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Effects of vaccination against foot-and-mouth disease virus on reproductive performance of *Bos indicus* beef cows [1]

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ABSTRACT: This study compared reproductive performance of *Bos indicus* cows vaccinated against the foot-and-mouth-disease (**FMD**) virus prior to timed-AI or during early pregnancy (Exp. 1), as well as rectal temperature (**RT**) and plasma concentrations of the acute-phase protein haptoglobin in cattle vaccinated or not against the FMD virus (Exp. 2). Cattle utilized in Exp. 1 and 2 were originated from herds with no historical occurrences of FMD, and that received vaccination against the FMD virus biannually. In Exp. 1, 604 lactating, multiparous, non-pregnant Nelore cows were randomly assigned on d -31 of the experiment to receive: 1) **VACPRE** = vaccination against FMD virus on d -31 (n = 291), and 2) **VACGEST =** vaccination against FMD virus on d 30 (n = 313). From d -11 to 0, all cows were assigned to an estrus synchronization + timed-AI (d 0) protocol. Pregnancy status to AI was verified on d 30 and 90 via transrectal ultrasonography. A treatment × day interaction was detected ($P < 0.01$) for pregnancy rates to AI, which were similar ($P = 0.17$) between VACPRE and VACGEST on d 30 (61.8 vs. 56.2%, respectively; SEM = 2.8), but greater ($P < 0.01$) for VACPRE on d 90 (59.4 vs. 46.9%, respectively; SEM = 2.8). Pregnancy loss from d 30 to 90 was greater ($P < 0.01$) in VACGEST compared with VACPRE (16.5 vs. 3.9%, respectively; SEM = 2.2). In Exp. 2, 40 pregnant Nelore females (20 nulliparous and 20 multiparous cows; BCS = 4.73 ± 0.12) were ranked by parity and assigned to receive (**VAC**; n = 20) or not (**NOVAC**; n = 20) vaccination against FMD virus. Blood samples were collected and RT recorded prior to (h 0) and 24, 72, 120, and 168 h after treatment administration. Treatment × day interactions were detected ($P < 0.01$) for RT and plasma haptoglobin. The RT was greater ($P < 0.01$) in VAC compared with NOVAC at 24 h after treatment administration, and similar ($P \geq 0.31$) between treatments at all other sampling hours. Plasma haptoglobin concentration was similar ($P = 0.98$) between VAC and NOVAC prior to treatment administration ($P = 0.48$), and greater ($P < 0.01$) in VAC at 24,

72, 120, and 168 h after treatment administration. In summary, vaccinating *B. indicus* beef cows against FMD virus resulted in a 4-fold increase in pregnancy loss when the vaccine was administered 30 d after timed-AI compared with 31 d prior to timed-AI. These outcomes can be associated with inflammatory and acute-phase reactions elicited by the FMD vaccine, which are known to impair pregnancy maintenance in cattle.

Key Words: Acute-phase response, beef cattle, foot-and-mouth disease, inflammation, pregnancy loss

INTRODUCTION

Foot-and-mouth disease (**FMD**) is a severe, highly contagious viral disease that affects cloven-hoofed livestock species including cattle (Grubman and Baxt, 2004), and has been recognized as a major constraint to international trade in animals and animal products (Leforban, 1999). While FMD has been eradicated in North America and Western Europe, this disease is still endemic in Africa, South America, and Asia (USDA-APHIS, 2013). Vaccination against the FMD virus successfully reduced FMD outbreaks in many parts of the world (Brown, 1992; Kahn et al., 2002); therefore, vaccination is a common and often mandatory strategy used to mitigate FMD in endemic regions (Rodriguez and Gay, 2011).

Early pregnancy loss, particularly during the first trimester of gestation, is a major reproductive challenge in cow-calf systems (Humbolt, 2001). Hence, strategies to alleviate early pregnancy losses are warranted for optimal reproductive and overall efficiency of cow-calf operations. The majority of FMD vaccines used worldwide contain inactivated FMD virus serotypes and an oil-based adjuvant to elicit a greater immune protection to target antigens (Rodriguez and Grubman, 2009). In general, adjuvants elicit innate immune responses associated with antigen presentation to T cell lymphocytes, including inflammatory and acute-phase reactions (Tizard, 2004; Rodrigues et al., 2015) known to result in pregnancy losses in cattle (Hansen et al., 2004). Based on this rationale, we hypothesized that administration of a FMD vaccine during early pregnancy stimulates an acute-phase protein reaction and results in increased pregnancy loss in vaccinated cattle. To test this hypothesis, Exp. 1 compared reproductive performance of *Bos indicus* cows vaccinated against FMD virus prior to timed-AI or during early pregnancy, whereas Exp. 2 compared rectal temperature and plasma

concentrations of the acute-phase protein haptoglobin in cattle vaccinated or not against the FMD virus.

