Animal Health

Original

Prevalence of Brucellosis in Cattle and Buffaloes in Central America and the Caribbean, and South America. Systematic Review and Meta-Analysis

Cesar Augusto Zamora Macías *, Marina Dalila Zambrano Aguayo **, Gustavo Adolfo Navarrete Suarez **, Madeline Michelle Rezabala Zambrano ***, Osvaldo Fonseca-Rodríguez ****, Miguel Pérez Ruano *****

*Postgraduate Institute of the Technical University of Manabi (UTM), Avenida Urbina y Calle Che Guevara, Portoviejo, Manabí, Ecuador.
**Department of Veterinary Medicine, Faculty of Veterinary Sciences, the Technical University of Manabi (UTM), Avenida Urbina y Calle Che Guevara, Portoviejo, Manabí, Ecuador.
***Faculty of Health Sciences, the Technical University of Manabi (UTM), Avenida Urbina y Calle Che Guevara, Portoviejo, Manabí, Ecuador.
****Department of Epidemiology and Global Health, Umeå University, SE-901 87 Umeå, Sweden.
*****Chair One Health, the Agrarian University of Havana. Carretera de Tapaste y Autopista Nacional Km 23½, San José de las Lajas, Mayabeque, Cuba. P.O. Box 18. Cuba.

Correspondence: lolozamora1994@hotmail.com

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ABSTRACT

Background: Brucellosis produces losses in livestock raising in the Americas. This region reports prevalence variations associated with the implementation of control programs, thus requiring an analysis that permits the combination of results to reach conclusions, which may be conducted through meta-analysis. **Aim.** To estimate the combined prevalence of Brucellosis in Cattle and Buffaloes in Central America and the Caribbean, and South America in the 2010-2021 period, and to analyze the different time performances in all the regions and the species. **Materials and methods:** Several papers published in electronic databases, such as PubMed / PubMed Central, Science Direct, Scielo, Ebsco, and Google Scholar were selected. Original papers and postgraduate theses available were included, provided they offered information about cattle and buffaloes, using the serological techniques recommended by the World Animal Health Organization, and which provided the sample size and the number of positives required. A meta-analysis was performed to estimate the combined prevalence of the disease, and the effect on the

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subgroups was evaluated by meta-regression. **Results:** Overall, 65 papers that met the selection criteria were included, 56 of them on cattle, and 11 on buffalo-related studies. The combined prevalence was 3.0%. Differences between cattle (2.7%) and buffaloes (5.2%) were observed. The differences between the periods studied accounted for 4.3% (2011-2016) and 2.0% (2017-2021), respectively. **Conclusions:** The combined prevalence of the disease was 3.0%, which was higher in buffaloes, and dropped in the last five years. No differences were observed between the two regions studied.
Keywords: The Americas, bovids, Brucella, disease prevalence *(Source AGROVOC)*

INTRODUCTION

Latin America and the Caribbean produce a little over 23% of the meat from cattle and buffaloes in the world, with an enormous growth of these productions, especially in the South American countries, making it the region with the largest beef exports internationally (FAO, 2021).

In recent years, the region has included buffalo production, seeking the development of cost-effective and sustainable models (Bertoni *et al*., 2021), which has increased their relevance within the meat and milk production systems (Fosgate *et al*., 2011). In 2007, there was a steep growth of this species, reaching up to 12.7% annually, a great deal over the other continents (Zava, 2007), which has been kept so far, based on the data collected from Colombia, Argentina, Venezuela, and Cuba (Naveena *et al*., 2020).

Cattle and buffalo production is affected by infectious diseases that cause a negative impact on breeding. Some of these diseases are zoonotic and originate public health issues (Contreras *et al*., 2012). These diseases are an obstacle to proper productive and reproductive performance of these animals, resulting in huge economic losses (Fosgate *et al*., 2011; Alves *et al*., 2015; Villanueva *et al*., 2018).

Brucellosis stands out among the infectious diseases that affect bovines and bubaline, despite the losses caused by livestock raising, this disease consists of a zoonosis that affects most developing countries (Avila-Granados *et al*., 2019), particularly in the Mediterranean, Asian, Africa, and Latin American countries (Gioia *et al*., 2019), and it is endemic to Central America and the Caribbean (Cárdenas *et al*., 2019).

