *N. caninum* infections in wildlife are significant, as they can affect not only the health of the animals themselves but also the broader ecosystem and agricultural practices. While the primary hosts of *N. caninum* are dogs and cattle, the potential for zoonotic transmission to humans has been speculated due to the biological similarities between *N. caninum* and *Toxoplasma gondii*, a well-known zoonotic pathogen. Thus, this review document has been designed to comprehensively deal with the relevance of this issue.

Results: Research indicates that humans may be exposed to *N. caninum* through environmental contamination with oocysts shed in dog feces. This is similar to the transmission pathways of *T. gondii*, where the ingestion of oocysts can lead to infection. Studies have reported the presence of antibodies against *N. caninum* in human sera, indicating some level of exposure, in countries such as in Brazil, Egypt, the United States, and Japan. The seroprevalence of *N. caninum* in dogs widely varies across different regions of the world, influenced by factors such as age and geographical location.

Conclusion: Although *N. caninum* shares biological similarities with *T. gondii*, current evidence does not support its classification as a zoonotic pathogen. While serological studies indicate human exposure, no confirmed cases of infection have been reported, and the parasite remains primarily a veterinary concern; however, continued surveillance and research are needed to clarify its zoonotic potential, especially in immunocompromised populations.

Keywords: *Neospora caninum*, Protozoan parasite, Neosporosis, Zoonotic transmission, Vaccination

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Introduction

Neosporosis is a significant disease primarily affecting cattle, caused by the protozoan parasite *Neospora caninum*. *N. caninum* is an obligate intracellular protozoan that plays a significant role in veterinary medicine, particularly due to its impact on livestock, especially cattle. The life cycle of *N. caninum* is complex and involves canids as definitive hosts, where the parasite undergoes sexual reproduction and sheds environmentally resistant oocysts in feces. These oocysts can then infect a variety of intermediate hosts, including cattle, sheep, and other mammals, leading to significant economic losses in the agricultural sector due to abortion and other reproductive issues (1-3). Therefore, this review aims to assess the zoonotic potential of *N. caninum* and summarize current evidence regarding its implications for human health.

Life Cycle of Neospora caninum

The cell cycle of *N. caninum* is characterized by its ability to invade host cells and replicate intracellularly. Upon infection, the parasite enters the host cell and resides within a parasitophorous vacuole, where it can evade the host's immune response. The initial adhesion to host cells is mediated by surface antigens, which facilitate the invasion process (4,5). Once inside, *N. caninum* undergoes a series of asexual reproductive cycles, primarily through endodyogeny, where two daughter cells are formed within the mother cell (5). This process is crucial for the propagation of the parasite within the host and is influenced by various host factors, including immune responses and the physiological state of the host cells (6). Research has shown that the intracellular environment significantly affects the growth and development of *N. caninum*. For instance, studies utilizing cell lines and organotypic cultures have provided insights into the cellular events that occur during the parasite's proliferation (5,6). Additionally, the interaction between

N. caninum and the host cell is complex, involving various proteins that mediate adhesion and invasion, which are potential targets for vaccine development (4,5). The ability of *N. caninum* to manipulate host cell functions is a key factor in its pathogenicity, contributing to its success as a parasite (7).

Moreover, the immune response to *N. caninum* infection is characterized by the production of specific antibodies, which can be detected in infected hosts. For example, studies have documented the seroconversion of antibodies against *N. caninum*, indicating an active immune response following infection (8). This immune response plays a critical role in controlling the infection, although it may not always prevent the adverse reproductive outcomes associated with the parasite (3,8).

Neosporosis in Dogs and Cattle

Neospora caninum is an obligate intracellular protozoan parasite that primarily affects dogs and cattle, causing significant health issues in both species. In dogs, *N. caninum* is associated with a range of clinical manifestations, particularly neuromuscular disorders. The parasite was first identified in dogs in Norway in 1984 and subsequently described as a new genus and species in 1988 (9). The clinical presentation in dogs can include neurological signs, such as paralysis, which is more commonly observed in younger dogs, although cases in older dogs have also been documented (10,11). The association between seropositivity to *N. caninum* and the presence of musculoskeletal or neurological signs suggests that this parasite should be considered in the differential diagnosis of neurological conditions in canines (12).