MATERIALS AND METHODS

Experiment 1 was conducted on a commercial cow-calf operation located in Miranda, MS, Brazil, and cattle were cared for in accordance with the practices outlined in the *Guide for the Care and Use of Agricultural Animals in Agricultural Research and Teaching* (FASS, 2010). Experiment 2 was conducted at the Universidade Federal do Mato Grosso do Sul, located in Terenos, MS, Brazil, and cattle were cared for in accordance with acceptable practices and experimental protocols reviewed and approved by the Universidade Federal do Mato Grosso do Sul - Animal Ethics Committee. Cattle utilized in Exp. 1 and 2 originated from herds with no historical occurrences of FMD, and that received vaccination against the FMD virus twice a year. In addition, all cattle utilized herein were vaccinated against FMD approximately 6 mo prior to the beginning of each experiment.

Experiment 1

Animals and treatments. A total of 604 lactating, multiparous, non-pregnant Nelore cows (approximately 65 to 95 d days post-partum; BCS = 3.85 ± 0.05 according to Wagner et al., 1988), maintained in 2 groups of 266 and 338 cows each, were assigned to the experiment (d -31 to d 90 relative to timed-AI). Groups were maintained in individual *Brachiaria brizanta* pastures with ad libitum access to water and a commercial mineral-vitamin mix (DSM Produtos Nutricionais Brasil, São Paulo, SP, Brazil), and independently assigned to experimental procedures 1 d apart. Within each group, cows were randomly assigned on d -31 of the experiment to receive: 1) **VACPRE** = vaccination against the FMD virus (5 mL s.c. of Ourovac Aftosa; Ourofino Saúde Animal, Cravinhos, SP, Brazil) on d -31 of the experiment (31 d prior to

timed-AI), and 2) **VACGEST** = vaccination against FMD virus (5 mL s.c. of Ourovac Aftosa; Ourofino Saúde Animal) on d 30 of the experiment (30 d after timed-AI).

On d -11, both groups were assigned to the same estrus synchronization + timed-AI protocol (Meneghetti et al, 2009; d -11 to 0). More specifically, cows received a 2 mg injection (i.m.) of estradiol benzoate (Gonadiol; Zoetis, São Paulo, SP, Brazil) and an intravaginal progesterone releasing device (**CIDR**, containing 1.9 g of progesterone; Zoetis) on d -11. On d -2, CIDR was removed, cows received a 12.5 mg injection (i.m.) of $PGF_{2\alpha}$ (Lutalyse; Zoetis), in addition to 0.6 mg injection (i.m.) of estradiol cypionate (ECP; Zoetis) and 300 IU injection (i.m.) of eCG (Novormon; Zoetis). On d 0, cows were assigned to timed-AI. All cows were inseminated with semen from a single sire. Within each group, cows were inseminated by 1 of 2 technicians, and the distribution of cows inseminated by each technician was equal within each treatment.

Sampling. Cow BCS (Wagner et al., 1988) was assessed at timed-AI on d 0. Pregnancy status to AI was verified on d 30 and 90 of the experiment by detecting a viable conceptus with transrectal ultrasonography (5.0-MHz transducer; Chison 600, Chison Medical Imaging Co., Ltd., Wuxi City, Jiang Su Province, China). Cows were not exposed to bulls or to additional AI services between timed-AI and pregnancy evaluation on d 30. On d 31, cows were exposed to mature bulls for 50 d (1:25 bull to cow ratio). Cows diagnosed as pregnant on d 30, and then non-pregnant or with an estimated conceptus age of ≤ 60 d on d 90 (Curran et al., 1986) were considered to have lost the AI pregnancy.

