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Original Article

Heterologous antibody-based immunity in cattle naturally infected with *Ostertagia ostertagi* and *Haemonchus* sp.

Imunidade heteróloga baseada em anticorpos em bovinos naturalmente infectados por *Ostertagia ostertagi* e *Haemonchus* sp.

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Abstract

Heterologous antibody-mediated immunity was evaluated in cattle naturally infected with *Ostertagia ostertagi* (Oo) and *Haemonchus* sp. (Hp). Antibody responses were assessed using ovalbumin (OVA) as unrelated model antigen in three groups of eight heifers, matched for eggs per gram of feces (EPG) and allocated to independent, nematode-free pastures. Anti-OVA titers were determined in serum by ELISA. EPG counts and nematode genera were determined in feces using the modified McMaster technique and pooled cultures, respectively. All variables were analyzed using mixed models. One group was previously dewormed and considered the control (C) group. A second group was designated HO (90.4% Hp and 7.8% Oo). A third group was designated OH (19.6% Oo and 78.8% Hp). EPGs were absent in the C group, and no EPG differences were observed between the parasitized groups throughout the study. The OH group exhibited a lower anti-OVA titer peak compared with the C ($p = 0.015$) and HO ($p = 0.024$) groups. Moderate prevalences of Oo may reduce heterologous antibody peaks without affecting the overall curve, whereas high prevalences of Hp may not alter heterologous antibody-based responses in cattle.

Keywords: Gastrointestinal nematodiosis, antibody immune response.

Resumo

A imunidade heteróloga mediada por anticorpos foi avaliada em bovinos naturalmente infectados por *Ostertagia ostertagi* (Oo) e *Haemonchus* sp. (Hp). As respostas de anticorpos foram analisadas utilizando a ovalbumina (OVA) como antígeno modelo não relacionado em três grupos de oito novilhas, pareadas pelo número de ovos por grama de fezes (OPG) e alocadas em pastagens independentes e livres de nematódeos. Os títulos anti-OVA foram determinados no soro por ELISA. As contagens de OPG e os gêneros de nematódeos foram determinados em fezes pela técnica de McMaster modificada e por culturas agrupadas, respectivamente. Todas as variáveis foram analisadas utilizando modelos mistos. Um grupo foi previamente tratado com antihelmíntico e considerado como grupo controle (C). Um segundo grupo foi designado HO (90.4% Hp e 7.8% Oo). Um terceiro grupo foi designado OH (19.6% Oo e 78.8% Hp). Os OPGs estavam ausentes no grupo C, e não foram observadas diferenças de OPG entre os grupos parasitados ao longo do estudo. O grupo OH apresentou um pico de título anti-OVA inferior em comparação com os grupos C ($p = 0.015$) e HO ($p = 0.024$). Prevalências moderadas de Oo podem reduzir picos de anticorpos heterólogos sem afetar a curva global, enquanto prevalências elevadas de Hp podem não alterar as respostas imunológicas mediadas por anticorpos em bovinos.

Palavras-chave: Nematodiose gastrointestinal, resposta imune por anticorpos.

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Introduction

Gastrointestinal nematodiasis (GIN) is one of the most significant causes of production losses in growing grazing cattle. Gastroenteritis caused by nematode infections leads to reduced feed intake, impaired nutrient assimilation, hypoproteinemia, and anemia. These disruptions cause reduced weight gain, decreased carcass quality, lower milk production, and impaired fertility (Craig, 2018). Cattle become infected by grazing on pastures contaminated with nematode larvae, which develop into adult worms in the host's gastrointestinal tract. Adult worms shed eggs in the feces, which release larvae onto the pasture, and reinitiate the cycle when larvae are ingested by cattle. The count of nematode eggs per gram (EPG) of feces is positively correlated with adult worm burdens in young cattle; therefore, EPG monitoring is useful for determining the need for anthelmintic treatment (Sabatini et al., 2023).

Natural nematode infections in cattle are usually composed of multiple genera, with *Ostertagia ostertagi* (Oo) and *Haemonchus* sp. (Hp) being the most pathogenic, and responsible for the greatest productive losses worldwide (Myers & Taylor, 1989; Fávero et al., 2016; Charlier et al., 2023). Genus prevalences depend largely on climate: Hp is more prevalent in tropical regions, whereas Oo is well adapted to colder climates. However, a variable mix of both genera can be present in transitional temperate regions such as Córdoba Province in Argentina, particularly in the autumn (Nari & Fiel, 2013, Suárez et al., 2013). Even within the same region and season, the relative prevalence of Oo and Hp also varies according to the anthelmintic resistance profile of the herd or farm (Cristel et al., 2017; Craig, 2018). This highlights the importance of herd monitoring based not only on EPG counts but also on genus identification methods.

