



Minireview

Vaccines against neosporosis: What can we learn from the past studies?



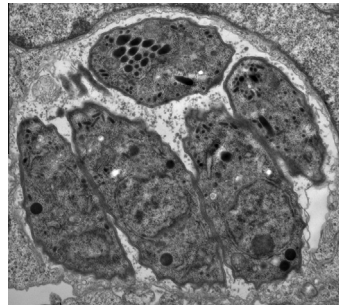
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HIGHLIGHTS

- *Neospora caninum* causes abortion in cattle, and is therefore of economical importance.
- Vaccine development has proven to be a difficult task.
- Different approaches and experimental models are reviewed.
- We highlight what has been learned from the studies so far.

GRAPHICAL ABSTRACT



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ABSTRACT

Neospora caninum is an intracellular apicomplexan parasite, which is a leading cause of abortion in cattle; thus neosporosis represents an important veterinary health problem and is of high economic significance. The parasite can infect cattle via trans-placental transmission from an infected cow to its fetus (vertical transmission), or through the oral route via ingestion of food or water contaminated with oocysts that were previously shed with the feces of a canid definitive host (horizontal transmission). Although vaccination was considered a rational strategy to prevent bovine neosporosis, the only commercialized vaccine (Neoguard®) produced ambiguous results with relatively low efficacy, and was recently removed from the market. Therefore, there is a need to develop an efficient vaccine capable of preventing both, the horizontal transmission through infected food or water to a naïve animal as well as the vertical transmission from infected but clinically asymptomatic dams to the fetus. Different vaccine strategies have been investigated, including the use of live attenuated vaccines, killed parasite lysates, total antigens or antigen fractions from killed parasites, and subunit vaccines. The vast majority of experimental studies were performed in mice, and to a certain extent in gerbils, but there is also a large number of investigations that were conducted in cattle and sheep. However, it is difficult to directly compare these studies due to the high variability of the parameters employed. In this review, we will summarize the recent advances made in vaccine development against *N. caninum* in cattle and in mice and highlight the most important factors, which are likely to influence the degree of protection mediated by vaccination.

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1. Introduction

Neospora caninum is an obligate intracellular apicomplexan parasite and a member of the coccidia (Ellis et al., 1994). *N. caninum* was first described in 1984 as an unidentified protozoan parasite that was found in tissue samples of canine pups that had suffered from paralysis and early death (Bjerkas et al., 1984). In 1988, the parasite was subsequently identified as a novel species and named *N. caninum* by Dubey et al. (1988a). The currently known definitive hosts of *N. caninum* are the dog (McAllister et al., 1998), coyote (Gondim et al., 2004), dingo (King et al., 2010) and grey wolf (Dubey et al., 2011). *N. caninum* is known to infect mainly cattle, sheep and goats, but also some wild ungulates, rodents, marine mammals and birds (reviewed in Dubey and Schares, 2011; Dubey et al., 2007; Gondim, 2006). Although experimental infection of pregnant rhesus macaques resulted in vertical transmission and fetal infections (Barr et al., 1994a), there is still no evidence that *N. caninum* can infect human (McCann et al., 2008; Petersen et al., 1999).

Reproductive failure in cattle represents the major economic loss of neosporosis. Fetal death represents the direct cost, but other indirect losses such as professional help and diagnosis (Dubey and Schares, 2006; Ortega-Mora et al., 2006), or rebreeding and replacement of culled cows, considerably increase the overall expenses for the farmer (reviewed in Dubey et al., 2007). The notion that there is a reduction of milk yield in infected herds is controversial, as different studies indeed showed a reduction (Hernandez et al., 2001; Tiwari et al., 2007), whereas others indicated increased (Pfeiffer et al., 2002) or not significantly different (Hall et al., 2005; Hobson et al., 2002) milk production. The same accounts for weight gain: a reduced post-weaning weight gain was observed in seropositive calves by Barling et al. (2000a), but no difference in weight gain between seropositive and seronegative calves were observed in more recent studies (Hoar et al., 2007; More et al., 2010).

It is difficult to have a reliable global overview of the economic losses caused by abortions due to *N. caninum*. Recently, a calculation based on the review of 99 publications from ten countries estimated the median losses of *N. caninum* induced abortion to be in excess of US\$ 1.298 billion per year, with two thirds incurred by the dairy cattle, and one third by the beef cattle industry (Reichel et al., 2013). The global costs were estimated to US\$ 852.4 million in North America (65.7%) (USA, Canada, Mexico), US\$ 239.7 million in South America (18.5%) (Brazil, Argentina), US\$ 137.5 million in Australasia (10.6%) (Australia, New Zealand) and US\$ 68.7 million in Europe (5.3%) (Netherlands, Spain, UK) (Reichel et al., 2013).

Different patterns of *Neospora* associated abortion occur: sporadic, epidemic and endemic. The epidemic pattern is defined by temporary abortion outbreaks (Davison et al., 1999a). The epidemic abortions are due to primary infection of previously uninfected dams exposed at almost the same time to a single source of contamination (McAllister et al., 2000). In the endemic pattern, the abortions happen intermittently for months or years and are due to persistently infected dams that transplacentally transmit the parasite to their progeny (Hall et al., 2005). The prevalence in dogs shows a correlation with the prevalence in cattle (Dubey, 1999). Although a sylvatic cycle for *N. caninum* has been demonstrated (Gondim, 2006; Rosypal and Lindsay, 2005), its importance as reservoir for the transmission to domestic animals has not been definitely elucidated, but seems to be of minimal significance at a large scale, although it can be significant locally (King et al., 2011, 2012).

The most important risks of infection are: (1) the age of cattle (Jensen et al., 1999; Rinaldi et al., 2005; Sanderson et al., 2000); (2) the number of definitive hosts in contact to cattle food (Barling et al., 2000b; Piagentini et al., 2012; Vanleeuwen et al., 2010); (3) farm management and housing, with higher risk at higher stocking density and large herds (Barling et al., 2000b; Moore et al., 2009; Schares et al., 2004); (4) rearing of own replacement heifer rather than from external sources (Barling et al., 2001). Risks associated with other factors such as the presence of other intermediate hosts, the feeding mode of cattle, co-infections, vegetation index, climate, size of farmland, calving management or feeding colostrum or milk were extensively reviewed (Dubey and Schares, 2011; Dubey et al., 2007). Seroprevalences in beef herds are usually lower than in dairy herds, but this may be due to different farm management practice (Bartels et al., 2006; Moore et al., 2009) rather than breed-related susceptibility (Eiras et al., 2011). However, some studies found different rates of abortion and immune responses between different breeds of cattle (Armengol et al., 2007; Sager et al., 2001; Santolaria et al., 2011).

In order to diminish the costs of *N. caninum* infections within herds, different strategies have been proposed, depending on the country or region, infection rate and associated risk factors (Dubey et al., 2007). In general, in farms with endemic abortions the most efficient method is to identify the infected animals and to cull or selectively breed them. In farms with epidemic abortions, the contact between definitive hosts and cattle has to be avoided and contamination of food and water by feces containing oocysts must be carefully controlled (Dubey et al., 2007). There are also standard measures that can be applied to prevent the introduction of new infection sources in a herd (Dubey et al., 2007). The replacement

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