Statistical analysis. Quantitative and binary data were analyzed, respectively, with the MIXED and GLIMMIX procedures of SAS (SAS Inst., Inc.; version 9.3) and Satterthwaite approximation to determine the denominator df for the tests of fixed effects, using cow as the

experimental unit and cow(treatment × group) as random variable. The model statement used for analysis of cow BCS on d 0 and pregnancy loss contained the effects of treatment, group, and the resultant interaction. The model statement used for analysis of pregnancy rates to timed-AI contained the effects of treatment, group, day of pregnancy diagnosis (d 30 or 90), and all resultant interactions. Results are reported as least square means and separated using LSD. Significance was set at $P \leq 0.05$, and tendencies were determined if $P > 0.05$ and ≤ 0.10. Results are reported according to treatment effects if no interactions were significant, or according to the highest-order interaction detected.

Experiment 2

Animals and treatments. A total of 40 pregnant Nelore females, being 20 non-lactating nulliparous and 20 lactating multiparous cows, were assigned to the experiment (BCS = 4.73 ± 0.12 according to Wagner et al., 1988). All cows were maintained in a single *B. brizanta* pasture with ad libitum access to water and a commercial mineral-vitamin mix (DSM Produtos Nutricionais Brasil). At the beginning of the experiment (d 0), cows were ranked by parity and assigned to receive: 1) **VAC** = vaccination against the FMD virus (5 mL s.c. of Ourovac Aftosa; Ourofino Saúde Animal) on d 0, and 2) **NOVAC** = no vaccination against the FMD virus on d 0.

Sampling. Rectal temperature was recorded (G-Tech digital thermometer; G-Tech; São Paulo, SP, Brazil) and blood samples were collected immediately prior to (h 0) and 24, 72, 120, and 168 h after treatment administration. Blood was collected via jugular venipuncture into commercial blood collection tubes (Vacutainer, 10 mL; Becton Dickinson, Franklin Lakes, NJ) with 158 USP units of freeze-dried sodium heparin, placed immediately on ice, centrifuged (2,500 × *g* for 30 min; 4°C) for plasma harvest, and stored at -20°C on the same day of collection. All plasma samples were analyzed for haptoglobin concentration according to

147 colorimetric procedures described by Cooke and Arthington (2013). The intra- and inter-assay
148 CV were, respectively, 2.4 and 7.6%.

149 ***Statistical analysis.*** Data were analyzed with the MIXED procedure of SAS (SAS Inst.,
150 Inc.; version 9.3) and Satterthwaite approximation to determine the denominator df for the tests
151 of fixed effects, using cow as the experimental unit and cow(treatment × parity) as random
152 variable. The model statement used for analysis of plasma haptoglobin and rectal temperature
153 contained the effects of treatment, parity, hour, and all resultant interactions. The specified term
154 for the repeated statements was hour, cow(treatment × parity) as subject, and the covariance
155 structure utilized was autoregressive based on the Akaike information criterion. Results are
156 reported as least square means and separated using LSD. Significance was set at $P \leq 0.05$, and
157 tendencies were determined if $P > 0.05$ and ≤ 0.10. Results are reported according to treatment
158 effects if no interactions were significant, or according to the highest-order interaction detected.

159 **RESULTS**

160 ***Experiment 1***

161 No treatment differences were detected ($P = 0.87$) for cow BCS at timed-AI (3.87 vs.
162 3.84 of BCS for VACPRE vs. VACGEST cows; SEM = 0.10),

163 A treatment × day interaction was detected ($P < 0.01$) for pregnancy rates to AI (Table
164 1), which were similar ($P = 0.17$) between treatments on d 30, but greater ($P < 0.01$) for
165 VACPRE compared with VACGEST cows on d 90. Accordingly, pregnancy loss from d 30 to
166 90 was greater (P < 0.01) in VACGEST compared with VACPRE cows (Table 1).

167 ***Experiment 2***

168 A treatment × hour interaction was detected ($P < 0.01$) for rectal temperature, which was
169 similar between VAC and NOVAC cows prior to treatment administration ($P = 0.48$), greater (P

170 < 0.01) in VAC compared with NOVAC cows at 24 h after treatment administration, and similar
171 ($P \geq 0.31$) between treatments at 72, 120, and 168 h after treatment administration (Figure 1).
172 A treatment × hour interaction was also detected ($P < 0.01$) for plasma haptoglobin
173 concentration, which was similar ($P = 0.98$) between VAC and NOVAC cows prior to treatment
174 administration ($P = 0.48$), and greater ($P < 0.01$) in VAC compared with NOVAC cows at 24,
175 72, 120, and 168 h after treatment administration (Figure 2).

