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VETERINARY MICROBIOLOGY - RESEARCH PAPER

Serological profile of respiratory viruses in unvaccinated steers upon their arrival at Brazilian feedlot facilities

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Abstract

Bovine viral diarrhea virus (BVDV), bovine alphaherpesvirus 1 (BoAHV1), bovine respiratory syncytial virus (BRSV), and bovine parainfluenza virus 3 (BPIV-3) are involved in bovine respiratory disease. These viruses can infect the respiratory system and cause considerable economic losses to beef and dairy cattle herds. This study aimed to determine the serological profiles of steers for BVDV, BoAHV1, BRSV, and BPIV-3 upon their arrival at Brazilian feedlot facilities. A total of 1,282 serum samples from unvaccinated steers were obtained on the first day of feeding. Samples were collected from 31 beef cattle herds reared in an extensive rearing system in six Brazilian states. Antibodies against BVDV, BoAHV1, BRSV, and BPIV-3 were detected using a virus neutralization test. The steers were distributed in agreement with their age and the Brazilian state of origin. The highest seropositivity was for BoAHV1 and BPIV-3 at 92.1% (1,154/1,253) and 86.6% (1,100/1,270), respectively. The seropositivity of BRSV was 77.1% (959/1,244). BVDV presented a lower rate, at slightly more than 50% (51.8%; 656/1,266). Age was a risk factor for the presence of antibodies against BVDV, BoAHV1, and BPIV-3 but not BRSV. A positive correlation was identified between BoAHV1 and BPIV-3 ($P=0.85$) and between BRSV and BPIV-3 ($P=0.47$). The high rate of seropositive steers for these four respiratory viruses on the first day of confinement identified in this serological survey provides important epidemiological information on respiratory infections, as the seropositivity of the four main bovine respiratory viruses in Brazilian beef cattle herds in an extensive rearing system.

Keywords Bovine viral diarrhea virus · Bovine alphaherpesvirus 1 · Bovine respiratory syncytial virus · Bovine parainfluenza virus 3 · Beef cattle · Virus neutralization test

Introduction

Bovine respiratory disease (BRD) is a major respiratory health problem in beef cattle feedlots worldwide [1], and the main concern in economic loss in the beef cattle industry [2] since it presents high morbidity and mortality in all ages of this cattle category and directly impact on animal health [3]. It has a multifactorial character, as steers are usually concomitantly infected by two or more infectious agents [3]. The occurrence of BRD in cattle herds is also associated with risk factors such as age, nutritional status, and stress factors, such as the commingling of animals from different origins, changes in diet, nutritional status, temperature variations, transportation distance, and health management such as vaccination programs [4, 5].

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Bovine viral diarrhea virus (BVDV), bovine alphaherpesvirus 1 (BoAHV1), bovine respiratory syncytial virus (BRSV), and bovine parainfluenza virus 3 (BPIV-3) are the main viral agents involved in BRD worldwide [6]. Viruses are considered primary pathogens of the upper respiratory tract (URT) and may predispose cattle to secondary bacterial infections caused by microorganisms constituting the URT microbiota itself or by opportunistic agents. As a result of primary viral infections, the microbial population can reach the lower respiratory tract, causing pneumonia [7–9].

The absence of antibodies, caused by the loss of passively acquired maternal immunity or vaccination failure associated with exposure to the antigen, generates a window of susceptibility to illness [10, 11]. However, antibodies can be found in unvaccinated animals without clinical signs of respiratory infection [12], suggesting that they are circulating in the cattle herd. In Brazil, the vaccination program for BVDV, BoAHV1, BRSV, and BPIV-3 infection control is managed by the veterinarian of each farm and, therefore, is still not widespread in both beef cattle herds and feedlots.

Although the rate of BRD-vaccinated animals is substantially higher in North American feedlots than in Brazil, the frequency of occurrence of BRD is higher [13, 14]. It has been asserted that the higher frequency of BRD in young non-seroconverted animals in North America may be related to feedlots [15].

The serological profile of the four main bovine respiratory viruses on arrival at feedlots in Brazil is unknown. Considering, the only Brazilian data available are the rate of occurrence of clinical BRD in animals already in feedlots and the etiology of the infection [13, 16].

Therefore, this study aimed to determine the antibody profiles of BVDV, BoAHV1, BRSV, and BPIV-3 in unvaccinated steers upon arrival at Brazilian feedlots, highlighting the immunological status of unvaccinated beef cattle herds to BRD before the animals enter feedlots facilities. To the best of our knowledge, there is no information on the health status regarding the involvement of these viruses and the ratio of the infection of the four viruses together.