Multiple species of the Brucella gender may affect animals and humans; however, B. abortus, B. melitensis, and B. suis are the most common species that infect food-producing animals (Poulsen *et al*., 2014).

In Latin America, the disease is widely distributed, with reports of prevalence variations associated with the implementation of control programs (Ojeda Gutierrez and Roman Cárdenas, 2018).

Several aspects, such as the vaccination status and the prevalence of the disease, are significant factors to adopt and evaluate the impact of brucellosis control/eradication programs (Mirnejad *et al*., 2017).

The collection of results from different fragmented studies based on the area and time permit researchers to demonstrate the status of a disease in a country or geographical region in a period of time (Tesfaye *et al*., 2021). In these regions, several research studies have shown variable results. In Latin America, a 0.4% prevalence was reported in Paraguay (Aznar *et al*., 2015); whereas a 65.5% prevalence was found in Brazil (Chiebao *et al*., 2015). Hence, a combined analysis of all the results is necessary to reach conclusions.

Meta analysis helps obtain a weighted average of the results from several studies, and estimate the frequency of the disease, as the case of prevalence (Barendregt *et al*., 2013). Accordingly, the purpose of this paper is to estimate the combined prevalence of brucellosis in cattle and buffaloes from Central America and the Caribbean, and South America in 2010-2021, and to analyze the possible difference in their performances over time, and between the two regions and species.

MATERIALS AND METHODS

Literature search strategy

This study relied on the information provided by several papers and master's degree theses published in Spanish, Portuguese, and English, found in the electronic databases PubMed / PubMed Central, Science Direct, Scielo, Ebsco, and Google Scholar in 2010-2021. The search followed the medical terms source MeSH. The keywords were (Brucellosis OR Brucella) AND (Bovine OR Buffalo) AND (Seroprevalence OR Prevalence OR Seroepidemiology) AND (South America OR Central America OR the Caribbean OR Particular Country).

Inclusion criteria

The following articles were included in the study: 1) published between 2010 and 2021; 2) peer-reviewed original research papers, and postgraduate theses from South America and Central America and the Caribbean; 3) those reporting the seroprevalence of brucellosis in bovine/bubaline species in any of the management systems (intensive or extensive); 4) available in fill text; 5) which used the serological techniques recommended by the World Organization for Animal Health (OIE) in the diagnostic for screening and confirmation (OIE, 2021); 6) that provide the necessary sample size and number of positive cases.

Quality analysis

Two specialists were selected for quality analysis, who used a methodology known as strengthening notification of observational studies in epidemiology (STROBE), which comprises 22 aspects, namely objectives, different components of materials and methods (study design, sample size, population in the study, bias, calibration methods, results, and limitations). The scores were determined between 0 and 44, and the articles found were classified into 3 groups: low quality (<15.5), good quality (15.5–29.5), and high quality: (30.0–44.0) (Von Elm *et al*., 2007), and the articles that met the high and good quality criteria were included, the rest were ruled out.

Study selection and data mining

The records identified from several electronic databases were indexed using software BIVET (Romero, 2019). The duplicated records were identified, recorded, and deleted. The titles and abstracts were examined independently using the predefined inclusion criteria; the full texts were compiled independently, and their eligibility for the final evaluation was evaluated for definitive inclusion.

A format for data retrieving was designed, based on the first author, publication year, research year, geographical location (countries), study design, sampling method, sample size, diagnostic test, species, number of positive and negative cases, individually and by herds. The seroprevalence of brucellosis was calculated by dividing the number of positive cases by the total number of individuals examined in the study, in a particular population and period, then it was multiplied by 100. The size of the effect of the study and its corresponding confidence intervals (CI) were calculated depending on the previously collected data. Microsoft Excel was used to codify and manage the information collected from relevant studies.

PRISMA was used to report the outcome of the study (Shamseer *et al*., 2015).

Statistical analysis

A meta-analysis test was performed to estimate the combined prevalence of brucellosis, using the formula suggested by Barendregt *et al*. (Barendregt *et al*., 2013). The variations between the studies and the results of the estimations of seroprevalence and their corresponding CI from every study were illustrated in a diagram, along with the size of the group effect. Similarly, a subgroup-based analysis was conducted to determine the effect of the geographical regions (South America and Central America and the Caribbean), the animal species (bovines and bubaline), and the time of publication (2010-2016 and 2017- 2021) of combined seroprevalence of brucellosis.