Extensive evidence supports GIN-induced immunomodulation in several mammalian species (van Riet et al., 2007; Zander & Butler, 2013; Wait et al., 2020), but data in cattle remain limited. The pathogenicity of a nematode genus is defined by the severity of the induced disease, and its ability to hinder the development of homologous immunity by the host (Gasbarre, 1997). Although cattle develop immunity to most genera by approximately 12 months of age, older cattle retain some level of susceptibility to Oo (Craig, 2018). Given the reduction in lymphoblastogenesis caused by Oo (Cross et al., 1986; Snider et al., 1986; Gómez-Muñoz et al., 2004), this nematode could modulate the bovine immune system to promote its own persistence (Gasbarre, 1997; Boschiero et al., 2025). Oo infections have been reported to elicit broad, nonspecific stimulation of T-helper (Th) cell responses, which may contribute to T-cell exhaustion and immune evasion by the parasite (Boschiero et al., 2025).

Some evidence suggests that Oo infections may reduce heterologous humoral immunity (i.e., immunity against non-helminth antigens) (Mansour et al., 1991, 1992), but no information is available regarding the effect of haemonchosis on bovine immnunity. As with many GINs, ovine haemonchosis skews host´s immune system toward Th2 responses, increasing antibody-mediated mechanisms (Gill et al., 2000, García-bernalt Diego et al., 2025). Therefore, Oo and Hp infections could alter the antibody response and efficacy of inactivated vaccines. Considering the widespread use of these vaccines and their reliance on antibody-mediated immunity (Yao et al., 2023), this overall issue may pose implications for cattle health. The rising prevalence of anthelmintic resistance emphasizes the matter even further, as it heightens the risk of helminthic persistence despite anthelmintic treatment (Craig, 2018). Nevertheless, information regarding effects of ostertagiosis on heterologous bovine immunity is scarce, and there is a knowledge gap about effects of pure Hp and combined Oo-Hp infections. Therefore, this study evaluated the heterologous antibody-based immunity in cattle naturally infected with high prevalences of Hp and varying prevalences of Oo.

Material and Methods

Grazing groups and natural infection

The study was conducted between April and September 2019 at the EEA INTA Marcos Juarez in Córdoba Province, Argentina. All procedures complied with the animal welfare guidelines established by the Institutional Committee for the Care and Use of Experimental Animals at INTA (Protocol E01-19.2017-741). Sixty 7-month-old Aberdeen Angus × Charolais female calves from the same cohort were randomly assigned to one of three groups of 20. During April and May, the three groups grazed on two independent alfalfa pastures: a first group and a second group were placed with the male calves from the same cohort as the females included in this study, whereas a third group was placed in a pasture grazed by and shared with yearling cattle. In June, 8 heifers from each group were homogeneously selected based on their EPG values and assigned to separate, parasitologically clean 2-ha *Triticosecale aestivum* plots. The day on which calves were introduced to these plots was designated as Day 0. Forage

availability was homogeneous across these plots, being subdivided into 10 subplots for rotational grazing. The animals grazed each subplot for 12 days, and alfalfa hay was supplemented *ad libitum*. The prevalence of nematode genera was determined at Day -15, revealing a clear predominance of Oo and Hp across all three groups. At Day -3, the first group was treated subcutaneously with levamisole (7.5 mg/kg, Fosfamisol®, Biogenesis Bagó, Argentina) and moxidectin (0.2 mg/kg, Cydectin Alfa®, Fort Dodge, USA), so was called Control (C) group. The second group was called HO after the higher prevalence of Hp and lower prevalence of Oo. The third group was called OH after the higher prevalence of Oo and lower prevalence of Hp. Instead of anthelmintic treatment, OH and HO groups received 18 ml of a saline solution subcutaneously, maintaining their original parasite burdens. Daily inspections were conducted to detect any signs of diarrhea or ill-thrift.

Ovoalbumin inmunization

To evaluate the antibody-based response, the animals were subcutaneously inoculated twice with 4 mL of an ovoalbumin (OVA, albumin from chicken egg, grade II, Sigma Aldrich ®, Germany) emulsion, and serum anti-OVA antibodies were quantified. The emulsion was prepared by dissolving OVA in sterile PBS at a 2:1 (mg/mL) ratio, then diluting it 1:1 (vol/vol) in MONTANIDE ISA 50 V2 oil adjuvant. The oil phase was stirred on ice, and the aqueous phase was added drop by drop. A pre-emulsion was generated by stirring for 1 hour, after which an IKA Ultra-Turrax® T 25 digital homogenizer was used at 20,000 rpm for 5 minutes to create the final emulsion. A drop test was performed to verify proper emulsification. The first OVA inoculation was administered on the day the animals were introduced to the *Triticosecale* plots, which was designated as Day 0. The second OVA inoculation was carried out on Day 30 of the study.