176 **DISCUSSION**

177 In FMD endemic regions, cattle are vaccinated against the FMD virus every 6 mo due to
178 the vaccine immuneprotection length (Parida, 2009). Based on the productive cycle of cow-calf
179 operations (Hixon and Sanson, 2012), vaccination against the FMD virus often occurs during or
180 shortly after the annual breeding season. Although previous research reported that FMD vaccines
181 impair cattle production traits, including decreased milk production (Yeruham et al., 2001) and
182 increased carcass lesions (Leal et al., 2014), the impacts of vaccination against the FMD virus on
183 reproductive performance of beef cows still warranted investigation. Therefore, results from Exp.
184 1 are novel and support our hypothesis that administering a FMD vaccine during early pregnancy
185 increased incidence of pregnancy loss in beef cows by 4-fold when compared with vaccine
186 administration prior to timed-AI. It is important to mention that these outcomes were
187 independent of cow BCS, and should not be associated with cow nutritional status during the
188 estrus synchronization + timed-AI protocol (Cooke et al., 2009).
189 The majority of FMD vaccines utilized worldwide contain inactivated FMD virus
190 serotypes, and an oil-based adjuvant that elicits innate immune responses associated with antigen
191 presentation to T cell lymphocytes, including inflammatory and acute-phase reactions (Tizard,
192 2004; Rodriguez and Grubman, 2009; Rodrigues et al., 2015). These immune responses,

193 however, have been negatively associated with pregnancy maintenance (Hansen et al., 2004) and
194 overall reproductive performance in cattle (Cooke et al., 2009). More specifically, adjuvants
195 stimulate synthesis of pro-inflammatory cytokines (Rodrigues et al., 2015), which in turn elicit 2
196 major acute-phase responses: 1) synthesis of prostaglandins that lead to hyperthermia, and 2)
197 altered liver metabolism and gene regulation, favoring hepatic synthesis of acute-phase proteins
198 such as haptoglobin (Carroll and Forsberg, 2007). Pro-inflammatory cytokines are known to
199 impact pregnancy maintenance via direct embryotoxic effects, reduced endometrial cell
200 proliferation, in addition to increased body temperature and endometrial $PGF_{2\alpha}$ synthesis to
201 levels that interrupt early pregnancy (Hansen et al., 2004). Conversely, haptoglobin does not
202 have detrimental effects on cattle productive and reproductive functions, although this acute-
203 phase protein is widely used to monitor inflammatory and acute-phase responses in cattle
204 (Horadagoda et al., 1999; Cooke and Arthington, 2013).

205 Supporting this rationale, results from Exp. 2 demonstrated that administering a FMD
206 vaccine elicited inflammatory and acute-phase responses, represented by treatment effects on
207 rectal temperature and plasma haptoglobin concentrations, which can be directly associated with
208 treatment effects detected for pregnancy loss in Exp. 1. Supporting findings from Exp. 2,
209 Arthington et al. (2013) and Rodrigues et al. (2015) also reported that administering a vaccine
210 containing inactivated pathogens + adjuvant to beef cattle receiving increased plasma
211 haptoglobin concentrations for up to 120 h, and associated these outcomes with reduced
212 performance traits. It is important to note that inflammatory and acute-phase responses may also
213 impair cattle fertility parameters such as follicle development and ovulation (Peter et al., 1989;
214 Battaglia et al., 2000; Williams et al., 2001), which were not directly assessed in the present
215 experiment although pregnancy rates to AI on d 30 were similar between treatments. Given that

the FMD vaccine utilized herein increased plasma haptoglobin concentrations for at least 7 d, it seems plausible that beef cows should be vaccinated against the FMD virus at least 1 wk prior to the beginning of the breeding season to prevent fertility and pregnancy losses, which supports that practical application of the VACPRE treatment evaluated in Exp. 1. Nevertheless, research is still warranted to determine the most appropriate timing for FMD vaccination to beef females.