The Cochrane Q statistics and the inverse variance index (I2) were calculated to determine the heterogeneity and inconsistency, respectively. Likewise, the I2 values (25, 50, and 75%) were considered with low, mid, and high heterogeneity, respectively (Higgins and Thompson, 2002).

The variance of the estimations of the size effects on the population was evaluated through the tau statistics ($\tau 2$). A Galbraith graph diagram was designed to evaluate the heterogeneities of the estimations at the study level. According to the heterogeneity evaluation, the Simonian and Laird method of random effects was used (if the value of p from the Q test was <0.05 and I2 was $>$ 50%), or the Mantel-Haenszel fixed-effect method to pool the estimations (Tufanaru *et al*., 2015).

Then, the effects of the small study and the presence of publication bias were illustrated through funnel diagrams and the Egger Begg asymmetry tests (Borenstein *et al*., 2009). A funnel diagram was designed using the logarithm of the size of the effect and its corresponding standard error of the effect size.

The meta-analysis was performed using the meta version software (4.18-1) from R (R Development Core Team, 2020)

The heterogeneity between the groups was also tested by using a meta regression analysis, which helped confirm the prevalence relation to the geographical area, the time of study, and the animal species. It was conducted as well for the variables included in the study by separate; the variables having P<0.1 were analyzed by multivariate meta-regression.

RESULTS AND DISCUSSION

The search helped identify 78 papers that met the inclusion criteria, with a definitive number of 65 (Fig. 1). The main quality aspects that limited the selection of the articles were associated with the design and the performance of internationally recognized diagnostic tests.