Fecal and blood sampling

Rectal fecal samples were collected on days -15, 0, 15, 30, 45, 60, 90, and 120 to determine EPG of feces and identify helminth genera. Blood samples were collected via jugular puncture on Days 0, 30, 37, 45, 60, 90, and 120 to determine serum anti-OVA titers, total proteins, albumin, and globulins.

Fecal determinations

EPG were determined using the modified McMaster technique (Roberts & O'Sullivan, 1950). Briefly, 3 g of fecal sample were mixed with 57 ml of a 17% sodium chloride solution. After 1.5 minutes of shaking with a hand mixer, 3 ml of the mixture were extracted and placed in an egg-counting slide containing four 0.75-ml chambers. Trichostrongylid eggs were counted in the four chambers under an optical microscope at 6.3× magnification and then multiplied by 10.

The relative frequency of nematode genera in feces was determined through pooled fecal larval cultures (Steffan et al., 1989) and visual identification of L3 larvae. Fecal cultures were prepared by mixing 24 g of pooled feces (3 g × 8 animals) from each grazing group with 5 g of polystyrene pellets in plastic cups suspended over another cup containing water, and then incubated at 25 °C for 10 days. Larvae were retrieved according to Baermann's principle. One hundred larvae were counted and identified per grazing group and sampling day, and the relative frequency of each genus was calculated.

Anti-OVA ELISA

Serum anti-OVA titers were measured by ELISA (Hanlon et al., 1994) according to the following procedure. Using 2 HB plates, 1 µg of OVA was added per well in CO_3^{2-}/HCO_3^- capture buffer (pH = 9.6) with a final volume of 100 µL, incubated overnight at 4 °C. Before plating the samples, the plates were washed 4 times with 0.05% phosphate buffered saline-Tween 20 (PBS-T20), blocked with 100 µL of 10% milk in 0.05% PBS-T20 for 1 hour at room temperature, and then washed 4 times with 0.05% PBS-T20.

Serum samples were plated at their corresponding dilutions in 0.05% PBS-T20, with a final volume of 100 µL per well. Incubation was performed for 1 hour at room temperature, followed by 4 washes with 0.05% PBS-T20. Next, 100 µL of conjugated antibody (Peroxidase AffiniPure Goat Anti-Bovine IgG, Jackson Lab) was added to a solution of 10% milk in 0.05% PBS-T20, followed by another 1-hour incubation and 4 additional washes. Finally, 100 µL of TMB in commercial developer solution was added, incubated for 10 minutes, and blocked with 100 µL of H_2SO_4 (12 M). Colorimetric readings were performed using an ELx800 spectrophotometer (BioTek Instruments,

USA). The titer for each sample was determined by the highest dilution with an optical density (OD) reading above 0.05. This cutoff value was obtained from the mean serum OD of sixty calves not exposed to OVA, plus three times the standard deviation.

Serum protein determinations

Total serum proteins were determined by spectrophotometric reading at 540 nm using a mixture of 50 µl EDTA–copper reagent and 3.5 ml of serum (Lubran, 1978). Serum albumin was determined by spectrophotometric reading at 625 nm using a mixture of 2.5 ml bromocresol green solution and 10 µl of serum (Webster et al., 1974). Serum globulins were calculated as the difference between total serum proteins and serum albumin.

Statistical analyses

Statistical analyses were conducted using the R software (version 4.1.3). The prevalence of Oo and Hp by grazing group was analyzed using mixed models with sampling day as random effect and grazing group as fixed. EPGs and anti-OVA titers were analyzed using generalized mixed models assuming a negative binomial distribution with a logarithmic link function. Serum protein concentrations were analyzed using mixed models. EPG, anti-OVA titers and serum proteins were modeled using animals as random effects, and sampling days, grazing groups, and their interactions as fixed effects. The effect of grazing group on the areas under the curve (AUC) of anti-OVA titers were analyzed by an ANOVA. AUCs were square root converted to meet normality assumption.

In all cases, mean multiple comparisons were performed using Tukey's tests, and statistical significance was considered at $p < 0.05$.

Results

There were no differences in EPG among groups before anthelmintic treatment on Day -15. Following treatment, EPG in the C group were absent, and no significant differences were observed between the EPGs of the infected groups (Figure 1).

