

The role of genetic variability of the host on the resistance to *Neospora caninum* infection in cattle

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Abstract

Neospora caninum is one of the most frequently diagnosed abortifacient pathogens in cattle. There is abundant genomic information about the parasite itself, but very little is known about the genetic variability of resistance in the most common intermediate host. The aim of this review was to compile all the available information about the genetic variability associated with the resistance to *N. caninum* both between and within cattle breeds. We systematically searched for published studies that investigated the influence of genetics of the host on the prevalence of *N. caninum* and risk of abortion. Beyond the potential confounding effects of feeding systems, management and animal density, some lines of evidence suggest that Holstein, the most popular breed for milk production, has a comparatively higher risk of abortion due to infections by *N. caninum*, whereas some beef breeds from Continental Europe seem to be more resistant. It is still not clear if different genetic mechanisms of resistance are involved in the two known routes of infection: postnatal ingestion of oocysts or transplacental transmission from the infected dam to the fetus. Genomic information associated with susceptibility to infection and risk of abortion in different cattle breeds is still scarce. The information reported here could be useful to identify new research alternatives and to define novel strategies to deal with this major problem of animal production.

KEY WORDS

dairy/beef cattle, genetics, *Neospora caninum*, resistance/susceptibility

INTRODUCTION

Neospora caninum is an obligate, intracellular cyst-forming protozoan parasite from the phylum Apicomplexa that is considered one of the most frequently diagnosed abortifacient pathogens in cattle. *Neospora caninum* has a heteroxenous life cycle; asexual reproduction occurs in cattle as intermediate hosts and sexual reproduction occurs exclusively in canid hosts (Dubey, 1999). Most research indicates that transplacental transmission is the primary route by which cattle become infected with *N. caninum*; horizontal transmission, on the other hand, is caused by ingestion of oocysts in food or water (Dubey & Lindsay, 1996). Due

to its worldwide distribution and its efficient transmission in cattle, *N. caninum* causes significant economic losses in the beef and dairy industries. Nowadays, there is no commercially available vaccine or effective chemotherapeutic agent to control the disease (Almería et al., 2017; Lindsay & Dubey, 2020; McAllister, 2016).

Significant advances have been achieved since the discovery of *N. caninum* in the 1980's (Dubey et al., 2007). Indeed, knowledge related to the parasite biology, epidemiology, immune-pathogenesis and diagnosis allowed for the development of efficient control measures to reduce reproductive losses in cattle (Almería et al., 2017; Dubey & Schares, 2011; McAllister, 2016). Nonetheless,

several aspects of the disease are still partially understood and there is ongoing research aimed to develop practical, economically justifiable and efficient tools to ameliorate the effects of this parasite.

Although not to the same extent as other organisms in the phylum Apicomplexa that are zoonotic (*Toxoplasma gondii*, *Plasmodium* sp.), there is abundant genetic and genomic information associated with different aspects of *N. caninum* biology. Results have been published about genetic diversity and geographic population structure (Dorsch et al., 2020; Regidor-Cerrillo et al., 2013), genome sequence and identification of mutational hotspots between strains (Berná et al., 2021; Calarco et al., 2018), transcriptomic and proteomic studies (García-Sánchez et al., 2019; Horcajo et al., 2018, 2023), and analysis of selective sweeps (Khan et al., 2019), among others. On the other side, very little is known about genetic susceptibility of the intermediate host against *N. caninum* infection. For example, a recent review addressed the influence of the source of the inoculum (tachyzoites and oocysts) in experimental *N. caninum* infections (Gondim & McAllister, 2022); however, a potential association with the genetic background of the intermediate host was not taken into account and the breeds involved in the experiments that were cited are not even mentioned. In fact, Benavides et al. (2014) did include breed as one of the factors to be considered in the definition of standard guidelines for experimental models of neosporosis.

The recently launched “One Health Initiative” (<https://onehealthinitiative.com/>) supports a synergistic approach to health care in humans, animals and the environment. Consistent with this initiative, innovative strategies for disease control in domestic animals are of the most importance. In this context, knowing aspects related to host resistance to *N. caninum* could generate a window of opportunity to improve control strategies against the disease. Knowledge of parasite–host interactions would provide better understanding of the infective process, which in turn would help in proposing control strategies to deal with this parasite, reducing the serious economic losses generated that were estimated in more than US\$1.298 billion per annum 10 years ago (Reichel et al., 2013). Therefore, we aimed to compile all the available information about the genetic variability associated with the resistance to *N. caninum* between and within cattle breeds.

STRATEGY FOR LITERATURE SEARCH

We systematically searched for published studies that investigated the influence of genetics of the host on the prevalence of *N. caninum* in cattle worldwide, using “neospora” and “cattle OR bovine” as search terms on PubMed (<https://pubmed.ncbi.nlm.nih.gov/>). We used the R packages Pubmed, mineR and Bibliometrix (Aria & Cuccurullo, 2017; R Core Team, 2020; Rani

et al., 2015) for a first selection of the downloaded abstracts, looking for relevant information (eg. variability in seroprevalence or risk of abortion between and within breeds and cattle biotypes). For this search we used keywords such as “breed”, “crossbred”, “beef”, “dairy” and “abortion”. Then, we screened individually the full articles corresponding to selected abstracts, to find those that: (a) unequivocally considered biotype or breed as a risk factor of either seroprevalence or abortion and (b) performed formal statistical analyses. From this group, we excluded experiments with clear evidence of the existence of confounding effects due to unequal management conditions among genetic groups.

In the third step, new articles of potential interest that were cited in the group generated in the second step and fulfilled the same selection criteria were also reviewed, whether or not they were included in the initial PubMed search.