The seroprevalence of *N. caninum* in dogs has garnered increasing interest due to its implications for both canine health and livestock industries. This protozoan parasite, primarily affecting dogs as definitive hosts, has been reported globally with varying seroprevalence rates. Studies indicate that seroprevalence can range significantly, from as low as 0.2% to as high as 54% in different regions, reflecting the influence of local epidemiological factors, including environmental conditions and animal management practices (9,13).

In Indonesia, a study reported a seroprevalence of 3.4% in dogs, while in Italy, seroprevalence rates were found to be 6.4% using indirect fluorescent antibody tests (IFATs) (14,15). In contrast, a study in northeastern China revealed a higher seroprevalence of 28.9% among dogs, indicating regional differences in exposure and infection rates (16). Similarly, in Egypt, seroprevalence rates were found to be at 5.8%, which is lower than in some other regions but still significant (17). Studies have reported seroprevalence rates ranging from 6.4% in Italy to 8.3% in Brazil, demonstrating the widespread distribution of the parasite among dog populations (14,18). In Iran, an increasing pattern of seropositivity with age has been observed, suggesting that older dogs may have a higher likelihood of exposure to the parasite (19).

These variations highlight the necessity for localized studies to understand the epidemiology of *N. caninum* in canine populations.

The transmission of *N. caninum* occurs primarily through the ingestion of oocysts shed in the feces of infected dogs, which can contaminate the environment and be ingested by other animals.

Additionally, vertical transmission from mother to fetus is a significant route of infection, particularly in cattle, but it is also relevant in dogs (20,21).

N. caninum in cattle leads to significant reproductive issues, including abortion and stillbirth. The transmission dynamics of *N. caninum* are complex, involving both vertical transmission from infected mothers to their offspring and horizontal transmission through environmental exposure to oocysts shed by definitive hosts, primarily dogs (22,23).

Infected cows can pass the parasite to their fetuses during gestation, resulting in congenital infections that often lead to abortion or the birth of persistently infected calves (3,23,24). The prevalence of *N. caninum* in cattle herds can be alarmingly high, with some studies reporting infection rates of up to 90% in certain populations (22,23). This high prevalence underscores the importance of monitoring and controlling *N. caninum* in cattle to mitigate economic losses in the livestock industry (16).

Horizontal transmission occurs when cattle ingest oocysts from contaminated feed or water, which are excreted by infected dogs (25). This route of transmission highlights the interspecies relationship between canids and cattle in the epidemiology of neosporosis. Dogs, as definitive hosts, can shed oocysts in their feces after ingesting tissue cysts from infected animals (25,26).

Neospora caninum in Wildlife

The presence of *N. caninum* in wildlife and its potential to infect various species highlights the need for ongoing surveillance and research to understand its epidemiology and control measures (27,28).

Recent studies have expanded the understanding of *N. caninum*'s impact on wildlife, revealing its presence in various species, including marsupials, birds, and even rodents (29-31).

The life cycle of *N. caninum* involves canids as definitive hosts and a range of intermediate hosts, including various wildlife species (1,24). For instance, studies have documented the infection in gray wolves, which are considered natural definitive hosts for the parasite (1). Furthermore, wildlife, such as white-tailed deer, has been identified as a significant reservoir for *N. caninum*, contributing to its transmission dynamics in natural ecosystems (32). The prevalence of antibodies against *N. caninum* in wildlife populations, including raccoons and coyotes, indicates that these animals can harbor the parasite without showing clinical signs (33,34).

Moreover, the role of wildlife in the epidemiology of *N. caninum* is complex and not fully understood yet. While

some studies suggest that wildlife may act as reservoirs, the extent of their contribution to the transmission cycle remains uncertain (30,35). For example, birds of prey have been found to carry the parasite, but their specific role in the life cycle of *N. caninum* is still under investigation (30). Additionally, the detection of *N. caninum* DNA in wild rodents suggests that these animals can also play a role in the transmission dynamics of the parasite (31).

The implications of *N. caninum* infections in wildlife are significant, as they can affect not only the health of the animals themselves but also the broader ecosystem and agricultural practices. Understanding the prevalence and impact of *N. caninum* in wildlife is crucial for developing effective management strategies to mitigate its effects on livestock and wildlife populations (28,35).

Neospora caninum and *Toxoplasma gondii* Similarities

Neospora caninum and *T. gondii* are two closely related protozoan parasites that belong to the phylum Apicomplexa, and share significant morphological, genetic, and immunological similarities. Both parasites are obligate intracellular organisms that form tissue cysts and are known to cause reproductive issues in various animal species, particularly livestock. The similarities between these two parasites extend to their genomic structures, with recent studies revealing that while a substantial portion of their genomes is syntenic, there are notable differences in chromosome organization and specific gene functions (36,37).