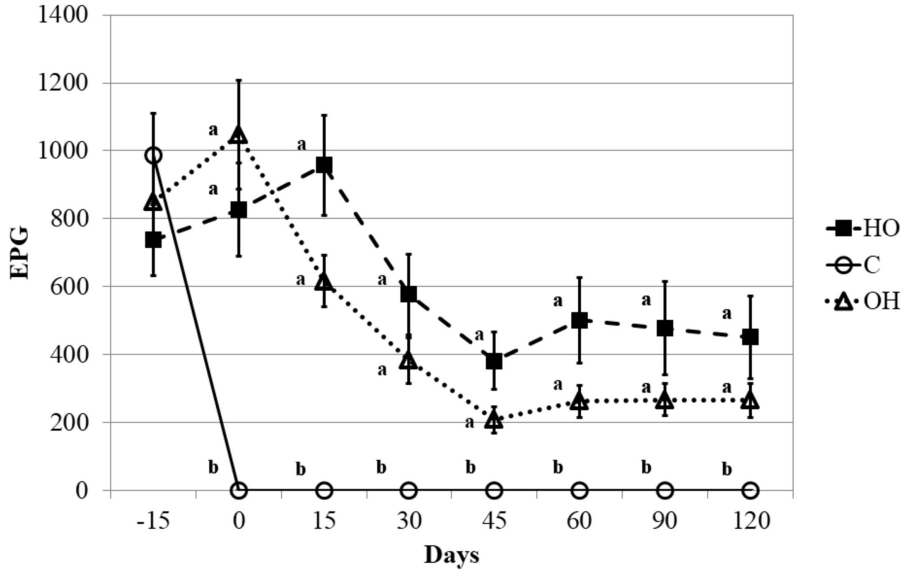

Figure 1. Eggs per gram (EPG) of feces in heifers naturally infected with *Ostertagia ostertagi* and *Haemonchus* sp. Values are means and standard errors. C: control. HO: 8% *Ostertagia*, 90% *Haemonchus*. OH: 20% *Ostertagia*, 80% *Haemonchus.* Different letters on the same day indicate significant differences (Tukey, $p<0.05$).

The average composition of genus profiles in the infected groups was predominantly Hp and Oo throughout the study (Figure 2). The Oo prevalence was statistically higher in the OH compared to the HO group, whereas the opposite pattern was observed for the Hp prevalence (Table 1).

Statistical differences in the anti-OVA response were observed only at the titer peaks, i.e., on day 45 of the study. The OH group exhibited a lower anti-OVA titer peak compared with the C (95% CI for C/OH ratio: 1.2-10.1; p = 0.015) and HO (95% CI for HO/OH ratio: 1.1-9.7; p = 0.024) groups, whereas no differences were detected between the latter two groups (Figure 3). Grazing group tended to affect the overall AUC of the anti-OVA titers (p = 0.092).

Although total serum protein concentrations increased over time across all groups (p < 0.001), they remained within reference ranges (Kaneko et al., 2008). However, total protein levels were significantly lower in the OH group than in the C group on Day 45, and in the HO group on Day 30 (Figure 4). A significant interaction was observed between the grazing group and sampling day regarding albumin levels (p < 0.001), with albumin reductions in the OH group compared to the C group from Day 30 to 60, and in the HO group compared to the C group on Day 30 and 45 (Figure 5). The nematode profile had no significant effect on serum globulin levels (p = 0.178, Figure 6).

Discussion

Extensive evidence supports GIN-induced immunosuppression in several mammalian species (van Riet et al., 2007; Zander & Butler, 2013; Wait et al., 2020), but data in cattle remain limited and inconclusive. Thus, no reduction

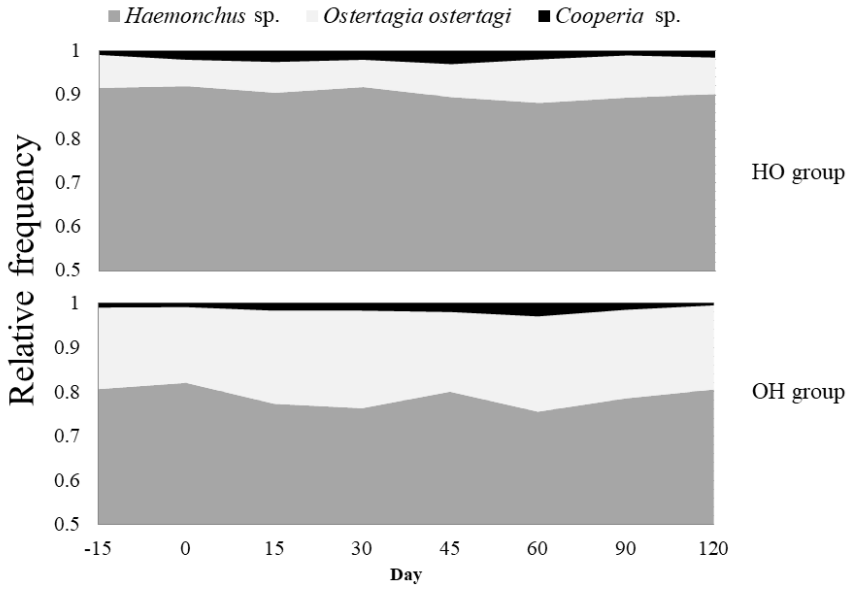

Figure 2. Relative frequency of gastrointestinal nematode genera by fecal larval culture in groups of naturally infected heifers.

