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Economic impacts of *Bovine alphaherpesvirus 1* infection in Brazil: Meta-analysis based on epidemiological indicators

Impactos econômicos da infecção por *Bovine alphaherpesvirus 1* no Brasil: Metanálise a partir de indicadores epidemiológicos

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Highlights

A prevalence of 54.12% was identified in cattle in Brazil.
The prevalence in herds was 88.53%.
The occurrence of 258,779 bovine abortions per year was estimated.
The annual impact on livestock was estimated at US$48,402,244.00 due to abortions.

Abstract

This study aimed to conduct a systematic review to estimate the economic impact of Bovine alphaherpesvirus 1 (BoAHV1) infection in Brazil using epidemiological indicators through a meta-analysis. Specific descriptors were used to retrieve studies from the Scopus, PubMed, Biblioteca Digital Brasileira de Teses e Dissertações, and Catálogo de Teses e Dissertações da Capes databases, selecting those that met the inclusion criteria established between the years 2000 and 2020. The selected studies were subjected to descriptive statistical analysis using prevalence data as the primary outcome with a 95% confidence interval (CI) with a meta-analysis of random effects and measures of heterogeneity, significance, magnitude of the effect, and measurement of publication bias. Abortion costs and estimates were calculated based on the prevalence of BoAHV1 infection in Brazil and the characteristics of the agent as viral subtypes that cause abortion, period of occurrence, average pregnancy rate, and morbidity applied to susceptible animals and animal replacement values. The results were obtained from 49 studies included for meta-analysis where a prevalence of BoAHV1 infection of 54.12% (95% CI: 49.07% - 59.26%) in the bovine population and 88.53% (95% CI: 82.97%–92.43%) was present. From the structured formula, it is estimated that 258,779 bovine abortions occur, which causes a total loss, based only on the occurrence of abortion, of US $ 48,402,244.00 to the country. It is noteworthy that because of the losses caused, strict control and eradication measures need to be implemented based on the elaboration of normative

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instruction that includes health education measures, vaccination, tests for traffic, and animal trade so that BoAHV1 infections do not continue to negatively impact national producers economically, productively, and socially.
Key words: Systematic review. IBR. Abortion. Cost. Prevalence.

Resumo

Objetivou-se com o presente estudo realizar uma revisão sistemática para estimar os impactos econômicos da infecção por Alfaherpesvirus Bovino 1 no Brasil a partir dos indicadores epidemiológicos por meio de uma metanálise. Foram usados descritores específicos para a recuperação de estudos a partir das bases Scopus, Pubmed, Biblioteca Digital Brasileira de Teses e Dissertações e do Catálogo de Teses e Dissertações da Capes, selecionando-se aqueles que se enquadraram nos critérios de inclusão estabelecidos entre os anos 2000 e 2020. Os estudos selecionados foram submetidos à análise estatística descritiva utilizando-se os dados de prevalência como desfecho primário com intervalo de confiança de 95%, sendo realizado metanálise de efeito randômico e avaliadas as medidas de heterogeneidade, significância, magnitude do efeito e aferição do viés de publicação. Os custos e estimativas de aborto foram calculados com base na prevalência encontrada para BoAHV1 no Brasil e as características do agente como subtipos virais que provocam o aborto, período de ocorrência, taxa média de prenhez e morbidade aplicados aos animais suscetíveis e aos valores de reposição animal. Os resultados foram obtidos a partir de 49 estudos incluídos para metanálise, onde se verificou uma prevalência de BoAHV1 de 54,12% (IC95%: 49,07% – 59,26%) na população bovina e 88,53% (IC95%: 82,97% – 92,43%) para os rebanhos. A partir da fórmula estruturada, se estima que ocorram 258.779 abortos bovinos, que totalizam um prejuízo, apenas baseado na ocorrência do aborto, de US$ 48.402.244,00 ao país. Destaca-se que em virtude dos prejuízos ocasionados, medidas de controle e erradicação mais rigorosas precisam ser implementadas a partir da elaboração de uma instrução normativa que contemple medidas de educação sanitária, vacinação, realização de exames para o trânsito e comércio de animais para que as infecções pelo BoAHV1 não continuem a impactar negativamente os produtores nacionais de forma econômica, produtiva e socialmente.
Palavras-chave: Revisão sistemática. IBR. Aborto. Custo. Prevalência.

Introduction

Changes in the eating habits of families have led to a worldwide increase in the demand for animal protein; the safest way to meet this demand is by increasing sanitary surveillance services. This will require a more vehement action due to the intensification of means of production, since the estimated loss, according to the World Organization for Animal Health (OIE), to the detriment of animal diseases is greater than 20% (World Organization for Animal Health [OIE], 2008). Regarding infectious diseases, although viral diseases cause significant losses in cattle ranching, their reproductive impact is underestimated (Wathes, Oguejiofor, Thomas, & Cheng, 2020).

The first report of infection by *Bovine alphaherpesvirus 1* (BoAHV1) in Brazil dates to the 1960s (Galvão, Doria, & Alice, 1962/1963), and its isolation was carried out more than 15 years later (Alice, 1978). Since then, many studies have reported the occurrence of this agent in Brazilian cattle herds (Pituco, 1988; Lovato, Weiblen, Tobias, & Moraes, 1995; Cerqueira et al., 2000; Poletto, Kreutz, Gonzales, & Barcellos, 2004; J. A. Dias et al., 2008; M. S. Lima, Nogueira, Okuda, Stefano, & Pituco, 2011; Oliveira, Lorenzetti, Alfieri, & Lisbôa, 2015; N. P. C. Bezerra, Bezerra, Santos, Pereira, & Silva, 2019; Haas et al., 2020). The form of presentation and severity of infections and their pathogenesis varies according to BoAHV1 virulence, in addition to the fact that the agent is able to establish latency, contributing to the maintenance of BoAHV1 infection in the herd through asymptomatic animals that spread the virus in healthy hosts (Biswas, Bandyopadhyay, Dimri, & Patra, 2013).

Infections caused by BoAHV1 cause several clinical conditions, among which are reproductive disorders that can range from inflammatory changes in the genital tract of affected animals to the onset of respiratory, ocular, and neurological clinical conditions (Nandi, Kumar, Manohar, & Chauhan, 2009; Graham, 2013). Once present in the herd, albeit subclinically, the infection has been associated with a decreased productive performance of affected animals (Statham, Randall, & Archer, 2015), which makes it important for the correct implementation of prophylactic measures to determine the prevalence of BoAHV1 infection in detriment of the socioeconomic impacts that the infection can cause (Chen et al., 2018).