Using the same tools, we also searched for articles reporting abortion rates of females from different cattle breeds in experimental infections with *N. caninum*.

As of May 2023, 1417 posts associated with neosporosis in cattle were retrieved from PubMed. A total of 31 articles considering biotype or breed effects as a risk factor of *N. caninum* seroprevalence were selected for consideration in this review. Surprisingly, we found articles reporting significant differences in seroprevalence among breeds, even when these differences were clearly justified by other systematic, non-genetic factors (e.g. Gharekhani et al., 2014; Kamga-Waladjo et al., 2010; Llano et al., 2018; Quintanilla-Gonzalo et al., 1999). From the selected group, only four articles considered intra-breed variability (estimation of heritability, genome-wide association study, candidate gene analysis) while the rest, related to inter-breed variability, evaluated breed effects on seroprevalence in commercial dairy or beef farms (13 articles) or the risk of abortion and associated traits (e.g. hormonal profiles) of *N. caninum* infected females (14 articles). All the studies considering breed or genetic group as a risk factor of *N. caninum* seroprevalence and also those that evaluated sire effects on the risk of abortion of crossbred pregnancies corresponded to natural infections. On the other hand, there were 35 articles evaluating the effects of experimental infections with *N. caninum* during pregnancy that clearly stated the genetic type of the females involved in the experiments.

GENETIC VARIABILITY BETWEEN AND WITHIN BREEDS IN *N. CANINUM* SEROPREVALENCE

Between breeds

In 2017, Dubey et al. reviewed all the reported information about the prevalence of *N. caninum* antibodies from most regions of the world. Although dairy and beef cattle

were both affected, they listed 207 reports in dairy cattle and only 63 in beef cattle. Although beef cattle is comparatively more numerous worldwide than dairy cattle, economic losses are higher in the dairy industry (Reichel et al., 2013).

Reichel et al. (2013) reviewed information about *N. caninum* infection in 10 countries (Australia, New Zealand, Canada, Mexico, U.S.A., Argentina, Brazil, the Netherlands, Spain and the United Kingdom) and concluded that the median seroprevalence of *N. caninum* worldwide was higher in dairy cattle (16.1%) than in beef cattle (11.5%), as it also was for the median specific risk of abortion due to *N. caninum* infection (14.3% and 9.1%, respectively). In our literature search we found 18 articles that reported *N. caninum* seroprevalence in populations of beef and dairy cattle (e.g. Bartels et al., 2006; Moore et al., 2009; Wilson et al., 2016), but in most of them single breeds were not identified. From 13 experiments with statistical comparisons, only five failed to detect significant differences between dairy and beef cattle and only one reported higher seroprevalence in beef cattle (Eiras et al., 2011). It is worth noting that the experiment of Eiras et al. (2011) was conducted in a region of Spain where dairy and beef cattle are managed under similar conditions. Moreover, the analysis was based on the largest sample size ever reported for this kind of studies.

Interestingly, *N. caninum* infected fetuses from dairy cattle also showed significantly more prominent and extensive intra-cerebral lesions than those from beef cattle (De Meerschman et al., 2002).

Although many scientists agree on a higher prevalence in dairy cattle compared to beef cattle, there is no consensus about the relative importance of genetics compared to other factors that markedly differ between the two production systems such as feeding systems, housing, pasture management and cattle density (Dubey et al., 2007; Moore et al., 2009). For example, in one experiment the two cattle types were grouped under “husbandry systems” for statistical analysis (De Meerschman et al., 2002) and therefore genetic and non-genetic factors are totally confounded. Due to the influence of confounding effects and the lack of breed identification, experiments comparing beef and dairy cattle (20 articles) were not considered in the present review.

More interesting from the point of view of genetics -and potentially more useful- are the studies that addressed differences in seroprevalence among individual cattle breeds.

The results of 13 experiments that evaluated seroprevalence in single breeds or their crosses are summarized in Table 1. In each case, the results correspond to serological surveys in different numbers of farms and the analyzed trait was the presence of antibodies to *N. caninum*, expressed as a percentage. Only eight experiments reported significant differences between genetic groups. Eleven experiments were conducted in dairy farms, while two included beef breeds. Unfortunately,

not all the articles disclosed all the breeds involved and reported results correspond to so-called “local breeds” or “local crossbreds”.

Armengol et al. (2007) evaluated 1758 cattle from 10 different genetic groups in 26 herds of Andorra, in one of the very few experiments that included beef breeds. The Limousin breed and its crosses had a risk of infection almost seven times lower than all the other genetic groups considered together. Interestingly, crosses with Limousin also stand out for a lower risk of abortion in matings with infected Holstein females, as it is discussed below.

In some cases, the analysis of the risk of infection by *N. caninum* involved the comparison of local versus imported, more selected breeds (Imre et al., 2012; Köse et al., 2021; Nazir et al., 2013). These studies are relevant because it is usually assumed that there is a genetic antagonism between productivity and adaptation or rusticity in livestock, which includes parasite resistance (e.g. Douhard et al., 2021). However, in any of those three experiments differences between local and exotic breeds were detected.

Although crossbred cattle were included in several experiments evaluating the prevalence of infection, the potential effects of heterosis have not been formally tested so far with appropriate experimental designs and therefore the relative performance of crossbred cattle involves both heterotic and additive breed effects. The simplest experimental design for the independent estimation of direct genetic, maternal and heterotic effects in either natural or artificial infections would be a diallel mating scheme involving females of at least two purebreeds and the corresponding F1 reciprocal crosses, all managed under the same conditions.

Nazir et al. (2013) showed that seroprevalence was significantly lower ($p < 0.05$) in purebred than crossbred cattle in Pakistan but did not find significant differences among local (Sahiwa, Rojan, Dajal and Dhanni) and exotic (Friesian and Jersey) pure breeds.