Materials and methods

Serum samples and study area

A total of 1,282 bovine blood serum samples were collected. The animals were all males, aged between eight and 32 months, with no history of respiratory disease or vaccination for BRD. Serum was collected from the animals after they arrived at the feedlots. All steers came from beef cattle herds in an extensive breeding system and were transported 100–1,000 km from their herd of origin to the feedlot.

The steers were housed in 31 feedlots located in the midwestern (Mato Grosso $n=11$, Mato Grosso do Sul $n=4$, and Goiás $n=8$), southeastern (São Paulo $n=3$ and Minas Gerais $n=3$), and northern (Tocantins $n=2$) regions of Brazil. All serum samples were stored at -80 °C until processing.

Virus neutralization test

The serum samples were evaluated for the presence of antibodies to BVDV, BoAHV1, BRSV, and BPIV-3 using the virus neutralization (VN) test, as described in the Manual of Diagnostic Tests and Vaccines for Terrestrial Animals of the World Organization for Animal Health [17], Affonso et al. [18], and Okur-Gumusova et al. [19], respectively. A volume of 50 µL of Madin-Darby bovine kidney cell culture at a concentration of 3.10^5 cells/mL was used with 50 µL of infective viral dose for each virus evaluated at 100 $TCID_{50\%}$. The serum samples were considered positive with neutralizing activity at a final dilution ≥ 1:2 for BoAHV1, ≥ 1:4 for BRSV, and ≥ 1:10 for BVDV and BPIV-3 after the evaluation of the cytopathic effect following 72 h of incubation at 37 °C in an atmosphere with a concentration of 5% CO_2. The serum samples were classified as low, intermediate, or high antibody titers, according to Table 1.

Statistical analysis

The frequency of antibodies against the four bovine respiratory viruses in each feedlot was expressed as the percentage of positive animals and the titration distribution for each virus in the samples evaluated. The animals' ages were classified as ≤ 12 months, 13 to 24 months, and > 24 months. The place of origin was used to compare the incidence of the diseases using Fisher's exact test with the OpenEpi application (www.OpenEpi.com). The correlation between the frequency of antibodies against the four viruses in the feedlots was estimated using RStudio 1.4.1106 (www.rstudio.com).

Table 1 Classification of antibodies titers (low, intermediate, and high) to bovine respiratory viruses evaluated by virus neutralization test

Virus [(#)]	Antibody titers		
	Low	Intermediate	High
BVDV	10—20	40—80	160 to ≥ 640
BoAHV1	2—8	16—32	64 to ≥ 128
BRSV	4—8	16—32	64 to ≥ 128
BPIV-3	10—20	40—80	160 to ≥ 640

[(#)] BVDV (Bovine viral diarrhea virus), BoAHV1 (Bovine alphaherpesvirus 1), BRSV (Bovine respiratory syncytial virus), BPIV-3 (Bovine parainfluenza virus 3)

Pearson's correlation test was performed using the ggpubr package [20]. For all analyses, the significance level was set at 5%.

Results

The serological profiles of the steers upon arrival at the Brazilian feedlots for the four bovine respiratory viruses evaluated in this study are shown in Table 2. The antibody titers identified by VN test were distributed on three scales (low, intermediate, and high). Most of the animals seropositive for BoAHV1 and BPIV-3 had high titers, whereas only a small proportion of the steers seropositive for BVDV and BRSV had high titers.

There was a statistical difference ($P \leq 0.05$) in the age of animals concerning the percentage of positive samples for the four viruses (Table 3), concluding that the oldest cattle presented the highest seropositivity rates for these viruses. The BoAHV1 and BPIV-3 viruses had the most significant statistical difference ($P \leq 0.001$). Additionally, it was possible to observe a relationship between breeds (Nelore × crossbreed) and age groups (≤ 24, and >24 months) of the evaluated animals with the seropositivity rates for BVDV, BoAHV1, BRSV, and BPIV-3. There was a statistical difference in the occurrence of all viruses in Nelore at >24 months old, suggesting that this breed is more susceptible than crossbreeds in this age range. However, in animals with ≤ 24 months, only BRSV didn't present differences between cattle breeds (Table 4). The frequencies of seropositive steers for these four viruses varied among the animal lots regardless of the breed but not age (Table 3). These results suggest that the epidemiological aspects of these infections in the herds of origin have a greater influence on the seroconversion rates.