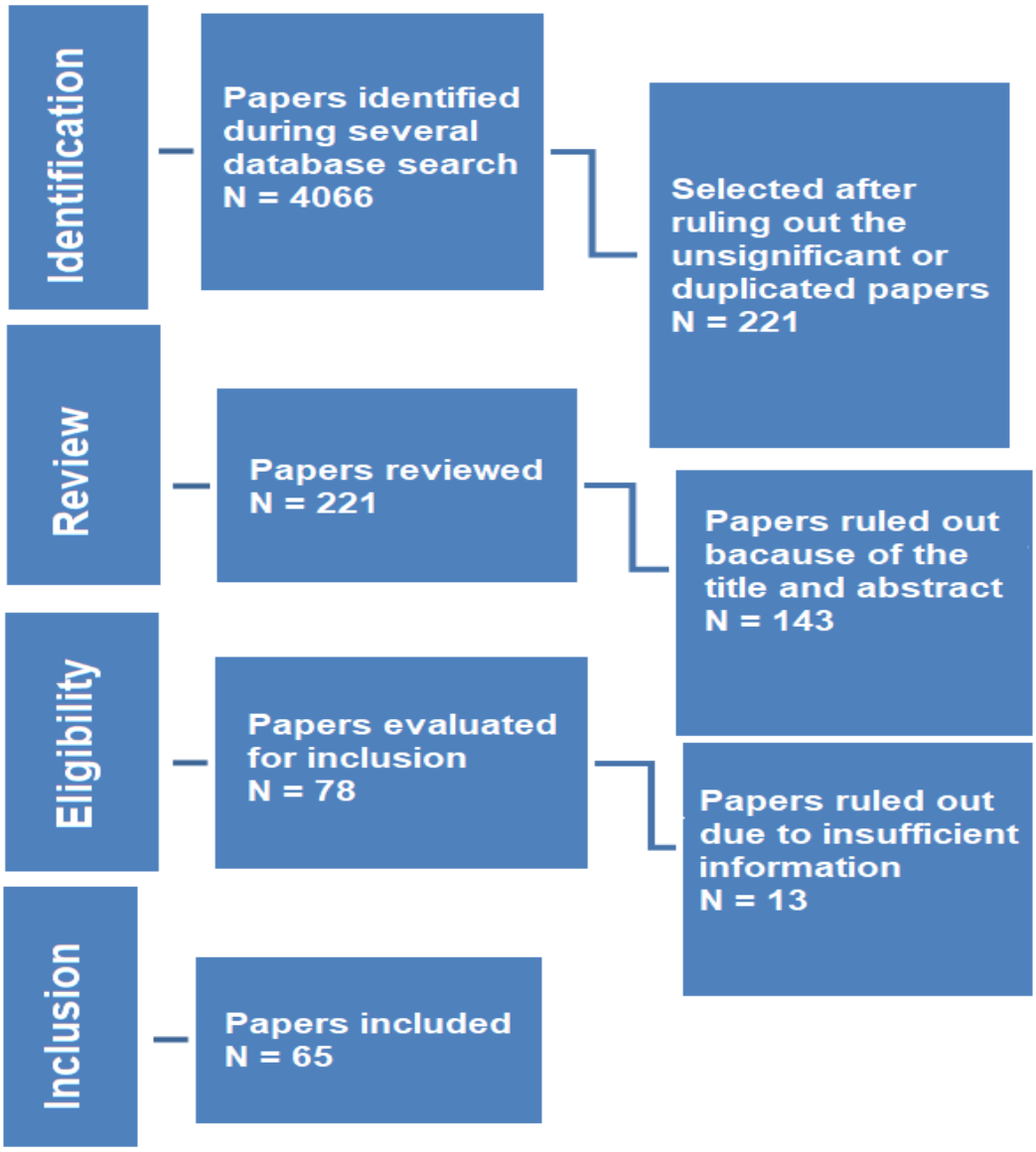

Figure 1. Flow diagram of the article selection process in the study

The reports were gathered from studies of brucellosis prevalence in 18 countries and territories of the regions, 10 from Central America and the Caribbean, and 8 from South America, 31.25% and 61.53% of the countries in those regions, respectively (Table 1); 75% was concentrated in 4 countries: Ecuador, Brazil, Mexico, and Colombia. This situation may become a hindrance to the results of the disease control program in those territories, as the knowledge of the prevalence and distribution of the disease is a critical factor to evaluate the impact of these programs and conduct the necessary adjustments (Mirnejad *et al*., 2017).

Table 1. Distribution of the scientific articles by countries and geographical area

Region and country	Papers included	Animals studied	Positive	Positive (%)	CI 95%
Central America and the Caribbean	13	604171	4557	0.75	0.73 0.78
Belize	1	14606	0	0.00	0.00 0.03
Costa Rica	2	547863	1173	0.21	0.20 0.23
Dominica	1	95	0	0.00	0.00 3.89
Grenada	2	154	9	5.84	3.10 10.73
Guatemala	1	31038	2890	9.31	8.99 9.64
Mexico	7	9915	485	4.89	4.48 5.33
Montserrat	1	12	0	0.00	0.00 24.25
Puerto Rico	1	184	0	0.00	0.00 20.50
Saint Kitts and Nevis	1	131	0	0.00	0.00 28.50
Saint Lucia	1	173	0	0.00	0.00 21.70
South America	52	2081452	12006	0.58	0.57 0.59
Argentina	3	10387	227	2.19	1.92 2.48
Brazil	17	743685	8787	1.18	1.16 1.21
Chile	1	400	0	0.00	0.00 0.95
Colombia	6	2365	140	5.92	5.04 6.94
Ecuador	19	88469	2257	2.55	2.45 2.66
Peru	2	4296	2	0.05	0.01 0.17
Uruguay	1	1230897	517	0.04	0.04 0.05
Venezuela	3	953	76	7.97	6.42 9.87
Total	**65**	**2685623**	**16563**	**0.62**	**0.61 0.63**

The need to access updated data to implement the strategy of controlling brucellosis is known (Zambrano Aguayo and Pérez Ruano, 2015); hence, it is necessary to conduct research based on diagnostic designs and schemes recommended to determine the seroprevalence of this disease with a higher certainty, as the basis for the establishment of strategies for the control of animals and the reduction of their impact on public health.

Depending to the animal species, of the 65 papers available, 56 reported on the prevalence of brucellosis in cattle, and 11 in buffaloes (Table 2). Therefore, studies of the former species

should be a priority in the regions studied, since the pace of growth is high (Naveena *et al*., 2020), which is acknowledged as a risk to cattle raising and humans. Although this species is thought to be more resistant to the disease, it plays the role of a reservoir (Barbosa da Silva *et al*., 2014b), as it disposes of the agent in the milk, posing a serious risk to public health (Rosales-Zambrano *et al*., 2015).