Asmare et al. (2013) found favorable effects of crossbreeding in Ethiopia, proposing that crossing pure dairy breeds such as Holstein and Jersey (*Bos taurus*) with local zebu (*Bos indicus*) might generate a protective effect against *N. caninum* infection. In turn, Munhoz et al. (2009) found no differences between Holstein cattle and crossbred Holstein-Zebu animals in Brazil, whereas in Argentina Moore et al. (2003) found no differences in odd ratios for infection in Brahman and composite beef breeds (Brangus, Braford, Santa Gertrudis) compared to Angus and Hereford.

There is also information available about comparisons among other species of the genus *Bos*. Based on a meta-analysis of results from several experiments in China, Wei et al. (2022) and Ying et al. (2022) reported that yaks (*Bos grunniens*) were less affected by *N. caninum* than cattle (*B. taurus*) and buffalos (*Bubalus bubalis*), but they acknowledged that this result could have

TABLE 1 Serologic prevalence of *Neospora caninum* antibodies in different cattle breeds.

| Country | Breeds | n (tested) | % Seroprevalence | Statistical analysis | Reference |
|-----------------------------|---|------------|------------------|---|----------------------------------|
| Argentina | <i>Bos taurus</i> (Angus, Hereford) | 138 | 6.5 | OR = 1 | Moore et al. (2003) |
| | <i>B. indicus</i> and composites (Brahman, Brangus, Braford, Santa Gertrudis) | 167 | 3.6 | OR = 0.53 (0.18–1.53) | |
| Brazil | Holstein | 558 | 15.1 | OR = 2.13 (1.42–3.18) $p < 0.001$ | Guimarães et al. (2004) |
| | Zebu and crossbreds | 65 | 7.7 | OR = 1 | |
| | Holstein | 55 | 38.2 | OR = 2.65 (1.36–5.15) $p = 0.003$ | Munhoz et al. (2009) |
| | Holstein × Zebu ^a | 222 | 25.2 | OR = 1.45 (0.93–2.26) $p = 0.11$ | |
| | Zebu | 286 | 18.9 | OR = 1 | |
| | Holstein | 543 | 22.3 | OR = 0.49 (0.27–0.87) $p = 0.021$ | Snak et al. (2018) |
| Costa Rica | Jersey | 52 | 38.5 | OR = 2.18 (1.20–3.95) $p = 0.014$ | |
| | Holstein | 2330 | 39.7 | OR = 1 | Romero et al. (2002) |
| | Jersey | 630 | 38.6 | OR = 1.9 (1.2–3.2) $p = 0.01$ | |
| Andorra | Holstein × Jersey | 42 | 53.6 | OR = 1.3 (0.6–2.9) $p = 0.57$ | |
| | Limousin – Limousin crosses | 155 | 1.3 | OR = 0.15 ($p = 0.002$) | Armengol et al. (2007) |
| Romania | Other beef/dual-purpose breeds ^b | 1603 | 8.0 | OR = 1 | |
| | Holstein | 200 | 25.0 | $p > 0.05$ | Imre et al. (2012) |
| Turkey | Surã de Stepã Transilvãneanã × Simmental | 176 | 30.7 | | |
| | Holstein | 98 | 8.2 | $p > 0.05$ | Sevgili et al. (2005) |
| | Brown Swiss | 90 | 6.7 | | |
| | Crossbreds | 117 | 7.7 | | |
| | Holstein | 283 | 5.7 | $p > 0.05$ | Köse et al. (2021) |
| | Simmental | 56 | 3.6 | | |
| | Montofon | 39 | 5.1 | | |
| | Crossbreds | 22 | 4.5 | | |
| | Holstein | 346 | 28.6 | OR = 2.3 $p < 0.001$ | Gharekhanli and Yakhchali (2019) |
| | Crossbreds | 130 | 14.6 | OR = 1 | |
| Pakistan | Holstein | 77 | 37.7 | Purebreds vs. crossbreds: $p < 0.05$ | Nazir et al. (2013) |
| | Jersey | 45 | 48.9 | | |
| | Sahiwal | 147 | 40.1 | Exotic vs. local purebreds: $p > 0.05$ | |
| | Rojan | 24 | 29.2 | | |
| | Dajal | 19 | 31.6 | | |
| | Dhanni | 31 | 35.5 | | |
| Crossbreds (local × exotic) | 213 | 54.9 | | | |

(Continues)

TABLE 1 (Continued)

| Country | Breeds | n (tested) | % Seroprevalence | Statistical analysis | Reference |
|----------|-----------------|------------|------------------|--|-----------------------|
| Algeria | Fleckvieh | 26 | 19.2 | OR = 0.973 (0.361–2.62) $p > 0.05$ | Ghalimi et al. (2012) |
| | Holstein | 210 | 21.9 | OR = 1.208 (0.821–1.778) $p > 0.05$ | |
| | Montbéliarde | 88 | 14.8 | OR = 0.682 (0.368–1.264) $p > 0.05$ | |
| | Crossbreeds | 370 | 18.6 | OR = 0.888 (0.625–1.262) $p > 0.05$ | |
| Ethiopia | Holstein × zebu | 311 | 7 | OR = 1 | Asmare et al. (2013) |
| | Holstein | 1873 | 14.3 | OR = 1.667 ($p = 0.049$) | |
| | Jersey | 150 | 19.6 | OR = 1.9 ($p = 0.002$) | |

Note: Significant comparisons between breeds within experiments are in bold.

Abbreviation: OR, odds ratio.

^a1/2 Holstein to 7/8 Holstein.