The minimum and maximum seroconversion rates identified in the cattle herds evaluated in this study ranged from 2.1% to 98.0% for BVDV and for BoAHV1, BRSV, and BPIV-3 ranging between 19.6–100.0%, 16.7–100.0%, and 11.8–100.0%, respectively (Table 3).

The percentage of seroconversion identified in the steers of the 31 groups evaluated distributed by the state of origin of the animals is shown in Table 5. The variations by state in the minimum and maximum seroconversion rates for BVDV, BoAHV1, BRSV, and BPIV-3 ranged from 40.6–72.0%, 72.8–100.0%, 67.8–94.0%, and 76.5–99.1%, respectively.

Tocantins state had the highest percentage of seropositive steers for BVDV, BoAHV1, and BRSV, and São Paulo state had the highest percentage of seropositive steers for BPIV-3. BoAHV1 also was found to have a high rate of seropositive animals in Minas Gerais and Goiás. Mato Grosso do Sul and Mato Grosso had the lowest percentages of positive samples for this virus.

Pearson's correlation analysis showed a strong positive correlation between the presence of antibodies against BoAHV1 and BPIV-3 ($P = 0.85$) and BRSV and BPIV-3 ($P = 0.47$), as shown in the supplementary Fig. 1.

Table 2 Distribution of the frequency of antibodies determined by virus neutralization test to bovine respiratory viruses in serum samples of unvaccinated steers of 31 Brazilian feedlots, according to antibodies titers

Virus [#]	Samples	Antibody titer / Sample *n* (%)			Total	
	(*n*)	Low	Intermediate	High	Positive (%)	Negative (%)
BVDV	1,266	200 (15.8)	264 (20.8)	192 (15.2)	656 (51.8)	610 (48.2)
BoAHV1	1,253	66 (5.3)	143 (11.4)	945 (75.4)	1,154 (92.1)	99 (7.9)
BRSV	1,244	421 (33.8)	406 (32.6)	132 (10.6)	959 (77.1)	285 (22.9)
BPIV-3	1,270	118 (9.3)	275 (21.6)	707 (55.7)	1,100 (86.6)	170 (13.4)

[(#)] BVDV (Bovine viral diarrhea virus), BoAHV1 (Bovine alphaherpesvirus 1), BRSV (Bovine respiratory syncytial virus), BPIV-3 (Bovine parainfluenza virus 3)

Table 3 Distribution of the results of serological surveys by virus neutralization test to the four main respiratory viruses in cattle at the arrival in Brazilian feedlots facilities, according to the age of the animals

Age group (mos)	Samples (*n*)	Average percentage (%) of positive samples [(#)] (minimum and maximum %)			
		BVDV	BoAHV1	BRSV	BPIV-3
≤ 12	101	31.7 (20.0—43.1) [a]	59.4 (19.6—100.0) [a]	58.4 (27.5—90.0) [a]	55.4 (11.8—100.0) [a]
13 – 24	723	50.7 (2.1—92.0) [b]	89.9 (72.0—100.0) [b]	77.0 (16.7—98.0) [b]	85.9 (25.0—100.0) [b]
>24	458	56.3 (18.0—98.0) [b]	96.9 (81.6—100.0) [c]	75.1 (33.3—100.0) [b]	92.8 (65.7—100.0) [c]

[(#)] BVDV (Bovine viral diarrhea virus), BoAHV1 (Bovine alphaherpesvirus 1), BRSV (Bovine respiratory syncytial virus), BPIV-3 (Bovine parainfluenza virus 3)

a,b, and c in the same column indicate a statistical difference ($P \leq 0.05$; Fisher's exact)

Table 4 Seropositive steers for the four main respiratory viruses at the arrival in Brazilian feedlots facilities, distributed according to age groups (≤ 24 mos and > 24 mos) and races (Crossbreed and Nelore)