Table 1. Relative prevalence (%) of *Haemonchus* sp. and *Ostertagia ostertagi* by fecal culture in grazing groups of heifers naturally infected throughout a 120-day trial. Different letters within the same column indicate significant differences (p<0.05) according to ANOVA.

Grazing group	*Haemonchus* sp. (%)		*Ostertagia ostertagi* (%)	
	Mean ± SD	95% CI	Mean ± SD	95% CI
OH	78.8 ± 2.3 b	77.3 - 80.4	19.6 ± 1.8 a	18.3 - 21.0
HO	90.4 ± 1.3 a	88.8 - 92.0	7.8 ± 1.4 b	6.4 - 9.1

SD = standard deviation; CI = confidence interval.

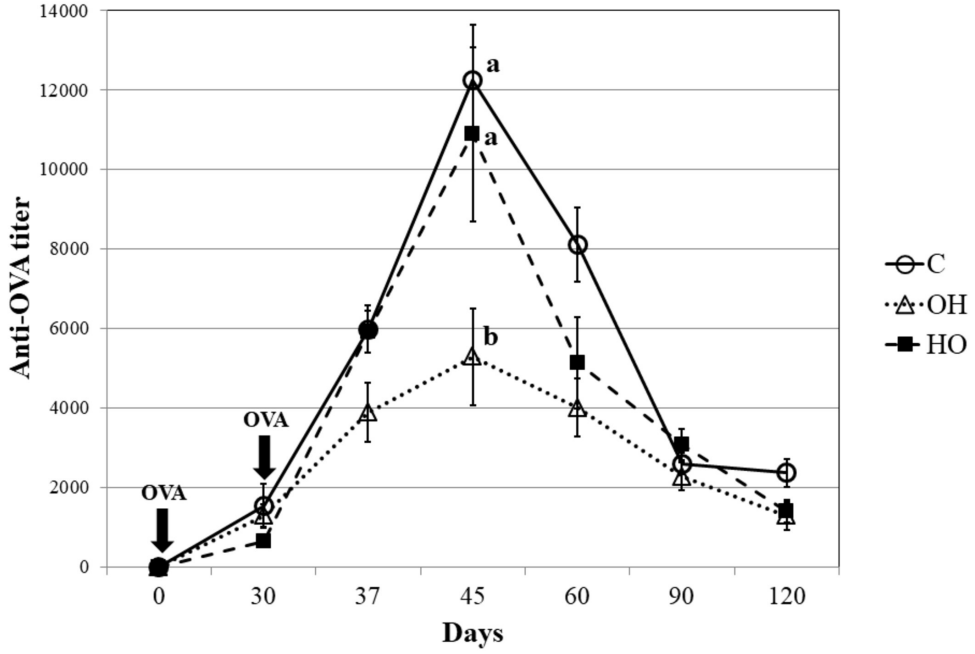

Figure 3. Serum anti-OVA titers in heifers naturally infected with *Ostertagia ostertagi* (Oo) and *Haemonchus* sp. (Hp) Values are means and standard errors. C: control. HO: 8% Oo, 90% Hp. OH: 20% Oo, 80% Hp. Different letters on the same day indicate statistically significant differences (Tukey, p<0.05).