The economic losses attributed to BoAHV1 infection consist of weight loss, decreased milk production, fertility problems, such as endometritis and heat repetition, the birth of weak animals, and embryo and neonatal mortality (Ata, Kocamüftüoğlu, Hasircioğlu, Kale, & Ğülay, 2012; Junqueira & Alfieri, 2006). As a result of economic impacts and damage to animal health, many European countries have been making efforts to control and eradicate BoAHV1 infections since the 1980s (Ackermann et al., 1990; Ackermann & Engels, 2006; Hage et al., 1998).

For the institution of disease prevention and control programs, knowledge of epidemiological factors, such as prevalence data, risk factors, prophylaxis programs, and the associated cost-benefit, are essential for estimating economic impacts and evaluating the best strategy to be implemented (Thrusfield, 2005).

To demonstrate the impact of infection by various reproductive infectious agents in cattle raising, several studies have been conducted worldwide (Statham et al., 2015; Bennett, 2003; Macías-Rioseco et al., 2020; Ran et al., 2019; Reichel, Ayanegui-Alcérrea, Gondim, & Ellis, 2013; Sayers, 2017; Wathes et al., 2020) to warn about the damage caused by them and the importance of veterinary attention services in promoting animal health and improving the quality of life of the population. Considering the economic, reproductive, and social impacts associated with abortion caused by infectious reproductive diseases, adding to the fact that BoAHV1 is an abortive agent widely disseminated in national herds and does not present a sanitary contingency norm, this systematic review aimed to calculate the prevalence of BoAHV1 infection in Brazil and estimate the direct losses associated with the occurrence of abortion in bovine species.

Material and Methods

Study design

This study consists of a systematic review aimed to synthesize BoAHV1 infection prevalence data in cattle in Brazil and analyze, through meta-analysis, the quantitative data from manuscripts available in selected databases and from the gray literature (theses, dissertations, and reference lists) to define the cost of abortion in cattle. The study was conducted following the methodological recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (Moher, Liberati, Tetzlaff, & Altman, 2009).

Databases and search strategy

For the research on the subject, the combined search terms were defined for each of the databases using different search strategies, as the different databases use different search algorithms, requiring different combinations of the main indexing terms of the studied topic. In addition, a survey of studies was conducted during the fourth quarter of 2020.

For Scopus, the following descriptors were used: "(ALL ("Incidence") OR ALL ("Prevalence") OR ALL ("occurrence") OR ALL ("Epidemiology") OR ALL ("Prevalência") OR ALL ("occurrência") OR ALL ("incidência") OR ALL ("epidemiologia")) AND (ALL ("Brazil") OR ALL ("Brasil")) AND ((TITLE-ABS-KEY ("Herpesvirus") OR TITLE-ABS-KEY ("Alfaherpesvirus") OR TITLE-ABS-KEY ("Alphaherpesvirus")) AND (TITLE-ABS-KEY ("bovine") OR TITLE-ABS-KEY ("Cattle") OR TITLE-ABS-KEY ("bovino"))) OR (TITLE-ABS-KEY ("BoHV-1" OR "BoHV1" OR "BHV-1" OR "HVB-1"))." For PubMed, the following were used: "("Incidence" OR "Prevalence" OR "occurrence" OR "Epidemiology" OR "incidência" OR "prevalência" OR "Ocorrência" OR "epidemiologia") AND ("Brazil" OR "Brasil") AND ((("Herpesvirus" OR "alfaherpesvirus" OR "alphaherpesvirus") AND (("bovine" OR "Cattle" OR "bovino")) OR ("BoHV-1" OR "BoHV1" OR "BHV-1" OR "HVB-1")))".

For the recovery of theses and dissertations, in the domain of the Biblioteca Digital Brasileira de Teses e Dissertações, the following combination was used: "(Todos os campos: Incidence OR Prevalence OR Occurrence OR Epidemiology OR prevalência OR ocorrência OR incidência OR Epidemiologia OR sorológico OR serological OR soroprevalência OR Seroprevalence E Todos os campos: Herpesvirus OR alfaherpesvirus OR alphaherpesvirus OR BoHV-1 OR BoHV1 OR BHV-1 OR HVB-1 E Todos os campos:bovine OR Cattle OR bovinos OR bovino)". In addition, for the Catálogo de Teses e Dissertações Capes, the following was used: "BoHV-1 OR herpesvirus AND bovino AND prevalência OR ocorrência OR incidência OR Epidemiologia OR soroprevalência".

Eligibility criteria

The inclusion criteria were observational prevalence studies as designed or that point to the occurrence, through direct and/or indirect diagnostic methods in cattle in Brazil, of BoAHV1 infection as part of their results. The types of publications included consisted of full articles, "short communication" articles, abstracts presented at conferences, dissertations, and theses. No restrictions were placed on the language of the returned studies.

Was excluded manuscripts that did not discriminate the occurrence of BoAHV1 infection and those in the form of observational studies, clinical studies, studies with species other than cattle, studies that did not focus on the research of the agent of interest or the disease caused by it, studies conducted outside Brazil, studies that showed bias, such as those conducted in herds known to be positive, and those that investigated the presence of the agent through the analysis of clinical samples involving its isolation. After recovering the manuscripts, those published between 2000 and 2020 were selected.

Selection of studies and data extraction

The selection of studies was carried out independently by two different researchers, where the differences were decided by consensus between the parties. The research was carried out in four stages: identification, selection, eligibility, and inclusion criteria.

The first step consisted of registering the total number of articles returned from the terms defined to perform the searches, excluding manuscripts in duplicate. In the second stage, the titles of the articles were read, excluding those that did not cover the study area. The third step consisted of reading the abstracts of articles selected from the titles selected for reading those with information of potential interest about the occurrence of BoAHV1 infections in cattle in Brazil. Finally, the manuscripts that presented prevalence data were read in full in the fourth stage. Thereafter, those that did not present relevant information to compose the study were excluded, and the manuscripts of interest were included for analysis from the reference lists of the selected studies.

Additionally, bibliographic reference lists of selected studies were scrutinized after the fourth stage to have great coverage of the included manuscripts since not all studies were necessarily indexed in the selected databases.