^bOther breeds: Bruna d'Andorra (Brown Swiss)-mixed Bruna d'Andorra, Charolais-mixed Charolais, Gascon-mixed Gascon, Aubrac, Deutsche Fleckvieh-mixed Deutsche Fleckvieh, Blonde d'Aquitaine-mixed Blonde d'Aquitaine, mixed Friesian, Deutsche Braunvieh, and mixed Montbéliarde.

been confounded by factors such as feeding density and temperature.

Considered overall, the information about breed differences in seroprevalence is not conclusive, due to potential weaknesses of experimental designs and sampling strategies (e.g. sample size). In fact, many more articles than those presented in Table 1 were found in the literature search, but reported information made us assume that breed comparisons were biased by systematic, non-genetic factors. Also, the number of dairy and particularly beef breeds evaluated so far is still comparatively small. Genetic differences among breeds in the response to *N. caninum* infection must be confirmed in experiments specifically designed to test this hypothesis. On the other hand, information emerging from better-designed experiments regarding the risk of abortion is more conclusive and suggests that there is indeed genetic variability between cattle breeds. Those experimental results are presented below. However, it remains to be demonstrated whether the genetic variability in the risk of abortion is linked to the risk of infection.

Within breeds

There are very few published experiments evaluating the genetic variability of resistance to *N. caninum* infection within breeds. Pan et al. (2004) estimated the heritability of susceptibility to *N. caninum* in 125 Holstein herds (9723 cows) from Ontario (Canada) with a mean antibody prevalence of 11.2%. The best statistical model for the estimation of heritability of susceptibility was the one including direct and maternal genetic effects, with heritability estimates of 0.094 and 0.257, respectively. It is worth noting that the experiment of Pan et al. (2004) is the only one among all those that considered seroprevalence and were included in this review that addressed the issue of routes of transmission. The detected vertical transmission rate was 40.7%, whereas horizontal transmission was only 6.7%. These results are consistent with the heritability estimations. Estimated maternal heritability was much higher than direct heritability, implying that the epidemiological status of a heifer depended mostly on the status of her mother. In view of all these results, the authors concluded that management practices would be more effective than selection to control neosporosis in this breed.

Schwab et al. (2009) followed a candidate gene approach and found no association between *N. caninum* seropositivity and allele frequency of two Class II genes of the major histocompatibility complex (BoLA), DRB3 and DQA1 in Canadian Holstein cattle. However, two alleles of DRB3 were significantly associated with the risk of abortion, independent of the serological status.

Freitas et al. (2021) also conducted a traditional candidate gene analysis in a local Brazilian breed (Curraleiro Pê-Duro). Thirteen candidate genes of immune response

were evaluated. The serological status against *N. caninum* was significantly associated with Single Nucleotide Polymorphisms (SNP) in genes such as *IL10*, *TLR2* and *TLR10*.

Twomey et al. (2019) conducted the only genome-wide association study (GWAS) of susceptibility to *N. caninum* reported so far. A total of 4597 females from dairy farms in Ireland were genotyped with different medium and high-density SNP panels and then imputed to whole-genome sequence. It is worth noting that in this comprehensive study the mean breed composition of the females included in the analysis was 84% Holstein–Friesian, 9% Jersey and 7% from other (undisclosed) breeds. Eight genomic regions on seven chromosomes were significantly associated with antibody response. Two important results of this study were firstly that none of the positional candidates in the most significant regions corresponded to conspicuous genes of the immune response, suggesting that novel metabolic pathways might be involved in this specific host–parasite interaction. Secondly, the favorable alleles in each of seven out of eight QTL were at very low frequency in the studied population. Moreover, the two most significant markers, which mapped to BTA25 and BTA21 respectively, resulted non-significant when only purebred Holstein cows were considered in the analysis. This result is relevant because it suggests that there are resistance alleles segregating in cattle, but many of them are at very low frequency in Holsteins, which is the most popular breed for milk production worldwide.

GENETIC VARIABILITY IN CATTLE BREEDS FOR THE RISK OF ABORTION CAUSED BY THE INFECTION WITH *N. CANINUM*

Even when neosporosis is the main cause of abortions in cattle, not all infected cows abort. The biological processes involved in the infection of a female and subsequent abortion are not fully clear. Epidemiological information about *N. caninum* infection collected from many different studies indicates that the gestation of an infected female has three possible outcomes: the born of an infected calf (the most frequent situation), the born of an uninfected calf or an abortion. Apart from the efficacy of maternal and foetal immune responses, the outcome of the infection would depend on factors such as parasite virulence and route of transmission (vertical or horizontal), type of infection (primary infection, recrudescence), stage of gestation and in experimental infections, even the source of the parasite and number of passages during in vitro culture (Benavides et al., 2014).

It could be hypothesized that different genetic processes are involved in vertical and horizontal transmission from natural infections that are not manifested in experimental infections. More importantly,

experimental infections are conducted under controlled conditions that minimize the influence of environmental variables that could mask real processes of resistance/susceptibility. In persistently infected females, recrudescence of infection during gestation can also occur due to immunosuppression originated by changes in hormonal profiles. Therefore, in either natural or experimental infections a parasite in different developmental stages may interact with varied cell types of the host and it would be important to consider both groups of studies when analyzing the genetic response of the host.

Experimental infection

In most experimental infections, the parasite is inoculated directly into the blood stream (see Table 2). Gene expression analyses could provide information about parasite–host interactions under particular, well defined physiological conditions. So far, a limited number of experiments addressing differential gene expression after infection have been reported, and none of them included breed comparisons. For example, García-Sánchez et al. (2019) evaluated gene expression in monocyte-derived macrophages that were differentiated in vitro and infected with either high-virulence or low-virulence strains. The gene expression profile of macrophages was modified by the virulence of the parasite strain. Horcajo et al. (2023) conducted a differential gene expression analysis in placentas from heifers infected with the same strains used by García-Sánchez et al. (2019). Gene expression differed between parasite strains and also between caruncle samples (maternal tissue) and cotyledon samples (foetal tissue, also influenced by the genome of the sire). An important conclusion of this study was that the maternal side of the placenta would be more relevant in defining the outcome of the infection.