Genomic analyses have proven that *N. caninum* and *T. gondii* diverged approximately 12 million years ago, yet they maintain a high degree of genetic similarity, which is evident in their shared morphological characteristics and life cycle strategies (38,39). For instance, both parasites utilize similar mechanisms for host invasion and manipulation, which is facilitated by their specialized organelles, such as rhoptries and micronemes (37,40). However, there are critical differences in their host ranges and transmission strategies; *T. gondii* has a broader host range, including humans, while *N. caninum* primarily affects canids and significantly causes the abortion in cattle (40,41).

Immunologically, cross-reactivity has been observed between *N. caninum* and *T. gondii*, complicating serological diagnostics for infections caused by these parasites (42,43). This cross-reactivity is particularly relevant in veterinary medicine, where accurate diagnosis is crucial for managing reproductive health in livestock. Furthermore, both parasites have been implicated in similar clinical outcomes, such as abortion and neonatal mortality, although the specific pathophysiological mechanisms may differ (9,28).

Recent research has also highlighted the advancements in developing therapeutic interventions targeting shared biochemical pathways in these parasites. For example, calcium-dependent protein kinases, which play essential roles in the life cycles of both *N. caninum* and *T. gondii*, have emerged as promising drug targets (44,45). This shared reliance on specific molecular pathways underscores the potential for cross-species therapeutic strategies, although the distinct biological behaviors of each parasite must be considered in treatment development (44,45).

Understanding these similarities and differences is crucial for effective diagnosis, treatment, and management of infections caused by these two important apicomplexan parasites.

Cross-reactivity Between *Neospora caninum* and *Toxoplasma gondii*

Neospora caninum and *T. gondii* are closely related protozoan parasites that cause infections in various animals. Due to their genetic and antigenic similarities, serological cross-reactivity between *N. caninum* and *T. gondii* is a major diagnostic challenge. Both parasites belong to the family Sarcocystidae and share tissue cyst-forming life cycles. Their antigenic similarities cause antibodies produced against one parasite to sometimes bind to antigens of the other, leading to false positives or difficulty differentiating infections in serological tests (46). This cross-reactivity complicates serological diagnosis, as routine immunological tests (enzyme-linked immunosorbent assay [ELISA], IFAT, and modified agglutination test) cannot reliably distinguish between the two infections. Studies have shown that at low serum dilutions, antibodies can cross-react strongly, confusing the interpretation of test results. The cross-reactivity between *N. caninum* and *T. gondii* remains a well-recognized diagnostic confounder, requiring careful choice of serological tests, appropriate serum dilution cut-offs, and use of specific antigens to differentiate infections effectively (47).

Neospora caninum Infection in Humans

Although the primary concern regarding *N. caninum* has been its impact on cattle, there is ongoing research into its potential zoonotic implications (48,49). This speculation arises from the close phylogenetic relationship between *N. caninum* and *T. gondii*, a well-established zoonotic agent that infects a substantial portion of the human population (37,50).

Despite the biological similarities, current evidence suggests that *N. caninum* is not classified as a zoonotic disease. Studies have reported the presence of antibodies against *N. caninum* in human sera, indicating some level of exposure. For instance, a study found anti-*N. caninum* antibodies in patients with the human immunodeficiency virus (HIV) and neurological disorders, suggesting that these populations may be more susceptible to exposure. In this study, a total of 256 serum samples (61, 50, 91, and 54 samples from HIV-positive patients, patients with neurological disorders, newborns, and healthy subjects, respectively) were assessed for *N. caninum* and *T. gondii* serologies by IFAT, ELISA, and immunoblotting. Immunoglobulin G antibodies

to *N. caninum* were predominantly detected in HIV-infected patients (38%) and patients with neurological disorders (18%), while newborns and healthy subjects demonstrated lower seropositivity rates (5% and 6%, respectively). Seropositivity to *N. caninum* was significantly associated with seropositivity to *T. gondii* in both HIV-infected patients and patients with neurological disorders. Seroreactivity to *N. caninum* was confirmed by immunoblotting, with positive sera predominantly recognizing the 29-kDa antigen of *N. caninum* (49).