Statistical analysis

Qualitative data were analyzed using descriptive statistics, using an absolute and relative distribution of positive cases for BoAHV1 infection, using raw prevalence data as the primary outcome with a 95% confidence interval (CI). To calculate the prevalence, the selected articles were subjected to a random model meta-analysis. Heterogeneity was assessed using Cochran's Q test, represented by the chi-square ($\chi 2$) test, with a significance of $P < 0.10$, and its magnitude measured by the I-square (I2) test (Deeks, Higgins, & Altman, 2019).

To check the consistency of the data from the studies selected for this systematic review, an analysis of publication bias was performed using a funnel chart. In this model, Egger's regression test was applied to assess whether the estimation of the effects presented bias or not.

Calculation of the cost of abortion owing to BoAHV1infection

The cost of abortion owing to BoAHV1 infection in Brazil was calculated by taking as reference parameters the number of animals at risk (n(v+nov)), the average pregnancy rate in the herd (Pr), the prevalence of the agent (Pv), the morbidity rate (Mb), the period of its occurrence to the detriment of the researched agent (PS), the viral subtypes of BoAHV1 (SV), and the abortion cost incurred calculated by the replacement cost of a pregnant cow minus the cost of a dry cow, adapted according to the proposed model Reichel et al. (2013). To do so, it was first necessary to calculate the number of abortions attributed to BoAHV1 infection (NBoAHV1) and then calculate the cost of abortion per BoAHV1 infection in Brazil according to the following formula:

$$\text{Economic impact} \times \text{NBoAHV1} = (n(v+nov)) \times Pr \times Pv \times Mb \times PS \times SV$$

Results and Discussion

The manuscript's scrutiny process is shown in Figure 1. The retrieved manuscripts were derived from databases of scientific articles and, like gray literature, from theses and dissertation deposit banks based on the descriptor terms. From the databases of scientific articles, 40 studies were retrieved from PubMed and 327 from Scopus, with the intersections of searches excluded by duplication (35), totaling 332 retrieved articles. Regarding the gray literature between theses and dissertations, 94 manuscripts from the Biblioteca Digital Brasileira de Teses e Dissertações (BDTD) and 35 from the Catálogo de Teses e Dissertações da Capes were retrieved. Excluding duplicate texts (17) resulted in a total of 112 manuscripts: 43 theses and 69 dissertations, which were added to the different databases, resulting in 444 manuscripts retrieved in total in the identification phase of the study.

In the selection stage, from the total identified manuscripts, 383 (295 articles and 88 theses and dissertations) were excluded by reading the titles, resulting in 61 manuscripts selected for reading the abstracts, 10 of which were excluded after reading the same. In the next step, eligibility, 51 manuscripts were read in full, of which 20 were excluded after the complete reading of the texts. Some studies were excluded at this stage because of the redundancy of information; only those published as scientific articles from research at the master's or doctoral levels were considered, with postgraduate manuscripts being deprecated to manuscripts published in journals.

Finally, in the inclusion stage, all 31 carefully selected studies had their reference lists scrutinized to include in the analysis of other manuscripts not covered by the search descriptors. Of these 31 studies, 18 (58.06%) were scientific articles, 5 (16.12%) were theses, and 8 (25.80%) were dissertations. After reading the lists, another 18 studies, all in the form of scientific articles, were included in the systematic review, totaling 49 studies covering an interval of published works from 2000 to 2020, as listed in Table 1.

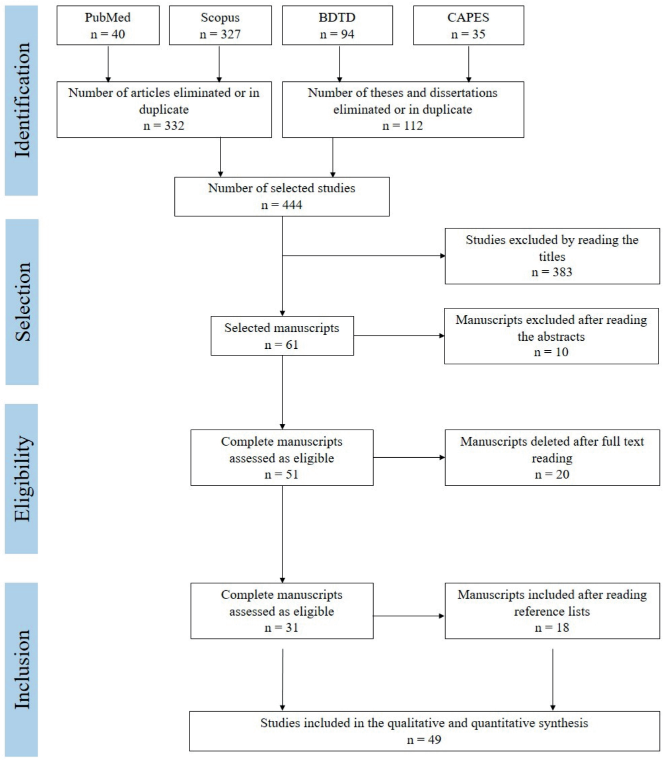

Figure 1. Study selection flowchart for inclusion in the systematic review.

Table 1
Number of isolated bacterial species analyzed per year

Authors	Region	State	Animal population			Properties		
			Cattle	Positives	%	Herds	Positives	%
Okuda et al. (2006)	N	RO	1988	1715	86.26	85	85	100
Arruda, Silva, Aragão, Castro and Gomes (2019)	N	AC	180	110	61.11			
Cerqueira et al. (2000)	NE	BA	558	314	56.27	15	13	86.66
Matos (2004)	NE	BA	764	145	18.97	13	13	100
Thompson et al. (2006)	NE	PB	2343	1093	46.6	72	72	100
D. C. Bezerra, Chaves, Sousa, Santos and Pereira (2012)	NE	MA	920	656	71.3	92	92	100
Sousa, Bezerra, Chaves, Santos and Pereira (2013)	NE	MA	160	108	67.5	4	4	100
Freitas et al. (2014)	NE	MA	1104	698	63.23	48	48	100
F. S. Silva et al. (2015)	NE	PE	380	302	79.5	20	20	100
Freitas (2016)	NE	MA	2455	753	30.67	86	67	77.91
F. A. B. Lima (2017)	NE	MA	364	313	85.96			
L. G. Fernandes et al. (2019a)	NE	PB	2443	1584	64.8	478	418	87.4
N. P. C. Bezerra et al. (2019)	NE	MA	160	109	68.12	16	16	100

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contuation...