The experiments that evaluated abortion events under experimental infections with *N. caninum* involved cattle breeds from both beef and dairy types (Table 2); however, comparatively few breeds have been considered so far and there is a clear predominance of two of the most popular breeds worldwide for beef and milk production (Angus and Holstein respectively). Due to the complexity of this kind of experiments, they all included one single breed and small sample sizes. Moreover, there are marked differences among experiments in what regards to the parasite strain, dose, route and timing of infection. First gestation heifers was largely the most frequent category across experiments. Although there were 13 different *N. caninum* strains involved, the most frequently used strain was NC1, followed by NC-Liverpool and NC-Spain7, whereas several strains were evaluated in only one experiment each. Very few experiments evaluated infections in the last third of gestation, whereas infections in early gestation and mid-gestation were evenly

TABLE 2 Abortion rates of pregnant females from different genetic groups in experimental infections with *Neospora caninum*.

| Breed | n | NC strain | Route of infection | Dose | Category | Timing ^a | Abortion rate ^b (%) | Group ^d | Reference |
|--------------------------------|----|--------------------------|--|--|----------|---------------------|--------------------------------|--------------------|----------------------------|
| Jersey | 3 | NC-1, NC-2, NC-3 (mixed) | Subcutaneous Intramuscular (combined) | 2.6×10^7 | Cows | E | 66 (2/3) | – | Dubey et al. (1992) |
| Beef | 2 | BPA-1 | Intravenous, intramuscular (combined) | 8×10^6 | Heifers | M | 0 | 4 | Conrad et al. (1993) |
| Simmental-cross | 2 | BPA-1 | Intravenous, intramuscular (combined) | 8×10^6 | Heifers | E | 0 | – | Barr et al. (1994) |
| | 2 | BPA-1 | Intramuscular in utero | $0.5\text{--}1 \times 10^6$ | Heifers | M | 100 (2/2) | – | |
| | 4 | BPA-1 | Intravenous, intramuscular (combined) | 8×10^6 | Heifers | M | 25 (1/4) | – | |
| Holstein | 6 | NC-Liverpool | Intravenous | 1×10^7 | Heifers | E | 83 (5/6) | 1 | Williams et al. (2000) |
| | 6 | NC-Liverpool | Intravenous | 1×10^7 | Heifers | L | 0 | – | |
| Beef | 5 | BPA-1 | Intravenous, intramuscular (both/animal) | 8×10^7 | Heifers | M | 0 | 4 | Andrianarivo et al. (2001) |
| Holstein | 6 | NC-1 | Subcutaneous | 5×10^8 | Heifers | M | 0 | 3 | Innes et al. (2001) |
| Hereford-Friesian | 3 | NC-Liverpool | Oral | 600 oocysts | Cows | E | 0 | – | Trees et al. (2002) |
| Angus | 4 | NC-Illinois | Intravenous | 1×10^7 | Heifers | M | 0 | 4 | Almeria et al. (2003) |
| Holstein | 14 | NC-1 | Subcutaneous | 1×10^7 – 5×10^8 | Cows | M | 0 | 3 | Maley et al. (2003) |
| Holstein | 4 | NC-Liverpool | Intravenous | 1×10^7 | Cows | E | 100 (4/4) | 1 | Williams et al. (2003) |
| Beef | 3 | NC-2 | Oral | 1500 oocysts | Cows | M | 0 | 4 | Gondim et al. (2004) |
| | 14 | NC-Beef | Oral | 1500; 15000, 41 000; 70 000 oocysts (3, 4, 4 and 3 cows, respectively) | Cows | E | 7 (1/14) | 3 | |
| Holstein | 8 | NC-1 | Intravenous | 5×10^8 | Cows | E | 75 (6/8) | 1 | Macaldowie et al. (2004) |
| | 8 | NC-1 | Subcutaneous | 5×10^8 | Cows | E | 38 (3/8) | 1 | |
| Angus, Hereford and crossbreds | 10 | NC-1 | Conjunctival | 1×10^8 | Heifers | M | 0 | 4 | de Yaniz et al. (2007) |
| | 9 | NC-1 | Intravenous | 1×10^8 | Heifers | M | 0 | 4 | |
| Holstein | 6 | NC-Liverpool | Oral | 40000 oocysts | Heifers | E | 0 | 1 | McCann et al. (2007) |
| | 6 | NC-Liverpool | Oral | 40000 oocysts | Heifers | M | 17 (1/6) | 3 | |
| | 6 | NC-Liverpool | Oral | 40000 oocysts | Heifers | L | 17 (1/6) | – | |
| Holstein | 6 | NC-Liverpool | Intravenous | 1×10^7 | Heifers | E | 83 (5/6) | 1 | Williams et al. (2007) |