Additionally, DNA from *N. caninum* has been detected in human umbilical cord blood, further supporting the notion of human exposure to the parasite (51). The seropositivity rates determined by the IFAT for *N. caninum* and *T. gondii* were 24.3% (49 samples) and 26.8% (54 samples), respectively. Nested-polymerase chain reaction positivity for *N. caninum* was observed in two samples of cord blood (1%) using the *Nc5* and *ITS1* genes, and positivity for *T. gondii* was detected in 16 samples using the primer for the *B1* gene (5.5% positivity in cord blood and 2.5% positivity in placental tissue) (51). However, these findings do not establish a direct link to human disease caused by *N. caninum*. Moreover, a comprehensive investigation involving 600 clinical samples from patients with the signs of toxoplasmosis found no evidence of *N. caninum* DNA, reinforcing the argument against its role as an opportunistic zoonotic agent (52). Similarly, a study in England, analyzing over 3,000 serum samples from both the general population and high-risk groups, reported no serological evidence of *N. caninum* infection, suggesting that human exposure is minimal (48).

The transmission dynamics of *N. caninum*, particularly from dogs to humans, have been a subject of considerable investigation. While the primary hosts of *N. caninum* are dogs and cattle, the potential for zoonotic transmission to humans has been speculated due to the biological similarities between *N. caninum* and *T. gondii*, a well-known zoonotic pathogen (9,50).

Research indicates that humans may be exposed to *N. caninum* through environmental contamination with oocysts shed in dog feces. This is similar to the transmission pathways of *T. gondii*, where ingestion of oocysts from contaminated food or water can lead to infection (9). The primary route of infection for *N. caninum* in intermediate hosts, such as cattle, is through the ingestion of oocysts from contaminated feed or water, which are excreted by infected dogs (53). This transmission mechanism highlights the importance of controlling dog populations and managing their fecal waste to mitigate the risk of environmental contamination. Additionally, vertical transmission from mother to fetus has been documented in cattle, further complicating the epidemiology of the disease (54).

Despite the theoretical risk of zoonotic transmission, the consensus in the literature suggests that *N. caninum* does not pose a significant risk to human health compared to *T. gondii*. The lack of serological evidence in human populations and the established transmission pathways primarily affecting livestock indicate that while *N. caninum* is a critical pathogen in veterinary medicine, its impact on human health remains minimal (48,50). Continued surveillance and research are essential to monitor any potential changes in this dynamic, particularly in immunocompromised populations where the risk of opportunistic infections is heightened (50,51).

Prevalence of *Neospora caninum* Antibodies in Different Human Populations

The reported seroprevalence of *N. caninum* antibodies in humans varies widely, depending on the population studied, geographic region, and applied diagnostic methods. Seroprevalence rates as high as 38% for immunoglobulin G antibodies have been reported among HIV-infected individuals (49). Similarly, patients with neurological disorders have shown a prevalence of approximately 18% (49). In contrast, studies on general populations or pregnant women have indicated lower rates, typically ranging from 0% to 8%. For instance, a study from Egypt reported 7.9% seropositivity among pregnant women (55), while another investigation from the same region found no evidence of antibodies in 48 examined subjects (56).

Serological assays, such as ELISA and IFAT, are commonly used for antibody detection; however, the presence of antibodies does not necessarily confirm active infection. Moreover, attempts to detect *N. caninum* DNA in human clinical samples have been unsuccessful, leaving its role as a human pathogen uncertain.

Control of Neosporosis and *Neospora caninum*

Effective control strategies are essential to mitigate the impact of *N. caninum* on the livestock industry. Current approaches to control *N. caninum* infection include vaccination, management practices, and an understanding of the immune response of the host. Vaccination is considered one of the most promising strategies for controlling *N. caninum* infection, especially given the lack of effective treatments for infected cattle. Recent studies have highlighted the development of vaccines that target specific antigens associated with the parasite. For instance, Fereig et al demonstrated that vaccination with Neospora GRA6 can interrupt vertical transmission and provide partial protection to both dams and their offspring against *N. caninum* infection in mice (57). Similarly, Nishikawa et al emphasized the potential of using recombinant vaccinia virus to deliver *N. caninum* surface proteins, which could enhance the immune response against the parasite (58). The identification of species-specific antigens through immunoproteomics also shows promise in developing effective vaccines (59).