B. P. Silva et al. (2019)	NE	PE	356	188	52.8	18	18	100
Vieira, Brito, Souza, Alfaia and Linhares (2003)	CO	GO	790	656	83.03	90	87	96.66
A. C. V. C. Barbosa, Brito and Alfaia (2005)	CO	GO	6932	3596	51.87	894	881	98.54
Tomich et al. (2009)	CO	MS	352	179	50.85	4	4	100
Afonso et al. (2010)	CO	GO	660	558	84.54			
Melo et al. (2002)	SE	MG	997	318	31.89			
Melo, Leite, Lobato and Leite (2004)	SE	MG	476	162	34	15	13	86.66
Junqueira, Freitas, Alfieri and Alfieri (2006)	SE	SP	208	142	68.26			
Mineo, Alenius, Näslund, Montassier and Björkman (2006)	SE	MG	230	172	74.78	2	2	100
Mendes et al. (2009)	SE	MG	126	101	80.15			
Alexandrino et al. (2011)	SE	MG;SP	278	152	54.67	5	5	100
E. C. M. Pereira (2011)	SE	MG	140	117	83.57			
M. C. O. P. Silva (2011)	SE	SP	6902	4856	70.35	1073		
J. A. Dias, Alfieri, Ferreira-Neto, Gonçalves and Müller (2013)	SE	PR	14803	7125	59	2018	1481	71.38
Santos et al. (2014)	SE	ES	1161	775	66.75	59	59	100
V. M. Barbosa et al. (2019)	SE	MG	264	165	62.5	20		
Queiroz-Castro et al. (2019)	SE	MG	75	41	54.7			
Haas et al. (2020)	SE	MG	476	231	48.6	46	45	97.5
Médici, Alfieri and Alfieri (2000)	S	PR	1235	540	43.72	81	75	92.59
Poletto et al. (2004)	S	RS	204	67	32.84	28	26	92.85
Quincozes (2005)	S	RS	1734	540	31.14	85	72	84.7
M. M. Dias (2006)	S	RS	1516	443	29.22	1		
J. A. Dias et al. (2008)	S	PR	1930			295	190	64.41
Frandoloso et al. (2008)	S	RS	765			26	15	57.69
Campos et al. (2009)	S	RS	200	144	72			
Holz et al. (2009)	S	RS	2200	538	24.45	390		
Fino (2011)	S	SC	309	84	27.18	6	6	100
Miranda (2012)	S	RS				269	75	27.88
Piovesan et al. (2013)	S	RS	2794	1654	59.19	157		
Sponchiado (2014)	S	PR	714	159	22.3	26	17	65.3
Becker et al. (2015)	S	RS	1224	299	24.42	93		
Evers (2015)	S	PR	363	216	59.5	32	30	93.8
Oliveira et al. (2015)	S	PR	400	70	17.5	90	35	38.9
Pasqualotto, Sehnem and Winck (2015)	S	SC	842	482	57.54	195		
Zardo (2017)	S	RS	258	24	9.3			
M. S. Lima et al. (2011)	BR	21 states	4460	3079	69.03	317	250	78.86

Abbreviations: N: North; NE: Northeast; CO: Middle West; SE: Southeast; S: South, BR: Brazil; RO: Rondônia; AC: Acre; BA: Bahia; PB: Paraíba; MA: Maranhão: PE: Pernambuco; GO: Goiás; MS: Mato Grosso do Sul; MG: Minas Gerais; SP: São Paulo; PR: Paraná; ES: Espíruto Santo; RS: Rio Grande do Sul; SC: Santa Catarina.

To calculate the prevalence, 67,498 animals and 7,294 herds were included in the analysis. The analysis of the included studies revealed a significant heterogeneity of the studies using the Q test ($P < 0.001$ and $I^2 = 99.32\%$) to calculate the prevalence per animal, with similar values being found to calculate the prevalence of herds ($P < 0.001$ and $I^2 = 94.47\%$). The results of asymmetries between the studies for different inferences, population, and herds, are represented in Figure 2 and Figure 3, respectively. The Egger test indicated no bias in the distribution of prevalence studies for the population of cattle ($P > 0.05$) but indicated the presence of bias for the studies among herds ($P < 0.05$).

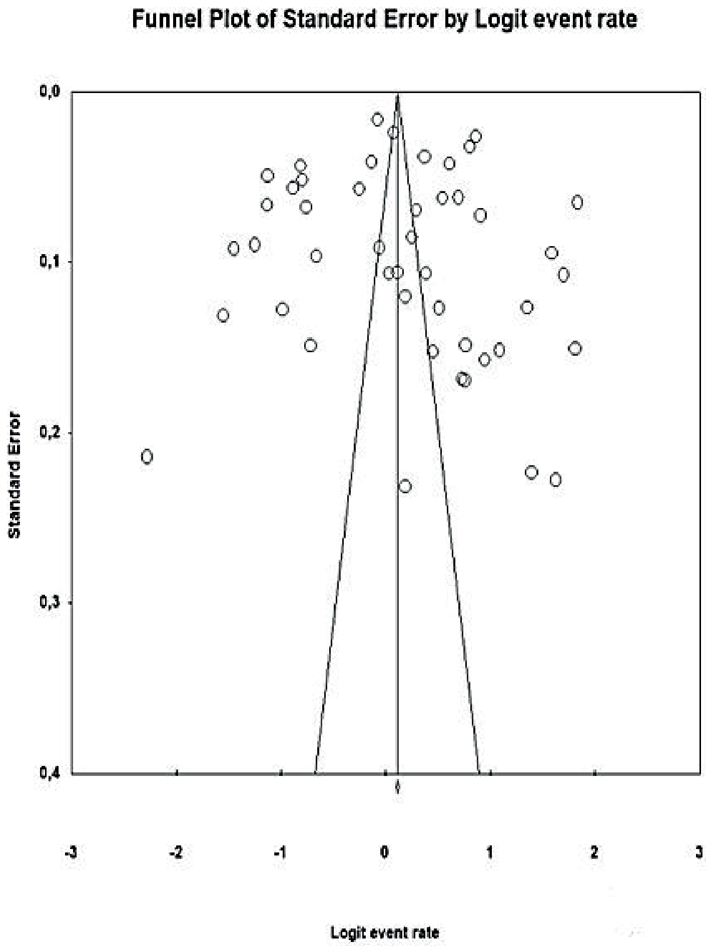

Figure 2. Funnel graph showing the asymmetric distribution of the prevalence studies of *Bovine alphaherpesvirus 1* infection among the bovine population in Brazil.