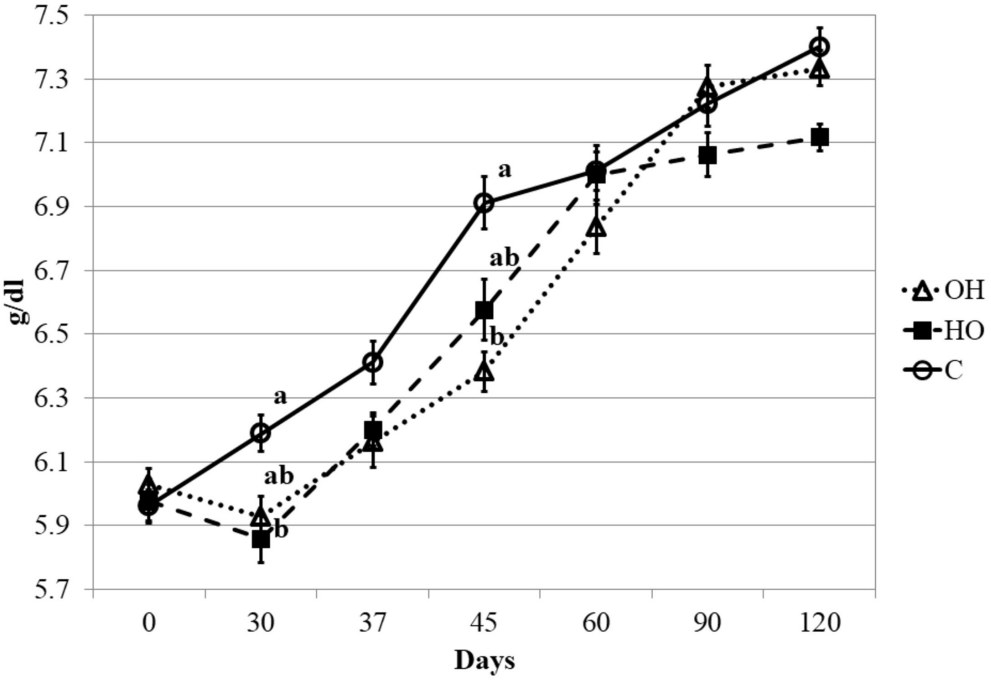

Figure 4. Total serum proteins in heifers naturally infected with *Ostertagia ostertagi* (Oo) and *Haemonchus* sp. (Hp) Values are means and standard errors. C: control. HO: 8% Oo, 90% Hp. OH: 20% Oo, 80% Hp. Different letters on the same day indicate statistically significant differences (Tukey, p<0.05).

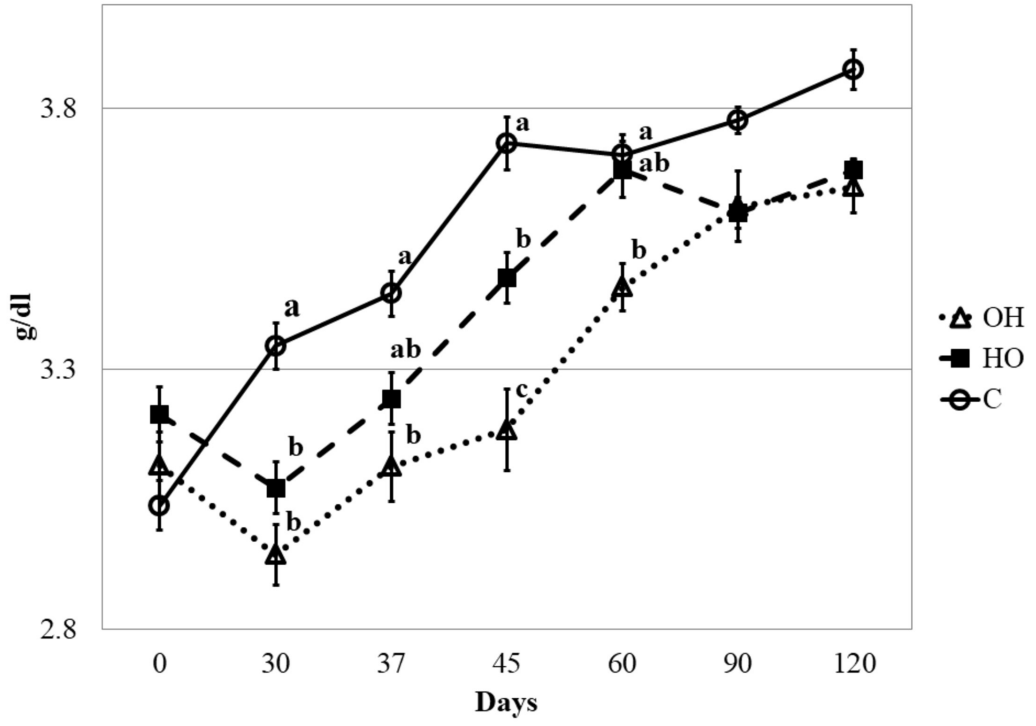

Figure 5. Serum albumin in heifers naturally infected with *Ostertagia ostertagi* (Oo) and *Haemonchus* sp. (Hp) Values are means and standard errors. C: control. HO: 8% Oo, 90% Hp. OH: 20% Oo, 80% Hp. Different letters on the same day indicate statistically significant differences (Tukey, $p<0.05$).

