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Comparative host–parasite relationships in ovine toxoplasmosis and bovine neosporosis and strategies for vaccination

Elisabeth A. Innes *, Paul. M. Bartley, Stephen W. Maley, Stephen E. Wright, David Buxton

Moredun Research Institute, Pentlands Science Park, Edinburgh EH26 OPZ, United Kingdom

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Abstract

Toxoplasma gondii and *Neospora caninum* are important causes of reproductive loss in ruminant species worldwide. Both parasites cause disease during pregnancy that may result in foetal death or birth of live congenitally infected offspring. *T. gondii* is also an important human pathogen with the main risk groups including pregnant women and immuno-compromised individuals, although clinical disease has also been observed in outbreaks among immuno-competent people. While the two parasites are closely related there are distinct differences between the two in their interactions with different host species and subsequent clinical outcome. This paper discusses the respective host–parasite relationships in ovine toxoplasmosis and bovine neosporosis and how the immune response may be host-protective, parasite-protective or contribute to disease pathogenesis, and how this knowledge may help in the development of more effective and targeted vaccination strategies.

Keywords: *Toxoplasma gondii*; *Neospora caninum*; Immune response; Vaccination

1. Introduction

A fascinating aspect of host–parasite relationships is how parasites interact with their hosts and why this can sometimes cause serious disease. Following initial invasion there is a constant interaction between the host immune system and the parasite which has varying consequences for both parties. The outcome of the different immune responses induced may be host-protective or parasite-protective and both may contribute towards disease pathogenesis. It is critical therefore to understand the consequences of inducing particular host immune responses when designing vaccines.

Toxoplasma gondii and *Neospora caninum* are important apicomplexan parasites causing a wide range of diseases in different host species. Although the two parasites are known to be closely related, they do exhibit important differences.

T. gondii is arguably the most successful parasite worldwide as it can infect all warm blooded animals, including man, with a range of different disease consequences in different host species [1,2]. This may reflect co-evolution of the parasite with its host and the adaptation of both to accommodate each other [2]. Comparatively less is known about *N. caninum*, but it does appear to have a more limited host range than *T. gondii* and causes disease in different animal species [3,4]. For example, *N. caninum* is known to be a major cause of reproductive failure in cattle [4] but does not appear to be an important pathogen in sheep [5], whereas the opposite is true for *T. gondii* [6–8]. In addition, while *T. gondii* is known to be an important human pathogen mainly causing disease in the developing foetus or in immuno-compromised individuals, there is no good evidence that *N. caninum* can infect or cause disease in people [9].

In this paper, we will look at the host–parasite relationships of *T. gondii* and *N. caninum* in sheep and cattle, respectively, and discuss how this knowledge may help to inform a disease control strategy based on vaccination.

2. Disease

T. gondii is a major cause of abortion in sheep and goats worldwide, particularly in the more temperate countries such as New Zealand, France, UK and Norway where climatic

* Corresponding author. Tel.: +44 131 445 5111; fax: +44 131 445 6111.
E-mail address: lee.innes@moredun.ac.uk (E.A. Innes).

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conditions for oocyst survival and sporulation are optimal [10]. In Europe there are 86 million farmed sheep with three-quarters located in UK, Spain, Italy and France [11]. A report estimated that in the UK infection with *T. gondii* was responsible for 1–2% of neonatal losses per annum [12]; if this frequency was extrapolated throughout Europe it would point to an estimated loss of around 1.25 million lambs each year.

Since the discovery [13] and isolation of *N. caninum* in tissue culture in the late 1980s [14,15], the parasite has emerged as a major cause of abortion in cattle worldwide [4]. Epidemiological studies in Scotland showed that 16% of aborted foetuses were sero-positive for *N. caninum* [16], and a further study in England and Wales indicated that the national seroprevalence was 6% and the proportion of abortions attributable to *N. caninum* was 12.5% [17]. A large scale supranational comparison of *N. caninum* herd seroprevalences was recently completed in Europe and showed national seroprevalences to vary between 16–76% for dairy cattle and 41–61% for beef cattle [18]. Cattle infected with *N. caninum* are three to seven times more likely to abort compared to uninfected cattle [19–21]. Therefore, *N. caninum* presents a major economic problem to cattle producers worldwide [22].