Virus	Age (months)					
	≤ 24 mos / breed (%)			> 24 mos / breed (%)		
	Crossbreed	Nelore	Total	Crossbreed	Nelore	Total
BVDV ($n=1,266$)	123 (9.7) [b]	199 (15.7) [a]	322 (25.4)	95 (7.5) [b]	239 (18.9) [a]	334 (26.4)
BoAHV1 ($n=1,253$)	254 (20.3) [b]	359 (28.6) [a]	613 (48.9)	186 (14.8) [b]	355 (28.3) [a]	541 (43.2)
BRSV ($n=1,244$)	245 (19.7) [a]	267 (21.5) [a]	512 (41.2)	156 (12.5) [b]	291 (23.4) [a]	447 (35.9)
BPIV ($n=1,270$)	242 (19.0) [b]	347 (27.3) [a]	589 (46.4)	166 (13.1) [b]	345 (27.2) [a]	511 (40.2)

Different superscript lowercase letter [a–b] indicates statistical difference ($P<0.01$) between breeds (Crossbreed *vs*. Nelore) within each age group and for each viral agent

Table 5 Distribution of seropositive steers to the main bovine respiratory viruses, according to the Brazilian geographical region and state of origin of the animals

Brazilian		Bovine respiratory virus [#] / Positive samples (%)			
Region	State [*]	BVDV	BoAHV1	BRSV	BPIV-3
Southeast	SP	43 (40.6) [a]	101 (95.3) [c]	90 (84.9) [b]	105 (99.1) [d]
	MG	41 (46.1) [a]	90 (100.0) [cd]	61 (67.8) [a]	77 (85.5) [b]
Midwest	MS	69 (52.7) [a]	91 (72.8) [a]	114 (83.8) [b]	104 (76.5) [ab]
	MT	222 (43.5) [a]	451 (88.4) [b]	350 (69.0) [a]	407 (79.8) [ab]
	GO	228 (64.2) [b]	354 (99.7) [d]	298 (83.9) [b]	343 (96.8) [cd]
North	TO	54 (72.0) [c]	67 (100.00) [cd]	47 (94.0) [b]	66 (90.4) [bc]

[*] Brazilian states: SP (São Paulo); MG (Minas Gerais); MS (Mato Grosso do Sul); MT (Mato Grosso); GO (Goiás); TO (Tocantins)

[#] Virus: BVDV (Bovine viral diarrhea virus), BoAHV1 (Bovine alphaherpesvirus 1), BRSV (Bovine respiratory syncytial virus), BPIV-3 (Bovine parainfluenza virus 3)

a,b, c, and d in the same column indicate a statistical difference ($P \leq 0.05$; Fisher's exact)

Discussion

Most seroepidemiological surveys that have aimed to identify antibodies against BVDV, BoAHV1, BRSV, and BPIV-3 in Brazil and other countries have been conducted in dairy cattle herds [21–28].

Only one Brazilian study has evaluated the antibody frequency rate for the same four bovine respiratory viruses investigated herein using the VN test [29]. In a small sample ($n=44$), the authors found that 32 (72.3%), 24 (54.4%), 29 (65.9%), and 28 (63.7%) of the animals were seropositive for BVDV, BoAHV1, BRSV, and BPIV-3, respectively. However, only serum samples from dairy calves aged zero to three ($n=10$), three to six ($n=21$), and six to 12 months ($n=13$) were evaluated. Positive results were most likely due to passive antibodies in animals aged zero to six months. In animals aged six to 12 months, there was a considerable increase in the rate of seropositivity and antibody titer, suggesting natural infection. However, due to many differences (age, breed, beef and dairy cattle, and management, among others) between the present study and the one performed by Hoppe et al. [29], it is difficult to establish comparative analyses between both studies.

Several surveys on the serological profile of adult animals, mostly beef and dairy cows, from cattle herds in Brazil have indicated that BVDV and BoAHV1 infections are common [30–34]. However, no seroepidemiological study of the frequency of antibodies to the four main respiratory viruses in steers entering feedlots was performed in Brazil. Young animals, such as pre-weaning calves, are very likely to be seropositive due to the interference of colostral antibodies. Adult animals (cows) are also seropositive due to previous infections or vaccination. This category of animals, young, male, and beef evaluated no longer has interference from colostral antibodies and is also not vaccinated. If they are positive is due to a natural infection. Additionally, these animals were submitted to transport stress and will be commingled in a new place with different animals from different origins causing a new stress situation. Furthermore, few similar surveys have been performed on steers in other countries.