In summary, administering a FMD vaccine to Nelore beef cows resulted in a 4-fold increase in pregnancy loss when vaccination occurred 30 d after timed-AI compared with 31 d prior to timed-AI. These outcomes can be associated with the inflammatory and acute-phase reactions elicited by the FMD vaccine, which are known to impair pregnancy maintenance in cattle (Hansen et al., 2004). Therefore, beef cows should not receive FMD vaccines based on inactivated virus and an oil-based adjuvant during early gestation; this should be administered prior to the beginning of the breeding season to prevent early pregnancy losses and optimize reproductive and overall efficiency of cow-calf operations.

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Table 1. Reproductive performance of *Bos indicus* beef cows vaccinated against foot-and-mouth disease virus (5 mL s.c. of Ourovac Aftosa; Ourofino Saúde Animal, Cravinhos, SP, Brazil) on d -31 (**VACPRE**; n = 291) or d 30 (**VACGEST**; n = 313) relative to timed-AI (d 0). [1]

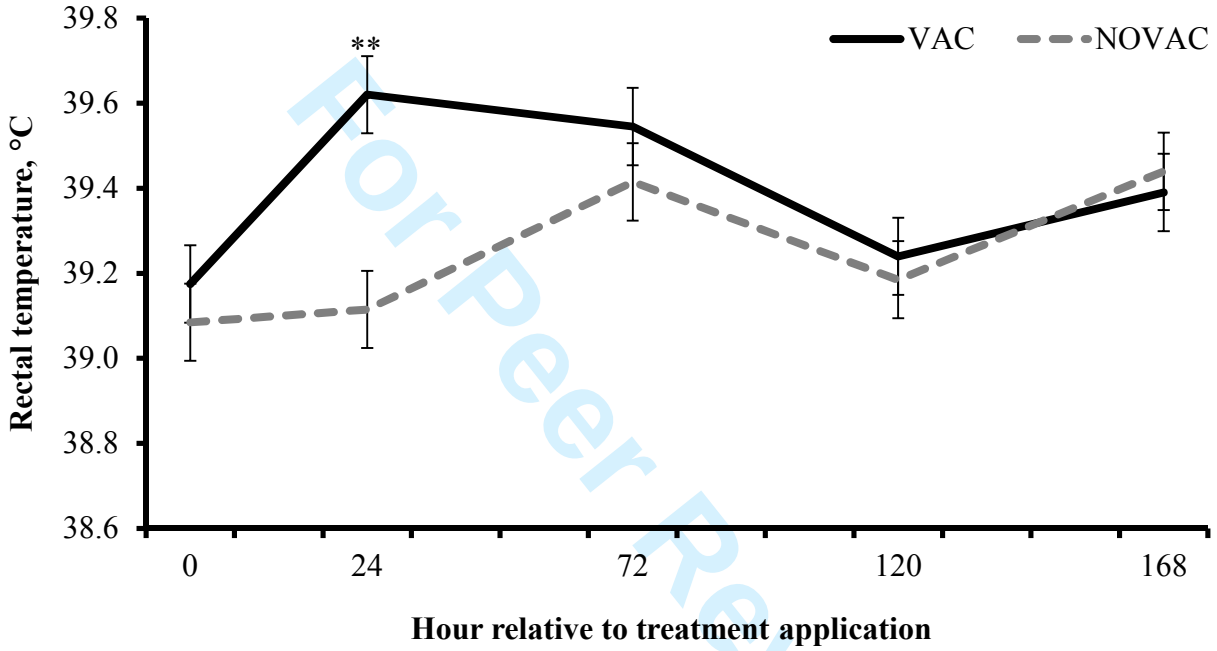
Item	VACPRE	VACGEST	SEM	*P*-value
Pregnancy rates to timed-AI,[2] %				
d 30	61.8 (180/291)	56.2 (176/313)	2.8	0.17
d 90	59.4 (173/291)	46.9 (147/313)	2.8	< 0.01
Pregnancy loss from d 30 to 90,[3] %	3.9 (7/180)	16.5 (29/176)	2.2	< 0.01

[1] On d -11, groups were assigned to the following estrus synchronization + timed-AI protocol. Cows received a 2 mg injection (i.m.) of estradiol benzoate (Gonadiol; Zoetis, São Paulo, SP, Brazil) and an intravaginal progesterone releasing device (**CIDR**, containing 1.9 g of progesterone; Zoetis) on d -11. On d -2, CIDR was removed, cows received a 12.5 mg injection (i.m.) of $PGF_{2\alpha}$ (Lutalyse; Zoetis), in addition to 0.6 mg injection (i.m.) of estradiol cypionate (ECP; Zoetis) and 300 IU injection (i.m.) of eCG (Novormon, Zoetis). On d 0, cows were assigned to timed-AI. Pregnancy status to AI was verified on 30 and 90 d after timed-AI by detecting a viable conceptus with transrectal ultrasonography (5.0-MHz transducer; Chison 600, Chison Medical Imaging Co., Ltd., Wuxi City, Jiang Su Province, China).