The meta-analysis performed for the studies included in the systematic review identified a pooled prevalence through the random model for cattle and herds, as shown in Figure 4 and Figure 5, respectively, of 54.21% (95%CI: 49.07% – 59.26%) and 88.53% (95%CI: 82.97 – 92.43%), respectively, both with significant heterogeneity ($P < 0.001$).

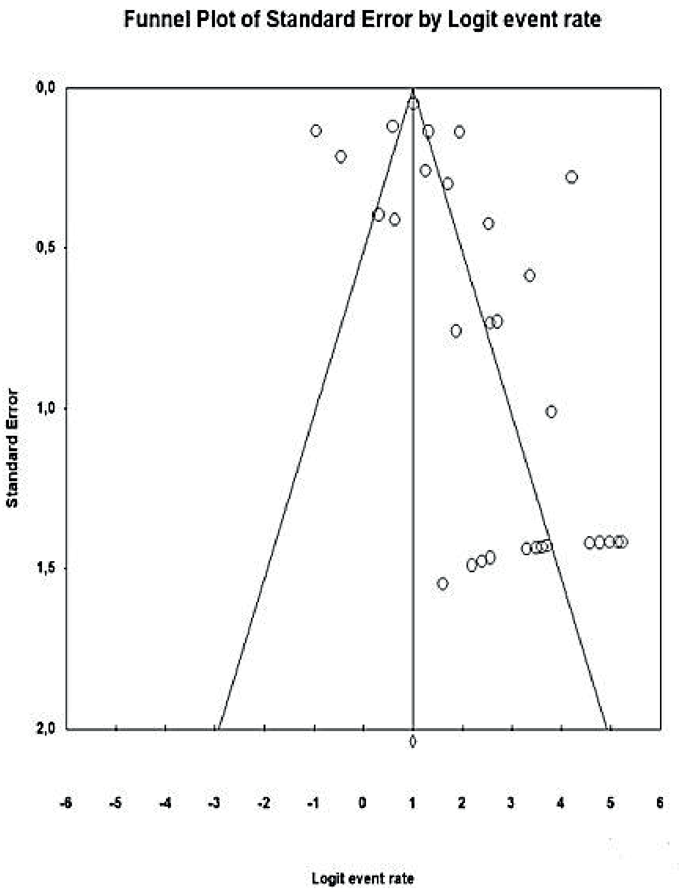

Figure 3. Funnel graph showing the asymmetric distribution of studies on the prevalence of *Bovine alphaherpesvirus 1* infection among cattle herds in Brazil.

Based on the data from the studies included in the meta-analysis and verifying the prevalence of 54.21%, this value was applied to the modified formula of Reichel et al. (2013) to calculate the direct losses caused by abortions owing to BoAHV1 infections in cattle in Brazil. The number of female bovines of reproductive age (n(v+nov)) corresponded to, according to the Instituto Brasileiro de Geografia e Estatística [IBGE] (2017), 59,670,476 heads; an average Pr of 60% (Vaz & Lobato, 2010; P. A. C. Pereira et al., 2013; Rosa et al., 2017; L. A. M. Fernandes et al., 2019b; E. T. N. Pereira, Freitas, Cordeiro, Silva, & Figueiredo, 2020) was considered based on the national literature; the Pv presented here; the Mb that, according to Constable, Hinchcliff, Done e Grünberg (2021), corresponded to a range that varied from 8 to 30%, being used the minimum value of 8% or 0.08; the PS considered only the final third of pregnancy (1/4 – considering the months of susceptibility during a year); and the SV of BoAHV1 that caused abortion (2/3) according to Flores (2017). Thus, the number of abortions attributed to BoAHV1 infections could be determined using the following equation:

$$NBoAHV1 = (n(v+nov)) \times Pr \times Pv \times Mb \times PS \times SV = 258{,}779$$

Study name	Subgroup within study	Event rate	Lower limit	Upper limit	Z-Value	p-Value	Total	Relative weight
Cerqueira et al., 2000	Blank	0,563	0,521	0,603	2,955	0,003	314 / 558	2,20
Médice; Alfieri; Alfieri, 2000	Blank	0,437	0,410	0,465	-4,399	0,000	540 / 1235	2,22
Melo et al., 2002	Blank	0,319	0,291	0,349	-11,163	0,000	318 / 997	2,21
Vieira et al., 2003	Blank	0,830	0,803	0,855	16,754	0,000	656 / 790	2,19
Melo et al., 2004	Blank	0,340	0,299	0,384	-6,841	0,000	162 / 476	2,19
Matos, 2004	Blank	0,190	0,164	0,219	-15,731	0,000	145 / 764	2,19
Poletto et al., 2004	Blank	0,328	0,267	0,396	-4,798	0,000	67 / 204	2,14
Quincozes, 2005	Blank	0,311	0,290	0,334	-15,301	0,000	540 / 1734	2,22
Barbosa; Brito; Alfaia, 2005	Blank	0,519	0,507	0,531	3,122	0,002	3596 / 6932	2,23
Thompson et al., 2006	Blank	0,466	0,446	0,487	-3,241	0,001	1093 / 2343	2,22
Mineo et al., 2006	Blank	0,748	0,688	0,800	7,159	0,000	172 / 230	2,13
Dias, 2006	Blank	0,292	0,270	0,316	-15,665	0,000	443 / 1516	2,22
Okuda et al., 2006	Blank	0,863	0,847	0,877	28,202	0,000	1715 / 1988	2,21
Junqueira et al., 2006	Blank	0,683	0,616	0,742	5,143	0,000	142 / 208	2,14
Tomich et al., 2009	Blank	0,509	0,456	0,560	0,320	0,749	179 / 352	2,18
Holz et al., 2009	Blank	0,245	0,227	0,263	-22,739	0,000	538 / 2200	2,22
Campos et al., 2009	Blank	0,720	0,654	0,778	5,997	0,000	144 / 200	2,13
Mendes et al., 2009	Blank	0,802	0,723	0,862	6,250	0,000	101 / 126	2,03
Afonso et al., 2010	Blank	0,845	0,816	0,871	15,781	0,000	558 / 660	2,18
Fino, 2011	Blank	0,272	0,225	0,324	-7,706	0,000	84 / 309	2,16
Pereira, 2011	Blank	0,836	0,765	0,888	7,132	0,000	117 / 140	2,02
Silva, 2011	Blank	0,704	0,693	0,714	32,793	0,000	4856 / 6902	2,23
Alexandrino et al., 2011	Blank	0,547	0,488	0,604	1,557	0,119	152 / 278	2,17
Lima et al., 2011	Blank	0,690	0,677	0,704	24,757	0,000	3079 / 4460	2,23
Bezerra et al., 2012	Blank	0,713	0,683	0,741	12,488	0,000	656 / 920	2,21
Sousa et al., 2013	Blank	0,675	0,599	0,743	4,330	0,000	108 / 160	2,11
Dias et al., 2013	Blank	0,481	0,473	0,489	-4,544	0,000	7125 / 14803	2,23
Piovesan et al., 2013	Blank	0,592	0,574	0,610	9,668	0,000	1654 / 2794	2,23
Freitas et al., 2014	Blank	0,632	0,603	0,660	8,682	0,000	698 / 1104	2,21
Santos et al., 2014	Blank	0,668	0,640	0,694	11,189	0,000	775 / 1161	2,21
Silva, 2014	Blank	0,795	0,751	0,832	10,658	0,000	302 / 380	2,16
Sponchiado, 2014	Blank	0,223	0,194	0,255	-13,897	0,000	159 / 714	2,20
Oliveira et al., 2015	Blank	0,175	0,141	0,215	-11,784	0,000	70 / 400	2,16
Evers, 2015	Blank	0,595	0,544	0,644	3,599	0,000	216 / 363	2,18
Pasqualotto et al., 2015	Blank	0,572	0,539	0,605	4,190	0,000	482 / 842	2,21
Becker et al., 2015	Blank	0,244	0,221	0,269	-16,976	0,000	299 / 1224	2,21
Freitas, 2016	Blank	0,307	0,289	0,325	-18,633	0,000	753 / 2455	2,22
Lima, 2017	Blank	0,860	0,820	0,892	12,015	0,000	313 / 364	2,13
Zardo, 2017	Blank	0,093	0,063	0,135	-10,625	0,000	24 / 258	2,04
Barbosa et al., 2019	Blank	0,625	0,565	0,681	4,018	0,000	165 / 264	2,16
Silva et al., 2019	Blank	0,528	0,476	0,579	1,059	0,289	188 / 356	2,18
Queiroz-Castro et al., 2019	Blank	0,547	0,434	0,655	0,807	0,420	41 / 75	2,01
Fernandes et al., 2019	Blank	0,648	0,629	0,667	14,442	0,000	1584 / 2443	2,22
Bezerra et al., 2019	Blank	0,681	0,605	0,749	4,477	0,000	109 / 160	2,11
Arruda et al., 2019	Blank	0,611	0,538	0,680	2,956	0,003	110 / 180	2,13
Haas et al., 2020	Blank	0,485	0,441	0,530	-0,642	0,521	231 / 476	2,19
		0,542	0,491	0,593	1,609	0,108		