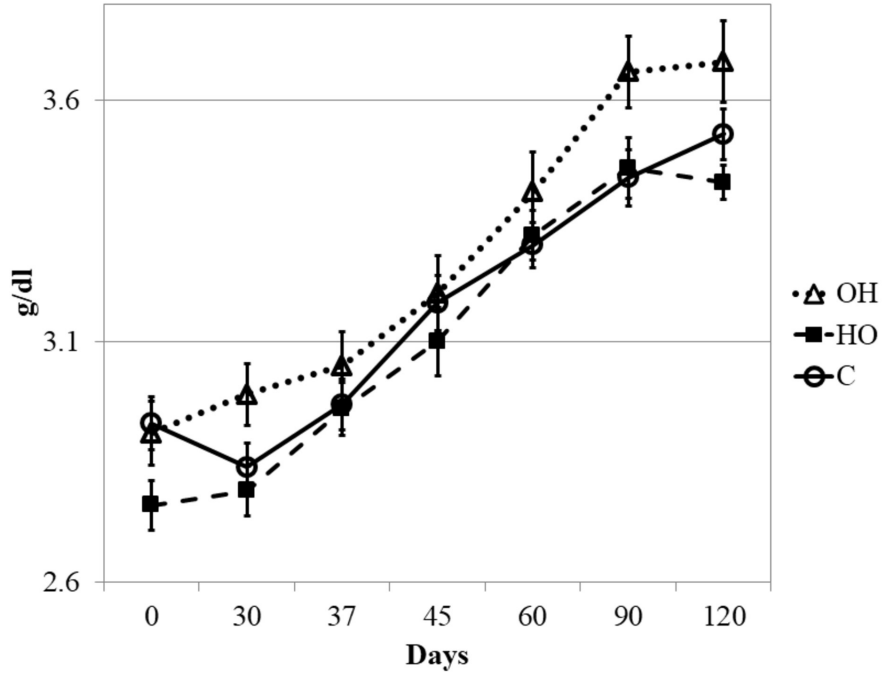

Figure 6. Serum globulins in heifers naturally infected with *Ostertagia ostertagi* (Oo) and *Haemonchus* sp. (Hp) Values are means and standard errors. C: control. HO: 8% Oo, 90% Hp. OH: 20% Oo, 80% Hp.

in anti-*Brucella* and anti-infectious bovine rhinotracheitis (IBR) virus titers was observed in calves artificially infected with Oo following vaccination with attenuated vaccines of these pathogens (Yang et al., 1993a, b). Similarly, no association was found between anti-*Ostertagia* serum antibodies and the antibody response to rabies vaccination (Charlier et al., 2013). On the other hand, and consistent with our findings in the OH group, reductions in the heterologous antibody response were observed in calves infected with Oo compared to uninfected animals (Wiggin & Gibbs, 1989; Mansour et al., 1991, 1992). It has been reported that Oo reduces lymphoblastogenesis (Snider et al., 1986) and induces exhaustion of both Th2 and Th1 responses (Boschiero et al., 2025), which may explain why our OH group exhibited a lower peak of anti-OVA titers.

In general, helminth infections tend to stimulate a Th2-type response, thereby enhancing antibody-based immunity. However, numerous factors may contribute to shifting host immunity toward a Th1 profile, to the detriment of antibody responses. Such factors include the helminth genus involved, infection stage, helminthic infective dose, concurrent helminth co-infections, the anatomical site of nematode infection, as well as the timing of helminth infection relative to immunization and subsequent evaluation of the immune response (García-bernalt Diego et al., 2025). Unfortunately, we cannot determine whether some of these factors contributed to our results.

Although immunomodulatory capacity of macrocyclic lactones is not clear, the immunostimulant properties of levamisole have been frequently reported (Sajid et al., 2006). Therefore, we cannot rule out the potential influence of the anthelmintic treatment in our C group. However, nearly all successful immunomodulatory protocols involve multiple doses of levamisole (Gholami et al., 2024) rather than a single administration, as in our study. Moreover, differences in antibody titers between our C and HO groups would have been evident if immunomodulation had occurred, but this was not the case. Ideally, levamisole or any anthelmintic should not have been used in the C group; nevertheless, this was not feasible due to the background of macrocyclic lactone and benzimidazole resistance in the herd.

In Argentina, warm weather is adverse for Oo larvae in pastures which leads to abomasal hypobiosis during late spring, resuming the life cycle in late summer (i.e., late February and March), being fully active during autumn, winter and early spring (March to September). The late development of immunity against Oo results in a significant amount of adult parasites emerging from hypobiosis, so most of EPG in yearling cattle comes from this genus (Suárez et al., 2013; Charlier et al., 2020). Accordingly, the higher prevalence of Oo in our OH group was attributed to their autumn grazing on pastures shared with, and previously grazed by, cattle over 1 year of age. Conversely to the low oviposition rate of Oo, the high oviposition of *Hp* results in overestimation of Hp burdens when these are estimated by EPG and fecal culture (Sabatini et al., 2023).