[2] Values within parenthesis represent number of pregnant cows divided by number of total cows assigned to timed-AI.

[3] Values within parenthesis represent number of cows that lost AI pregnancy divided by number of diagnosed as pregnant to timed-AI on d 30.

317 **Figure 1.** Rectal temperature of *Bos indicus* beef cows vaccinated (**VAC;** n = 20) or not
318 (**NOVAC**; n = 20) against foot-and-mouth disease virus (5 mL s.c. of Ourovac Aftosa; Ourofino
319 Saúde Animal, Cravinhos, SP, Brazil). A treatment × hour interaction was detected ($P < 0.01$).
320 Treatment comparison within hour; ** $P \leq 0.01$.
321



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323 **Figure 2.** Plasma haptoglobin concentrations in *Bos indicus* beef cows vaccinated (**VAC;** n =
324 20) or not (**NOVAC**; n = 20) against foot-and-mouth disease virus (5 mL s.c. of Ourovac Aftosa;
325 Ourofino Saúde Animal, Cravinhos, SP, Brazil). A treatment × hour interaction was detected (P
326 < 0.01). Treatment comparison within hour; ** $P \leq 0.01$.
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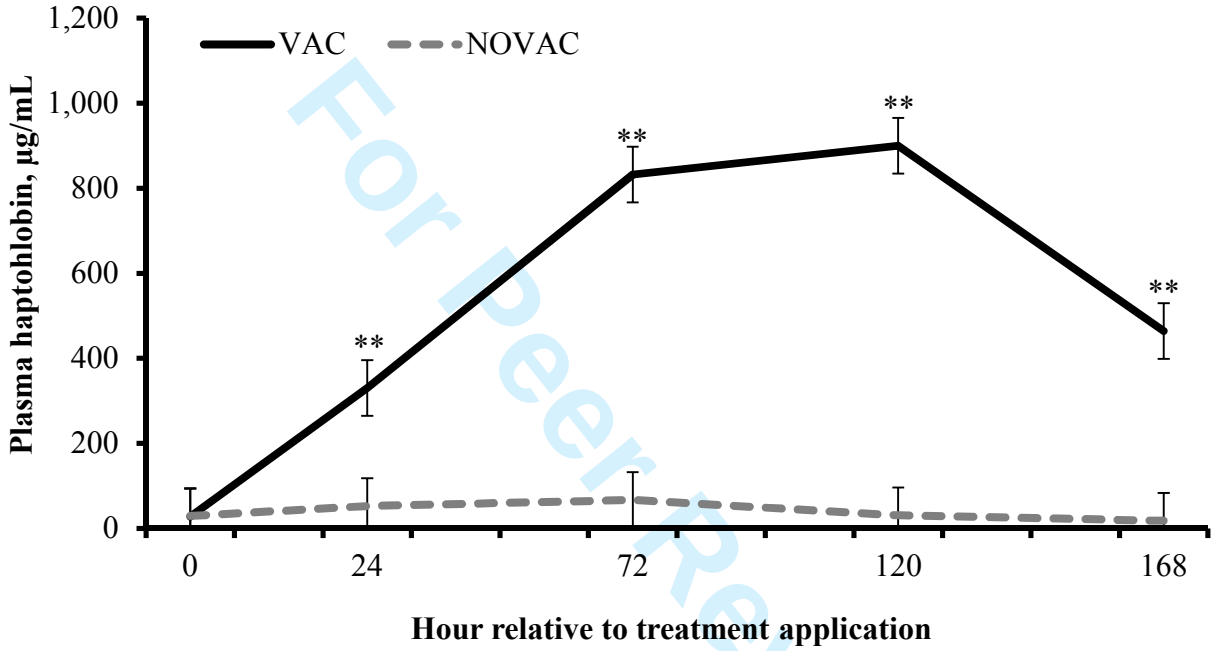

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