A primary infection of pregnant sheep with *T. gondii* may result in foetal death and resorption/abortion, production of a mummified foetus, a stillborn lamb; birth of a live weak lamb or a live, infected but clinically normal lamb [8]. A major contributing factor in determining severity of disease is the stage of gestation when infection first occurs. The earlier infection occurs in gestation the more severe the consequences to the developing foetus [8,23–25]. Following infection, sheep normally remain persistently infected with the parasite in the form of bradyzoites contained within tissue cysts in the brain and muscle of the animal [8].

With bovine neosporosis, the main clinical manifestation in both dairy and beef cattle is abortion with most being diagnosed between 3 and 8 months of gestation [26]. However, *N. caninum* infection early in gestation, which can be difficult to diagnose, may result in the foetus being reabsorbed and the animal presenting as infertile. Experimental infection of cattle with *N. caninum* at day 70 of gestation resulted in loss of the foetus [27,28]. A recent case study on a closed dairy herd in UK analysed the breeding history in groups of cattle on the farm and found a statistically significant increase in the number of artificial insemination (AI) services per successful pregnancy in *N. caninum* sero-positive cattle compared to sero-negative cattle [29]. Similarly to ovine toxoplasmosis, the earlier in gestation that *N. caninum* infection occurs the more severe the consequences to the bovine foetus [27,28,30,31], although the relative risk of transmission to the foetus in early gestation is lower [32]. The pattern of abortions may present as epidemic if more than 10% of cows at risk abort within a 6–8-week period [33,34], or endemic when cattle on the farm have sporadic abortions. The various patterns of abortions may be related to the routes of transmission as discussed below.

3. Transmission of infection

3.1. Ovine toxoplasmosis

The cat is the definitive host of *T. gondii* with young cats frequently contracting a primary infection, following the consumption of bradyzoites within tissue cysts in infected rodents and birds, when they first start hunting for food [1]. The oocyst stage of the parasite is shed in cat faeces 5–14 days post-infection and may remain viable and infective in the environment, following sporogony, for up to 18 months depending on temperature and relative humidity [1]. Toxoplasma abortion in sheep has been linked to the contamination of feed or pasture with sporulated oocysts [35,36] and associations have been made between the presence of cats on farms and exposure of sheep to *T. gondii* [37]. Studies showing an increasing seroprevalence to *T. gondii* related to age indicate that there is extensive environmental contamination with oocysts and that the majority of ovine infections are acquired post-natally [38–40]. Some recent data may suggest that in some instances sheep persistently infected with *T. gondii* may pass the infection to the foetus in subsequent pregnancies [41,42]. While these are interesting observations and warrant further investigation, a recent more complete study provided confirmatory evidence that there does not appear to be significant congenital transmission of *T. gondii* from persistently infected sheep to their offspring [43].

3.2. Bovine neosporosis

Cattle may become infected with *N. caninum* through the consumption of oocysts shed in the faeces of infected dogs or vertically from dam to calf during pregnancy [26]. However, *N. caninum* infection in cattle differs from *T. gondii* infection in sheep in the high rate of endogenous transplacental infection, estimated at between 78 and 95% [44,45], and occurring over several generations and in successive pregnancies [46,47]. Endogenous transplacental infection is defined as a foetal infection acquired from a recrudescent persistent maternal infection that was acquired prior to pregnancy [48]. While in ovine toxoplasmosis the major danger is a primary infection during pregnancy, in bovine neosporosis both this and an endogenous transplacental infection are important [26].

4. Disease pathogenesis and host–parasite interaction

4.1. Ovine toxoplasmosis

In ovine toxoplasmosis, once the sheep has ingested the oocysts the parasites excyst in the gut and the sporozoites invade and multiply within the cells of the gut and mesenteric lymph node before initiating a parasitaemia and spreading to other parts of the body [8]. A fever usually accompanies early infection until around day 10, when parasites may be detected in the blood [49–51]. Efferent lymphatic cannula-