In this study, the seropositivity rates of BVDV, BoAHV1, BRSV, and BPIV-3 were 51.8% (656/1,266), 92.1% (1,154/1,253), 77.1% (959/1,244), and 86.6% (1,100/1,270), respectively (Table 2). A study conducted in Australia evaluated 7302 to 7314 serum samples of beef cattle by enzyme-linked immunosorbent assay (ELISA), and described seroprevalence rates for BVDV, BRSV and BPIV-3 higher, between 14.4%, 12.1% and 4.9% of variability, respectively to those in the present study (Table 6); however, the rates of seropositive animals

for BoAHV1 varied considerably [36]. Studies conducted in Saudi Arabia [38] and Türkiye [39] by ELISA and VN, respectively, found similar results to those of the present study. High BoAHV1 seroprevalence rates were also reported by Leon et al. [35] in beef and dairy cattle in Colombia.

Table 6 presents the seroconversion rates for the four main respiratory viruses identified in this study and other studies conducted in South America and other parts of the world. There are great variations in the frequencies of seropositive animals for each virus, which makes a comparative analysis between the studies impractical. Aspects related to the epidemiology of infections, the purpose of creation (beef and dairy), type of management, sanitary programs, biosecurity, and age of the animals, influence the frequency of seropositive animals identified in each study.

The serological profile of the four main BRD viruses indicates that infections caused by BVDV, BoAHV1, BRSV, and BPIV-3 are common in animals both younger and, especially, older than 12 months from Brazilian beef cattle herds in an extensive rearing system. In the group of animals aged ≤ 12 months, the youngest was eight months old. In this age group, there is likely no risk of passive antibody identification. Therefore, the frequency of neutralizing antibodies identified in this survey was due to natural infection post-weaning, indicating that the circulation of the four viruses is high in Brazilian beef cattle herds. These infections appear to mostly present asymptomatically, causing the development of active immunity [35].

For the four bovine respiratory viruses, the seroconversion rates showed great variation when evaluated individually by herd, even considering the distribution by age group. This result indicates that the epidemiology of intra-herd infections has individual characteristics. The averages of the seroconversion rates demonstrate that, except for BVDV, most steers enter feedlots already seropositive for BoAHV1, BRSV, and BPIV-3. However, this should not be interpreted as a rule since natural infection rates vary widely between cattle herds.

Regardless of age, origin, and breed, most steers seropositive for BoAHV1 and BPIV-3 had high antibody titers (> 64 and > 160, respectively), with about three-quarters (75.4% BoAHV1) and more than half (55.7% BPIV-3) of the samples showing elevate titers. However, in BVDV and BRSV seropositive animals, a small proportion had high antibody titers (15.2 and 10.6%, respectively). This suggests that the circulation of BoAHV1 and BPIV-3 in beef cattle herds in Brazil is much higher than that of BVDV and BRSV. The mechanism of viral latency of BoAHV1, with recurrent episodes of re-excretion, may contribute to its high prevalence [43, 44]. Regarding BPIV-3, serological studies carried out in adult beef and dairy cattle in Brazil showed a wide spread of the agent, with a prevalence of antibodies greater than 80% [37]. This prevalence may explain the high frequency of young animals positive for BPIV-3 in our study.

In the Northern Hemisphere, the main health problem in cattle feedlots in the first 15–20 days in the feedlot is BRD. In Brazil, BRD is also a health problem that affects the early stages of feedlots. In contrast to Brazil, the vaccination of steers entering confinement in North American feedlots is routine sanitary management. Nevertheless, the frequency of occurrence and severity of BRD in confined steers in the United States is much higher than that observed in Brazil [13, 14]. Most likely, the two main factors that explain this

Table 6 Results of serological surveys for the identification of seropositive cattle to the four main viruses involved in the etiology of Bovine Respiratory Disease identified in this and other studies carried out worldwide

Country	Functional traits	Age (mos)	Test (†)	Samples (*n*)	Percentage of positive samples (#)				Reference
					BVDV	BoAHV1	BRSV	BPIV-3	
Brazil	beef	7–36	VN	1,282	51.8	92.1	77.1	86.6	This study
Brazil	dairy	< 12	VN	44	72.3	54.5	65.9	67.3	[29]
Colombia	dairy/beef	>24	ELISA	977	35.0	95.0	98.6	47.3	[35]
Australia	beef	NI (*)	ELISA	243	58.0	43.0	50.0	88.0	[36]
Australia	beef	NI (*)	ELISA	7314	66.2	22.2	87.4	90.2	[37]
Saudi Arabia	dairy	12–48	ELISA	460	26.0	17.4	75.6	69.1	[38]
Türkiye	dairy	> 12	VN	584	41.4	17.1	73.0	43.0	[39]
Türkiye	dairy	< 12	VN	94	71.1	24.1	98.6	78.7	[26]
Türkiye	dairy	> 48	ELISA	56	50.0	7.1	94.6	94.6	[40]
India	dairy	Adult	ELISA	132	1.5	24.2	50.0	57.6	[41]
Iran	dairy	Adult	ELISA	642	49.2	72.0	51.1	84.4	[42]