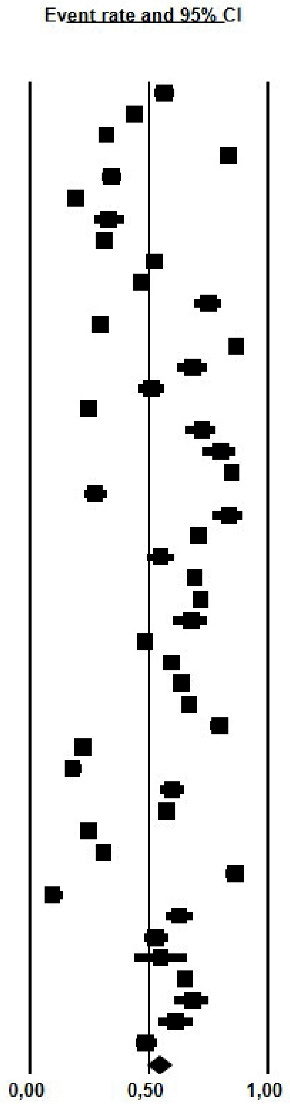

Figure 4. Prevalence of *Bovine alphaherpesvirus 1* infection in the bovine population in Brazil.

local	Study name	Subgroup within study	Event rate	Lower limit	Upper limit	Z-Value	p-Value	Total	Relative weight
BA	Cerqueira et al., 2000	.	0,867	0,595	0,966	2,464	0,014	13 / 15	3,27
PR	Médice; Alfieri; Alfieri, 2000	.	0,926	0,845	0,966	5,953	0,000	75 / 81	4,29
GO	Vieira et al., 2003	.	0,967	0,902	0,989	5,734	0,000	87 / 90	3,80
MG	Melo et al., 2004	.	0,867	0,595	0,966	2,464	0,014	13 / 15	3,27
BA	Matos, 2004	.	0,964	0,616	0,998	2,289	0,022	13 / 13	1,73
RS	Poletto et al., 2004	.	0,929	0,755	0,982	3,495	0,000	26 / 28	3,35
RS	Quincozes, 2005	.	0,847	0,754	0,909	5,680	0,000	72 / 85	4,61
GO	Barbosa; Brito; Alfaia, 2005	.	0,985	0,975	0,992	15,090	0,000	881 / 894	4,66
PB	Thompson et al., 2006	.	0,993	0,900	1,000	3,507	0,000	72 / 72	1,77
MG	Mineo et al., 2006	.	0,833	0,194	0,990	1,039	0,299	2 / 2	1,57
RO	Okuda et al., 2006	.	0,994	0,914	1,000	3,625	0,000	85 / 85	1,77
PR	Dias et al., 2008	.	0,644	0,588	0,697	4,877	0,000	190 / 295	4,92
RD	Frandoloso et al., 2008	.	0,577	0,385	0,748	0,781	0,435	15 / 26	4,36
MS	Tomich et al., 2009	.	0,900	0,326	0,994	1,474	0,140	4 / 4	1,65
SC	Fino, 2011	.	0,929	0,423	0,996	1,748	0,081	6 / 6	1,69
MG;SP	Alexandrino et al., 2011	.	0,917	0,378	0,995	1,623	0,105	5 / 5	1,67
21 estados	Lima et al., 2011	.	0,789	0,740	0,830	9,572	0,000	250 / 317	4,90
RS	Miranda, 2012	.	0,279	0,228	0,335	-6,990	0,000	75 / 269	4,90
MA	Bezerra et al., 2012	.	0,995	0,920	1,000	3,681	0,000	92 / 92	1,77
MA	Sousa et al., 2013	.	0,900	0,326	0,994	1,474	0,140	4 / 4	1,65
PR	Dias et al., 2013	.	0,734	0,714	0,753	20,139	0,000	1481 / 2018	4,98
MA	Freitas et al., 2014	.	0,990	0,857	0,999	3,218	0,001	48 / 48	1,76
ES	Santos et al., 2014	.	0,992	0,880	0,999	3,365	0,001	59 / 59	1,76
PE	Silva, 2014	.	0,976	0,713	0,999	2,594	0,009	20 / 20	1,75
PR	Sponchiado, 2014	.	0,654	0,457	0,809	1,543	0,123	17 / 26	4,32
PR	Oliveira et al., 2015	.	0,389	0,294	0,493	-2,090	0,037	35 / 90	4,78
PR	Evers, 2015	.	0,938	0,782	0,984	3,708	0,000	30 / 32	3,36
MA	Freitas, 2016	.	0,779	0,679	0,854	4,849	0,000	67 / 86	4,70
PE	Silva et al., 2019	.	0,974	0,690	0,998	2,519	0,012	18 / 18	1,74
PB	Fernandes et al., 2019	.	0,874	0,842	0,901	14,061	0,000	418 / 478	4,90
MA	Bezerra et al., 2019	.	0,971	0,664	0,998	2,436	0,015	16 / 16	1,74
MG	Haas et al., 2020	.	0,978	0,861	0,997	3,765	0,000	45 / 46	2,59
			0,885	0,830	0,924	8,713	0,000		