TABLE 2 (Continued)

| Breed | n | NC strain | Route of infection | Dose | Category | Timing ^a | Abortion rate ^b (%) | Group ^d | Reference |
|--------------------|----|----------------|---------------------------|-----------------------|----------|---------------------|--------------------------------|--------------------|--------------------------------|
| Asturiana | 7 | NC-1 | Artificially spiked semen | 1 × 10 ² | Heifers | E | 43 (3/7) ^c | – | Serrano-Martinez et al. (2007) |
| | 8 | NC-1 | Artificially spiked semen | 1 × 10 ³ | Heifers | E | 12 (1/8) ^c | – | |
| | 9 | NC-1 | Artificially spiked semen | 1 × 10 ⁴ | Heifers | E | 11 (1/9) ^c | – | |
| | 5 | NC-1 | Artificially spiked semen | 1 × 10 ⁵ | Heifers | E | 0 ^c | – | |
| Holstein | 6 | NC-Livepool | Intravenous | 1 × 10 ⁷ | Heifers | E | 100 (6/6) | 1 | Gibney et al. (2008) |
| | 6 | NC-Livepool | Intravenous | 1 × 10 ⁷ | Heifers | L | 0 | – | |
| Holstein | 5 | NC-1 | Intravenous | 1 × 10 ⁷ | Heifers | E | 60 (3/5) | 1 | Rojo-Montejo et al. (2009) |
| | 5 | NC-Spain 1H | Intravenous | 1 × 10 ⁷ | Heifers | E | 0 | 1 | |
| Angus | 8 | NC-Illinois | Intravenous | 1 × 10 ⁷ | Heifers | M | 12 (1/8) | 4 | Almeria et al. (2010) |
| Belgian Blue cross | 11 | NC-1 | Subcutaneous | 5 × 10 ⁸ | Heifers | L | 0 | – | Benavides et al. (2012) |
| Angus | 4 | NC-1 | Intravenous | 1 × 10 ⁸ | Heifers | E | 50 (2/4) | 2 | Caspe et al. (2012) |
| | 7 | NC-Spain 7 | Intravenous | 1 × 10 ⁸ | Heifers | E | 100 (7/7) | 2 | |
| Angus | 4 | NC-6 Argentina | Intravenous | 5 × 10 ⁷ | Cows | E | 25 (1/4) | 2 | Bacigalupe et al. (2013) |
| Angus | 8 | NC-1 | Intravenous | 4.7 × 10 ⁷ | Heifers | E | 0 | 2 | Hecker et al. (2013) |
| Holstein | 5 | NC-1 | Intravenous | 1 × 10 ⁷ | Heifers | E | 83 (5/6) | 1 | Rojo-Montejo et al. (2013) |
| | 4 | NC-1 | Intravenous | 4 × 10 ⁸ | Heifers | M | 25 (1/4) | 3 | |
| Hereford × Nelore | 7 | NC-1 | Intravenous | 1 × 10 ⁶ | Heifers | E | 71 (5/7) | 2 | Pereira et al. (2014) |
| Crossbreeds | 2 | NC-1 | Intravenous | 5 × 10 ⁸ | Cows | E | 100 (2/2) | – | Chryssafidis et al. (2014) |
| | 5 | NC-Bahia | Intravenous | 5 × 10 ⁸ | Cows | E | 20 (1/5) | – | |
| Angus | 2 | NC-1 | Intravenous | 2.5 × 10 ⁸ | Cows | M | 0 | 4 | Moore et al. (2014) |
| | 2 | NC-1 | Conjunctival | 2.5 × 10 ⁸ | Cows | M | 0 | 4 | |
| Holstein | 6 | NC-Spain7 | Intravenous | 1 × 10 ⁷ | Heifers | E | 100 (6/6) | 1 | Regidor-Cerrillo et al. (2014) |
| | 6 | NC-Spain8 | Intravenous | 1 × 10 ⁷ | Heifers | E | 100 (6/6) | 1 | |
| Friesian | 6 | NC-Spain7 | Intravenous | 1 × 10 ⁷ | Heifers | M | 50 (3/6) | 3 | Almeria et al. (2016) |
| Holstein | 6 | NC-Spain7 | Intravenous | 1 × 10 ⁷ | Heifers | M | 33 (2/6) | 3 | Mur-Novales et al. (2016) |
| Angus | 4 | NC-1 | Intravenous | 1 × 10 ⁸ | Cows | M | 0 | 4 | Dorsch et al. (2019) |
| | 9 | NC-Spain7 | Intravenous | 1 × 10 ⁷ | Heifers | M | 22 (2/9) | 4 | Jiménez Pelayo et al. (2019) |
| | 9 | NC-Spain1H | Intravenous | 1 × 10 ⁷ | Heifers | M | 0 | 4 | |

(Continues)

TABLE 2 (Continued)

| Breed | n | NC strain | Route of infection | Dose | Category | Timing ^a | Abortion rate ^b (%) | Group ^d | Reference |
|-----------|---|-----------|--------------------|---------------------|----------|---------------------|--------------------------------|--------------------|-----------------------|
| Asturiana | 6 | NC-Spain7 | Subcutaneous | 1 × 10 ⁵ | Heifers | M | 17 (1/6) | 4 | Vázquez et al. (2019) |
| | 6 | NC-Spain7 | Intravenous | 1 × 10 ⁷ | Heifers | M | 66 (4/6) | 4 | |
| | 6 | NC-Spain7 | Intravenous | 1 × 10 ⁵ | Heifers | M | 50 (3/6) | 4 | |
| | 6 | NC-Spain7 | Intravenous | 1 × 10 ³ | Heifers | M | 17 (1/6) | 4 | |
| | 5 | NC-Spain7 | Intravenous | 1 × 10 ² | Heifers | M | 40 (2/5) | 4 | |
| Angus | 4 | NC-1 | Intravenous | 1 × 10 ⁸ | Heifers | L | 0 | – | Hecker et al. (2022) |

^aInfections in early (E), mid (M) or late (L) gestation, respectively.

^bAbortion rates include dead fetuses found during necropsy.

^cIn this experiment, the analyzed trait was Pregnancy rate.