Management practices play a crucial role in controlling *N. caninum*. de Abreu et al outlined that understanding the transmission pathways of *N. caninum* is vital for implementing control measures, which include the

culling of seropositive animals and management of the access of definitive hosts, such as canids, to cattle (60). Furthermore, effective management strategies can significantly reduce the incidence of horizontal transmission, which is primarily facilitated by environmental contamination with oocysts shed by infected definitive hosts (1).

The immune response of the host is another critical factor in controlling *N. caninum* infection. Research has shown that a T-helper 1-type immune response, characterized by the production of interferon-gamma, plays a pivotal role in controlling the acute phase of the disease (61). Studies indicate that interferon-gamma can inhibit the growth of *N. caninum* tachyzoites in bovine brain cells, highlighting the importance of cytokines in the host defense mechanisms (62). Understanding these immune responses can inform the development of vaccines and therapeutic strategies aimed at enhancing the protective immunity of cattle against *N. caninum*.

Treatment of Neosporosis

The treatment of neosporosis remains a challenge, as there are currently no specific drugs approved for its management, and existing therapies have shown limited efficacy and mixed responses, often leading to relapses in infected animals (63-65).

Current therapeutic strategies primarily involve the use of antibiotics, such as clindamycin and sulfonamides, which have been reported to yield variable results. For instance, in a case study, a dog with suspected neosporosis was successfully treated with supportive therapy and clindamycin, resulting in negative serological titers for *N. caninum* after three months (66). However, the reliance on these antibiotics is complicated by their potential side effects and the need for combination therapies to enhance effectiveness (65).

Research has also explored the immunotherapeutic potential of *N. caninum* itself. Studies have indicated that *N. caninum* can activate immune responses and directly target tumor cells, suggesting its potential as an anti-cancer agent (42,67,68). For example, engineered strains of *N. caninum* that secrete interleukin-15 have demonstrated enhanced immunotherapeutic effects in murine models of cancer (68). This dual role as both a pathogen and a potential therapeutic agent highlights the complexity of managing neosporosis and the need for innovative approaches in treatment. Moreover, the development of new pharmacological agents targeting the parasite is critical. Recent studies have identified compounds such as bumped kinase inhibitors that exhibit activity against *N. caninum*, indicating a promising avenue for future drug development (69). Additionally, the exploration of allosteric inhibitors and other novel compounds could provide more effective treatment options that minimize adverse effects associated with current therapies (70). Continued research into the biology of *N. caninum* and its interactions with the host immune system will be essential for developing effective treatments.

Conclusion

Neospora caninum is integral to its life cycle and pathogenicity, characterized by its intracellular replication and complex interactions with host cells. *N. caninum* represents a critical health issue for dogs, characterized by a spectrum of neurological signs and varying seroprevalence across different regions. *N. caninum* poses a significant threat to cattle health through both vertical and horizontal transmission. *N. caninum* is a multifaceted parasite with a complex life cycle involving various wildlife species. Its presence in wildlife underscores the need for continued research to elucidate its epidemiology and impact on both domestic and wild animal populations. Controlling *N. caninum* infection requires a multifaceted approach that includes the development of effective vaccines, the implementation of management practices to reduce transmission, and a deeper understanding of the host's immune responses. In spite of the fact that *N. caninum* and *T. gondii* exhibit significant similarities in their biology, morphology, and genetic makeup, they also possess distinct differences that influence their pathogenicity and host interactions. While *N. caninum* is primarily a concern for canids and livestock, the risk of transmission to humans appears to be negligible based on current evidence. While *N. caninum* is primarily a concern for canines and livestock, the risk of transmission to humans is not unlikely based on current evidence. Continued surveillance and research are vital for monitoring potential changes in this dynamic, especially in immunocompromised populations among which the risk of opportunistic infections is high. Further research is essential to fully understand the zoonotic potential of *N. caninum* and its implications for human health.

Authors' Contribution

Conceptualization: Razieh Hosseini.
Data curation: Ali Hajimohammadi.
Formal analysis: Razieh Hosseini, Ali Hajimohammadi.
Investigation: Razieh Hosseini.
Methodology: Ali Hajimohammadi.
Project administration: Ali Hajimohammadi.
Resources: Razieh Hosseini, Ali Hajimohammadi.
Software: Razieh Hosseini.
Supervision: Razieh Hosseini.
Validation: Ali Hajimohammadi.
Visualization: Razieh Hosseini, Ali Hajimohammadi.
Writing–original draft: Razieh Hosseini.
Writing–review & editing: Ali Hajimohammadi.

Competing Interests

The authors declared no conflict of interests.

Ethical Approval

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