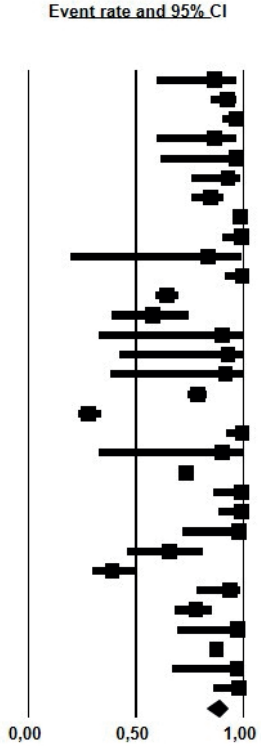

Figure 5. Prevalence of *Bovine alphaherpesvirus 1* infection in cattle herds in Brazil.

To calculate the costs associated with abortion, the model adopted by Reichel et al. (2013) was considered, and for the replacement of dairy cows, the average value of a pregnant cow (US$ 1,000) was subtracted from the value of an animal with the same score (considering the average of 450 kg of live weight) sold for slaughter (US$750), which equates to a cost of US$250 per abortion in dairy animals. To calculate the cost of abortion in beef animals, the replacement price of a weaned calf was calculated as 165 kg (US$ 458) less than the slaughter value of an animal of the same weight (US$ 286), which resulted in a loss of $172 per abortion. For the calculation basis, the variations in the price of the ox's arroba, the replacement price of calves, and the average value of pregnant cows in December 2020 were used as a reference through the market quotation available in advertisements and national databases.

According to the IBGE (2017), 11,506,788 dairy cows were milked in Brazil. Subtracted from the total number of animals of reproductive age in the national territory for the same year, it has 48,163,688 heads of beef cows of reproductive age. Applying these values to the previous formula, we have:

NBoAHV1(dairy cattle) = (n(v+nov)) × Pr × Pv × Mb × PS × SV = 49,902

NBoAHV1 (beef cattle) = NBoAHV1 – NBoAHV1 (dairy cattle) = 208,877

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The estimate of the economic impact caused by abortion attributed to BoAHV1 for the different categories can be defined as follows:

NBoAHV1 (dairy cattle) × associated cost (dairy cattle) = 49,902 × 250 = US$ 12,475,500.00

NBoAHV1 (beef cattle) × associated cost (beef cattle) = 208,877 × 172 = US$ 35,926,844.00

Therefore, the economic impact of abortion owing to BoAHV1 infection in Brazil is on the order of US$ 48,402,244.00, considering both categories of affected animals.

This study is the first meta-analysis of the global prevalence of BoAHV1 infection in cattle in Brazil; it is also the first study to propose a model for calculating the economic impact of abortion in cattle owing to BoAHV1 infections based on the application of epidemiological data associated with BoAHV1.

Due to the variation in prevalence data and the number of studies included, statistical tests to assess the heterogeneity of the studies were significant ($P < 0.001$). Therefore, to estimate the magnitude of the effect or the variety of effect estimates due to the heterogeneity, the I^2 test was used, whose value was found $I^2 = 94.47\%$, indicating considerable heterogeneity of the included studies ($75\% \leq I^2 \leq 100$) according to Deeks et al. (2019). This is due to the wide variation in the distribution of BoAHV1 infection in cattle in Brazil.

At least one study from 14 different Brazilian states was included. In addition, one of the studies (M. S. Lima et al., 2011) contained data from eight other states, totaling 22 states covered in the survey. The prevalence of the included studies ranged from 9.3% (Zardo, 2017) to 86.28% (Okuda et al., 2006) for animals and 27.88% (Miranda, 2012) to 100% for herds (Alexandrino et al., 2011; D. C. Bezerra et al., 2012; N. P. C. Bezerra et al., 2019; Fino, 2011; Freitas et al., 2014; Matos, 2004; Mineo et al., 2006; Okuda et al., 2006; Thompson et al., 2006; Tomich et al., 2009; Santos et al., 2014; B. P. Silva et al., 2019; Sousa et al., 2013). These data show that BoAHV1 is widely distributed in Brazilian herds, as can be confirmed through the meta-analysis of the included studies for herds and animals with 88.53% (95%CI: 82.97% – 92.43%) and 54.21% (95%CI: 49.07% – 59.26%), respectively, from 2000 to 2020.

The prevalence of BoAHV1 infections found in animals (54.21%; 95%CI: 49.07% – 59.26%), considering the CI, is following the prevalence values observed in studies by Alexandrino et al. (2011), A. C. V. C. Barbosa et al. (2005), Cerqueira et al. (2000), J. A. Dias et al. (2013), Pasqualotto et al. (2015), Piovesan et al. (2013), Queiroz-Castro et al. (2019), B. P. Silva et al. (2019) and Tomich et al. (2009). In a similar study that determined the prevalence of BoAHV1 infection in China through a systematic review with meta-analysis, Chen et al. (2018) identified a prevalence of 40.0% in cattle from that country from 41 selected manuscripts with a total sample of 43,441 cattle. Together, the animals sampled from eligible manuscripts totaled 67,498 bovines to compose the meta-analysis of this study. It is noted that the impact in Brazil, verified by the data of higher prevalence, larger number of studies, and larger population of sampled cattle, is greater than the data pointed out in the study by Chen et al. (2018). Considering the size of the national herd associated with the higher prevalence of BoAHV1 infections in Brazil compared to the study by Chen et al. (2018), the economic and productive consequences are further deepened, especially since cattle raising is a commodity and China is a commercial partner and direct consumer of beef produced in Brazil.