^dGroups defined for the estimation of the odds ratio of abortion between Holstein (cases) and beef cattle (controls) in early gestation (1. Holstein; 2. Beef cattle) and mid-gestation (3. Holstein; 4. Beef cattle).

distributed in the rest of the studies. Based on abortion rates presented in Table 2, we attempted to perform a very preliminary comparison between dairy and beef types. We estimated the odds ratio (OR) of abortion in Holstein females (“cases”; no crossbreds) and beef females (“controls”) in early gestation and mid-gestation, averaging across the other factors mentioned above. There was a higher risk of abortion in Holstein than in beef cattle in early gestation (OR = 6.39; 95% CI: 2.75–14.85; $p = 0.0001$), but not in mid-gestation (OR = 0.98; 95% CI: 0.37–2.60; $p = 0.96$). Interestingly, Holstein had a larger OR in early gestation, when a higher risk of abortion is expected under experimental infections. Although this result is very suggestive, it must be interpreted with caution. Neosporosis is not the only factor related to the risk of abortion in cattle (for a recent review see Mee, 2023). Inbreeding of the calf, for example, could be particularly relevant in the case of a highly selected breed with a comparatively small effective population size (N_e) such as Holstein. Therefore, these preliminary odd ratios could probably be biased upwards. Moreover, there could be an advantage in survival of crossbred embryos compared to purebred embryos, regardless of *N. caninum* infection. Melendez et al. (2023) reported a significant difference in late embryo mortality (32–53 days of gestation) in Holstein cows bred with either Holstein or Limousin semen (15.2% and 9.8%, respectively), and this result was attributed to hybrid vigor in the crossbred calf.

Natural infection

Natural infection is caused by the ingestion of sporozoite-containing oocysts shed by a definitive host. Despite the inherent differences between beef and dairy production systems and their influence on the prevalence of *N. caninum* infections, the apparent advantage of beef breeds over dairy breeds led López-Gatius, Santolaria, et al. (2005) to conduct the first experiment aimed to evaluate the potential effects of crossbred gestations to decrease the risk of abortions derived from *N. caninum* infection. Mature, naturally infected Holstein cows were inseminated with semen from either Holstein, Limousin or Belgian Blue sires. Breed of the sire had a significant effect on abortion rates (34.6% for Holstein, 16.7% for Limousin and 21.7% for Belgian Blue, respectively) with a clear advantage of beef breeds. This finding was later confirmed by another study (López-Gatius, García-Ispierto, et al., 2005).

Another experiment with a similar objective evaluated 1115 pregnancies corresponding to Holstein cows inseminated with Holstein, Limousin, Belgian Blue, Piedmontese and Charolais sires (Almería et al., 2009). Cows were grouped according to *N. caninum* antibody titer (low, <30 relative index units and

high, ≥ 30 relative index units, respectively). Abortion rates were 32.2% and 15.2% for dairy and beef bulls, respectively. Among beef breeds, abortion rates were 9.9%, 19.9%, 22.4% and 19.1% for Limousin, Belgian Blue, Charolais and Piedmontese, respectively, but there were also significant interactions between sire breed and the *N. caninum* antibody titer of the cow. Taking as a reference the group with the lowest abortion rates (Limousin on low-titer cows, 2.1% abortion), the risk of abortion for low-titer cows was similar for Piedmontese and Charolais bulls, whereas it was higher than the reference with Belgian Blue (OR = 7.2) or Holstein bulls (OR = 17.9). Among high-titer cows, the OR compared to the same reference was 37.8, 30.0, 21.1, 15.3 and 8.9 for Piedmontese, Holstein, Belgian Blue, Charolais and Limousin bulls, respectively. In view of these results, it was proposed that placental function is improved in crossbred pregnancies; among other factors, probably because they have higher levels of Pregnancy-associated glycoproteins (PAGs) (Serrano et al., 2009; Zoli et al., 1992); also, the magnitude of the effect would be proportional to the genetic distance (lower degree of genetic similarity) between the breeds involved. PAG-1 has a protective effect on pregnancy and is considered a marker of fetal/placental wellbeing (Patel et al., 1997).

An interesting feature of PAGs, that provides indirect evidence about the existence of genetic variability of foetal wellbeing and reproductive success and could be important in the case of gestating infected females, arises from the experiment reported by López-Gatius, Garbayo, et al. (2007), who analyzed PAG-1 levels in early gestation of Holstein cows. Not only cow PAG-1 mean plasma concentrations were negatively correlated with milk production, but there were also significant differences in cow PAG-1 levels among the 10 sires used for the A.I., indicating that the sire's genotype was also involved to some extent in the definition of placental physiology. Yániz et al. (2010) also evaluated the effect of the paternal breed on the risk of abortion associated with *N. caninum* infection. In this experiment, abortion rates were 2.3% and 23.6% for seronegative and seropositive females, respectively. Limousin bulls reduced the risk of abortion 7.4 and 4.8 times in heifers and cows, respectively when compared to Holstein, whereas in the case of Belgian Blue sires the risk in cows was 3.0 times lower.

It is worth noting that in the previously mentioned experiment and also in the one reported by Almería et al. (2009), the sires belonged to breeds commonly used in Continental Europe but they are not fully representative of other breeds that are very popular worldwide (e.g. British breeds). Also relevant is that Limousin appears as comparatively more resistant breed in terms of both infection (Armengol et al., 2007) and risk of abortion. In fact, Almería and López-Gatius (2013) recommended this breed in particular as part of a package

of proven management practices for the control of bovine neosporosis. The relative advantage of crossbred pregnancies in relation to the risk of abortion has been justified by a protective effect of higher levels of PAG-1 that raise the threshold to the inflammation process triggered by the production of Interferon-gamma (*IFN- γ*) (Almería et al., 2017; López-Gatius, Almería, et al., 2007; Serrano-Pérez et al., 2014). Interferon-gamma (*IFN- γ*) has been attributed a protective role against abortion in *N. caninum* infected cows. In fact, in the experiment of López-Gatius, Almería, et al. (2007) there were no differences in the risk of abortion between seronegative Holstein cows not producing *IFN- γ* and seropositive cows that produced *IFN- γ* , whereas seropositive cows not producing *IFN- γ* had a risk of abortion 15.6 times higher. On the other side, high production of *IFN- γ* could trigger a pro-inflammatory response that is detrimental for the pregnancy, and this is why there is a relevant role of PAG-1.