The prevalence of Oo varies throughout the year, being primarily determined by climatic conditions, host immunity, and cattle age. In the southeastern region of Córdoba Province, fecal cultures show peak prevalences of Oo during winter, ranging from 30 to 40% in growing cattle (Suárez et al., 2013). Accordingly, we consider the prevalence of nearly 20% in our OH group to be moderate. Nevertheless, a twofold increase in prevalence between our HO and OH groups was significant and sufficient to reduce the anti-OVA peak and albuminaemia. This demonstrates a more pronounced effect of Oo infection, despite the animals being predominantly infected with Hp. This scenario differs from studies designed to compare groups infected versus non-infected with Oo (i.e., 100% vs. 0% infection) (Wiggin & Gibbs, 1989; Yang et al., 1993a). However, the present study compared prevalences of 7.8% and 19.6% under field infection conditions, which are more representative of real-world situations.

The quality of this study is limited by the lack of adult worm counts and individual coprocultures. Our estimation of worm burdens based on EPG is hindered by the reduction in worm fertility as cattle develop immunity against gastrointestinal nematodes. Moreover, EPG shows a better correlation with adult burdens of Hp than those of Oo (Sabatini et al., 2023). Nevertheless, we provide insights into the immunological impact of natural GIN, as assessed through the most widely recommended and applied methodology in the field, i.e., individual EPG counts and pooled coprocultures over time (Sabatini et al., 2023).

Haemonchus sp. is better adapted to warm climates, so low temperatures of winter reduce larval survival in pastures. In Southeastern Córdoba Province, the highest prevalence of Hp was reported in summer and early fall (Suárez et al., 2013). Despite our study was conducted during fall and winter, the high prevalence of Hp is explained by the absence of reinfection in nematode-free pastures, which otherwise would have decreased its relative prevalence during winter. Despite the high EPGs from Hp, no effect on antibody response was observed in our HO group. Given the highest prevalence of Hp in this group, we suggest that Hp infections may not induce immunological interference to the same extent as Oo infections. However, this statement requires further evidence, as we found no references about the effects of Hp infections on heterologous antibody responses. Additionally,

since our animals were initially placed in nematode-free plots, we cannot determine whether the same effects would occur under continuous reinfection.

To prevent reduced weight gain, anthelmintic treatment is recommended for herds when their average EPG count exceeds 200 (Charlier et al., 2023; Sabatini et al., 2023). The initial average EPG of 800 and its persistence above 200 throughout our study, along with the reduction in serum protein levels, confirm that nematode infections in our infected groups ranged from moderate to severe. Cattle's immune response reduces oviposition and promotes the expulsion of adult worms; thus, following a single-dose infection with Oo or Hp, EPGs peak rapidly and then decline at a slower rate (Michel, 1969; Harness et al., 1971). Therefore, the EPG decrease in our infected groups following the cessation of reinfection aligns with the EPG dynamics previously described.

The upward trend in serum proteins across all groups may be partially explained by the same factors responsible for the reduction in EPGs, i.e., cessation of helminthic reinfection due to grazing on parasite-free pastures in all groups, effective anthelmintic treatment in the C group, and the development of immunity in the infected groups. The albuminemia reduction observed in the infected groups aligns with findings reported for *Oo* (Myers & Taylor, 1989) and Hp infections (Gennari et al., 1991) in cattle. Oo induces hypoalbuminemia through abomasitis and reduced feed intake (Charlier et al., 2020), whereas Hp causes it due to its hematophagous activity (Gennari et al., 1991) and dyspepsia (Rodrigues et al., 2024).

Conclusions

Moderate EPG counts combined with moderate prevalences of Oo may reduce the heterologous antibody peaks without altering the overall antibody curve in naturally infected cattle. Conversely, high prevalences of Hp may not affect the antibody-based responses in cattle. Further studies are required to clarify this issue.

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Data availability

The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics declaration

All procedures carried out during this experiment were approved by the INTA ethics committee for the use of animals (CICUAE) (protocol number E1-19, resol. 2017-741-APN-CRCRC-APN#INTA).

Conflict of interest

The authors have no competing interests to declare.

Author contributions

Damián Jesús Castro: writing - original draft preparation, methodology development, funding acquisition, project administration, formal analysis, and conceptualization. Diego Daniel González: methodology development. Carlos Augusto Margineda: writing - original draft preparation, methodology development, and conceptualization.

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