The prevalence of infection in herds (88.53%; 95%CI: 82.97% – 92.43%) is in agreement with the findings of Cerqueira et al. (2000), L. G. Fernandes et al. (2019), Melo et al. (2004) and Quincozes (2005). The number of studies that showed a higher prevalence of herds compared to that found in this meta-analysis is associated with a great predominance of positive herds. Given that the median prevalence is 96.66%, this high value and its proximity to the indicated values of prevalence per herd strengthens the evidence that BoAHV1 is widely distributed in herds since more than half of the studies point to a prevalence higher than that found in the present study.

Egger's test indicated no bias for prevalence studies in the animal population ($P > 0.05$), and the funnel graph (Figure 2) showed a symmetrical distribution of the included studies, with their predominance at the apex which indicated a smaller standard error of the selected manuscripts. The absence of bias in studies on the prevalence of infection in animals is because prevalence and risk factor surveys consider animals as sampling units when herds are the most assertive parameter for the analysis of risk factors due to the specificity of each property, such as reproductive, sanitary, and feeding management particular to each one.

The same was not observed when applied to the calculation to obtain the prevalence in herds ($P < 0.05$). This can be attributed to the fact that when considering the properties as sampling units, the minimum number of herds required to compose a prevalence study, with 5% error and 95% CI in an infinite population, would be approximately 400. Of the 32 studies considered to calculate the prevalence of herds, 26 sampled less than 100 properties, with a median of 47 and a range from 2 to 2018 herds sampled per study. Therefore, considering 100 properties as a minimum "n" sample, 5% error, and 95% CI, each study should be carried out in a population of up to 134 properties per state or region studied, which explains the bias detected by the Egger test to calculate the prevalence of BoAHV1 in herds. In Figure 3, the presence of bias is verified by the asymmetry in the funnel graph, where some studies can be observed displaced out of the axis and closer to the base, showing a high standard error according to Begg and Berlin (1988).

Based on the parameters of prevalence, the number of animals at risk in the country, morbidity, period of susceptibility, and viral subtypes of BoAHV1 that are more closely related to abortion and reproductive parameters, were projected 258,779 abortions and an economic impact on livestock of US$ 48,402,244.00. This value is related to loss to the detriment of abortion related to BoAHV1 infections is below the values pointed out by Reichel et al. (2013), who reported an annual loss of US$152.3 million from abortions related to *Neospora caninum* infections.

These values are subject to fluctuations due to variations in the price of animals in different regions of the country. It is important to highlight that the economic impact mentioned here concerns the direct losses related to the occurrence of abortion and the expenses associated with the replacement of animals in these cases. Considering that indirect losses also occur due to negative impacts on growth and reproduction (Biswas et al., 2013) and other forms of presentation of herpetic infections, such as respiratory, ocular, neurological, genital, and reproductive (Junqueira & Alfieri, 2006; Nandi et al., 2009), it is inferred that the values presented here represent only a part of a higher cost.

According to Can, Ataseven and Yalçin (2016), significant changes in production and performance can also occur in infected cows, even if they do not show clinical signs or reproductive problems, which reinforces that the losses caused are high when considering only abortion as a single nosological entity. According to the authors, costs related to losses not associated with abortion, characterized by decreased milk production (US$177) and animal weight (US$154), represent 65.0% (US$331) of the total costs related to cases where abortion occured. Hage et al. (1998) indicated a statistically significant association between animals infected with BoAHV1 and a drop in milk production during the first 14 days of infection. Van Schaik et al. (1999) found that during an outbreak caused by BoAHV1, there was a drop in the production by 0.92 kg per animal per day for 9 weeks. According to Statham et al. (2015), estimated losses due to decreased production reach 1,000 kg of milk per lactation in seropositive animals compared to seronegative animals. According to Can et al. (2016), considering the probability of abortion, infection with BoAHV1 causes an impact of US$ 379 per infected animal.

The values budgeted in this study provide a basal estimate of the economic and sanitary impacts caused by direct losses (abortion) associated with BoAHV1 infection in cattle in Brazil. Energetic actions related to appropriate sanitary measures should be carried out in the planning of preventive strategies with regard not only to BoAHV1 infection but also to other reproductive diseases of an infectious nature, such as the institution of sanitary prevention and control programs by the agencies of inspection and animal health protection. Regarding BoAHV1, the production of educational pamphlets, the delivery of lectures, radio advertisements, and other means of communication are good means of informing producers about the economic impacts, risks, and the need to adopt appropriate sanitary measures. In addition to health education actions, the institution of restrictive measures for animal transit and trade, such as the requirement of vaccination certificates for cattle, are necessary.

It is noteworthy that the results estimated in this study do not represent the totality of the impacts caused by herpetic infections in cattle in Brazil when considering only direct measurement losses, such as abortion. Nevertheless, beyond national borders, European Union countries have directed efforts toward the control and eradication of BoAHV1 infection since the 1980s (Ackermann & Engels, 2006), and considering the customs protection mechanisms that can be adopted by economy and defense countries are consolidated, BoAHV1 infections can constitute an obstacle, in the near future, to the trade of animals of national origin, causing possible embargoes on cattle raising.

Conclusion

Analogous to biology, BoAHV1 infections are a latent problem concerning sanitary strategies to contain the agent, while at the same time representing a cost for producers, from small to large, who need attention in planning and maintenance of a production system. Therefore, it can be concluded that BoAHV1 is widely disseminated in national herds, as can be seen from the numbers presented by different studies, silently causing significant economic, productive, and social impacts on Brazilian producers.

It is essential for the prophylaxis of infection by BoAHV1 to implement a program in the form of normative instruction, which covers educational campaigns on the risk of infection to the requirement of a vaccination certificate for trade and animal transit in the national territory. In addition, information about the economic impacts and health risks associated with infectious reproductive diseases in cattle needs to reach the producer so that a change in the national scenario can materialize in the medium-to-long-term. For this, animal health defense agencies and higher education institutions are essential for the planning, assistance, education, and inspection of adequate prophylactic measures to promote good health in national bovine herds.

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