With the same rationale underlying breed replacement experiments, research was extended to the evaluation of hormonal parameters during gestation. Santolaria et al. (2011) evaluated gestations in adult naturally infected cows; Holstein cows were inseminated with either Holstein or Limousin semen whereas Rubia Gallega cows were inseminated with semen from the same breed. Differences in humoral mechanisms against *N. caninum* infection and abortion were detected between purebred and crossbred gestations. Purebred, non-aborting Rubia Gallega cows had higher IgG1 and IgG2 antibodies through gestation than the other females. Purebred Holstein gestations showed the lowest values whereas crossbred gestations had intermediate values.

The breed of sire replacement strategy described above, which proved to be efficient for the amelioration of the effects of *N. caninum* infections in Spanish dairy farms was replicated in Italy and Argentina with contrasting results. Sala et al. (2018) described a 5-year program that effectively reduced prevalence and abortion rate in Holstein cows by using beef-breed semen on seropositive females, even when culling of positive cows was not deliberately practiced. Unfortunately, the breed of the sires was not specified.

A similar management scheme was deployed in an Argentinean dairy farm with a history of abortions by *N. caninum* (Lagomarsino et al., 2019). In this case, Hereford bulls were used to breed seropositive crossbred females (Jersey, Holstein, Fleckvieh). Surprisingly, the probability of abortion of pregnant dairy females was higher (OR = 1.51; 95% CI: 1.0–2.2; $p = 0.03$) using Hereford bulls compared to dairy bulls.

Taken together, these results suggest that genetic distance and heterozygosity per se would not be the only cause of reduction in abortion rates in infected females as suggested by crossbreeding experiments such as those ones mentioned above, but rather that

there could be resistance alleles segregating in specific cattle breeds. Also, the influence of other complex genetic mechanisms in the placenta, such as genomic imprinting (parent-of-origin-specific allelic expression; Hanna, 2020) that could be relevant in crossbred pregnancies cannot be ruled out. García-Ispierto et al. (2015) evaluated endocrine patterns during gestation in non-infected and naturally infected females from four different treatments: Holstein cows bred to Holstein or Limousin bulls, Holstein cows that were recipients of transferred Rubia Gallega embryos and Rubia Gallega suckling cows mated to bulls of the same breed. Embryo transfer maximized the genetic distance between the mother and the foetus. Crossbred pregnancies (Limousin-Holstein and Rubia Gallega transferred embryos) showed significantly higher PAG-1 concentrations throughout gestation whereas the Rubia Gallega suckled cows had the lowest concentrations. On the other side, the latter group of cows had the highest concentrations of Prolactin, a cytokine-like hormone with immunostimulatory properties and proinflammatory effects. *N. caninum* infection influenced the endocrine pattern of PAG-2 and progesterone, but not PAG-1 and Prolactin.

CONCLUSIONS

Despite the lack of information in many areas of research in bovine neosporosis, particularly host-parasite interactions, the evidence reported here is encouraging, because it suggests that real differences in resistance/susceptibility among breeds exist, and that it would be worthwhile to continue the investigation of genetic mechanisms involved in the natural resistance of the intermediate host to infections by *N. caninum*. Research particularly designed for breed evaluation under controlled conditions that include experimental infections with *N. caninum* for example, would be very helpful on this regard. This future research could include not only experiments in vivo, but also in vitro models and associated studies such as gene expression. Also, as new results from both natural and experimental infections are reported that include properly described classification variables, they could be integrated into a meta-analysis to produce more conclusive information.

The use of beef breeds in matings with dairy females is a recommended management practice for the control of neosporosis. However, almost all the evidence on this regard comes from a rather limited group of breeds and therefore the list of evaluated breeds should be expanded. Moreover, in several countries crossbreeding with beef breeds is not a common practice of the dairy industry.

Genome-wide association studies are a first step for candidate gene prioritization and ultimately the identification of polymorphisms underlying genetic variability of

complex traits in animal production. This kind of studies are still scarce in the case of bovine neosporosis. It would be worthwhile to identify resistance alleles, in order to better understand the biology of host-parasite interactions in the course of infection, and to take advantage of them in breeding strategies.

In summary, we have presented an updated review about the genetic variability of cattle associated with the resistance against *N. caninum* infection. This information can be useful to identify new research alternatives (e.g. candidate gene analyses and metabolic pathway prioritization, analysis of genetic mechanisms of infection and genetic host/parasite interactions in intermediate hosts with different genetic background) and also to define novel strategies (e.g. crossbreeding strategies, selection of sire breeds, mating design in pure breeds) to deal with this major problem of animal production.

AUTHOR CONTRIBUTIONS

Anabella Dinon: Data curation; software; writing – original draft. **Franco Fiorani:** Writing – review and editing. **Lucía María Campero:** Data curation; writing – review and editing. **Dadín Prando Moore:** Funding acquisition; writing – review and editing. **Pablo Marcelo Corva:** Conceptualization; funding acquisition; methodology; writing – review and editing.

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CONFLICT OF INTEREST STATEMENT

The authors declare no competing interests.

DATA AVAILABILITY STATEMENT

The data that support this study are available on request from the corresponding author.

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