(†) Test: VN (virus neutralization), ELISA (Enzyme-linked immunosorbent assay)

(#) Virus: BVDV (Bovine viral diarrhea virus), BoAHV1 (Bovine alphaherpesvirus 1), BRSV (Bovine respiratory syncytial virus), BPIV-3 (Bovine parainfluenza virus 3)

(*) NI (not informed)

difference in susceptibility to BRD are the age of the steers entering the feedlots and genetics.

In Brazil, the age of most steers that enter confinement is around 33 months [45], higher than that of animals in the United States that slaughter between 15 to 28 months [46]. Therefore, young, non-seroconverted animals may be responsible for the higher BRD frequency observed in United States feedlots [15]. Studies reported that seroprevalences generally increase with the age of unvaccinated cattle [47]. Hay et al. (2016) described that animals were progressively at increased risk of BRD when testing seronegative to an increasing number of viruses. These results suggest that animals seronegative for all four viruses were at higher risk than those infected by one of the four main respiratory viruses.

In this study, which involved considerable sampling (n = 1,282) and included 31 feedlots located in important Brazilian beef producing regions, most animals were already seropositive for the four viruses evaluated on arrival (Table 6). The presence of antibodies against the four viral agents in unvaccinated beef cattle herds shows that the wild-type virus was circulating in the beef herds of origin, resulting in seroconversion.

The second factor that may explain the lower frequency of BRD in Brazilian feedlots is genetics. Breeds of European origin are more susceptible to infections that cause BRD or stressors that trigger disease than Zebu breeds, including crossbreeding that predominates in Brazilian beef cattle herds [48–50].

A high seroprevalence of diseases of viral etiology is associated with adult animals due to repeated exposure to the virus throughout their life and the possibility of reinfection [51]. However, there is no consensus that increasing age is a risk factor for infection by viruses involved in the etiology of BRD. The results reported have been contradictory depending on the animals' age, breed, and aptitude (beef × dairy), breeding region, and even the respiratory virus evaluated. Consequently, it is not possible to perform a critical and definitive comparative analysis of the results of previous studies [22, 35, 47, 52].

The fattening of confined beef cattle is increasing in Brazil. BRD is responsible for considerable economic losses in Brazilian feedlots. Assessing the financial losses of viral illnesses can contribute to the adoption of measures to minimize losses and maximize productivity. The control of BRD is essential to improve herd health, animal welfare, and business profitability. Epidemiological information is a relevant tool for designing sanitary management to reduce the frequency of BRD in cattle feedlots.

Conclusion

The immune status of the four main bovine respiratory viruses in beef cattle on the first day at feedlots has never been described together or separately in Brazil; however, it has already been described in dairy calves and beef and dairy cows. It was possible to observe that BoAHV1 and BPIV-3 have a high rate of animal seropositive. Steers infected with BoAHV1 showed the highest antibody titers. On the other hand, approximately half of the steers were seronegative to BVDV, with the seropositive animals with around 35% with low titers. Age is a risk factor for BoAHV1, BVDV, and BPIV-3 infection but not for BRSV. The incidence of the four viruses differs statistically by each region addressed in this study. A positive correlation between BoAHV1/BPIV-3 and BPIV-3/BRSV increases the possibility of BRD in the feedlots.

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Author contributions Conceptualization and design: LMC, JTTF, EL and AAA; Sample collection: EM and ERC; Methodology: LMC and JTTF; Statistical analysis: ARC; Writing—original draft preparation: LMC; Writing—review and editing: JTTF and EL; Supervision: AFA and AAA. All authors have read, critically analyzed, and approved the final draft of this manuscript.

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

Declarations

Ethics approval This study was approved by the Ethics Committee on the Use of Animals in Teaching and Research of the Universidade Estadual de Londrina (UEL), Londrina, Brazil, under number 59/2019. All applicable international, national, and/or institutional guidelines for the care and use of animals were followed.

Conflict of interest The authors declared no potential conflicts of interest concerning the research, authorship, and/or publication of this article.

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