Table 2. Distribution of the scientific articles by animal species

Species	Papers included	Animals studied	Positive	Positive (%)	CI 95%
Cattle	56	2672009	16026	0.60	0.59 0.61
Bubaline	11	13614	537	3.94	3.63 4.28
Total	65*	2685623	16563	0.62	0.61 0.63

*** Two articles report the data from the two species.**

The scientific papers retrieved through the search correspond to the 2010-2016 period (36), and the 2017-2021 period (29) (Table 3).

Table 3. Distribution of the scientific articles included in the analysis by time period.

Period	Papers included	Animals studied	Positive	Positive (%)	CI 95%
2010 2016	36	124747	2468	1.98	1.90 2.06
2010	3	1331	156	11.72	10.10 13.56
2011	2	873	71	8.13	6.50 10.13
2012	2	732	210	28.69	25.53 32.07
2013	4	1889	91	4.82	3.94 5.88
2014	5	15715	553	3.52	3.24 3.82
2015	10	51881	573	1.10	1.02 1.20
2016	10	52326	814	1.56	1.45 1.67
2017-2021	29	2560876	14095	0.55	0.54 0.56
2017	11	589076	4752	0.81	0.78 0.83
2018	6	3923	157	4.00	3.43 4.66
2019	7	1255253	1054	0.08	0.08 0.09
2020	4	690032	7634	1.11	1.08 1.13
2021	1	22592	498	2.20	2.02 2.40
Total	65	2685623	16563	0.62	0.61 0.63

Upon an evaluation of the bias and effects of the short papers by observing the funnel graph and the Egger and Begg test for those effects, the authors determined that the prevalence studies in cattle and bubaline in the same regions were biased (Fig. 2); it may be associated with the fact that very few articles on the prevalence of brucellosis in cattle and bubaline were available, and limited to a reduced number of countries within a region.

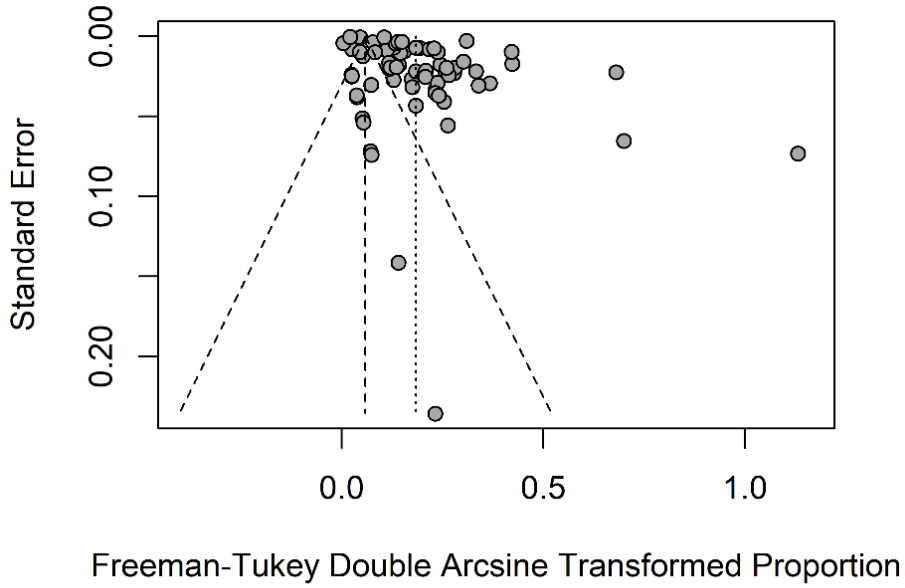

Figure 2. Publication bias analysis of the scientific papers used in the analysis

The meta-analysis of the random effects indicated a high variability of the studies (τ 2 = 0.0041; I2 = 100%, Q-test = 30409.47, gl = 72 and P<0.001). The studies were equally weighted as individual evaluations, which varied between 0.1% and 1.6%, due to the high heterogeneity between them. Figure 3 shows a tree diagram derived from the meta-analysis.

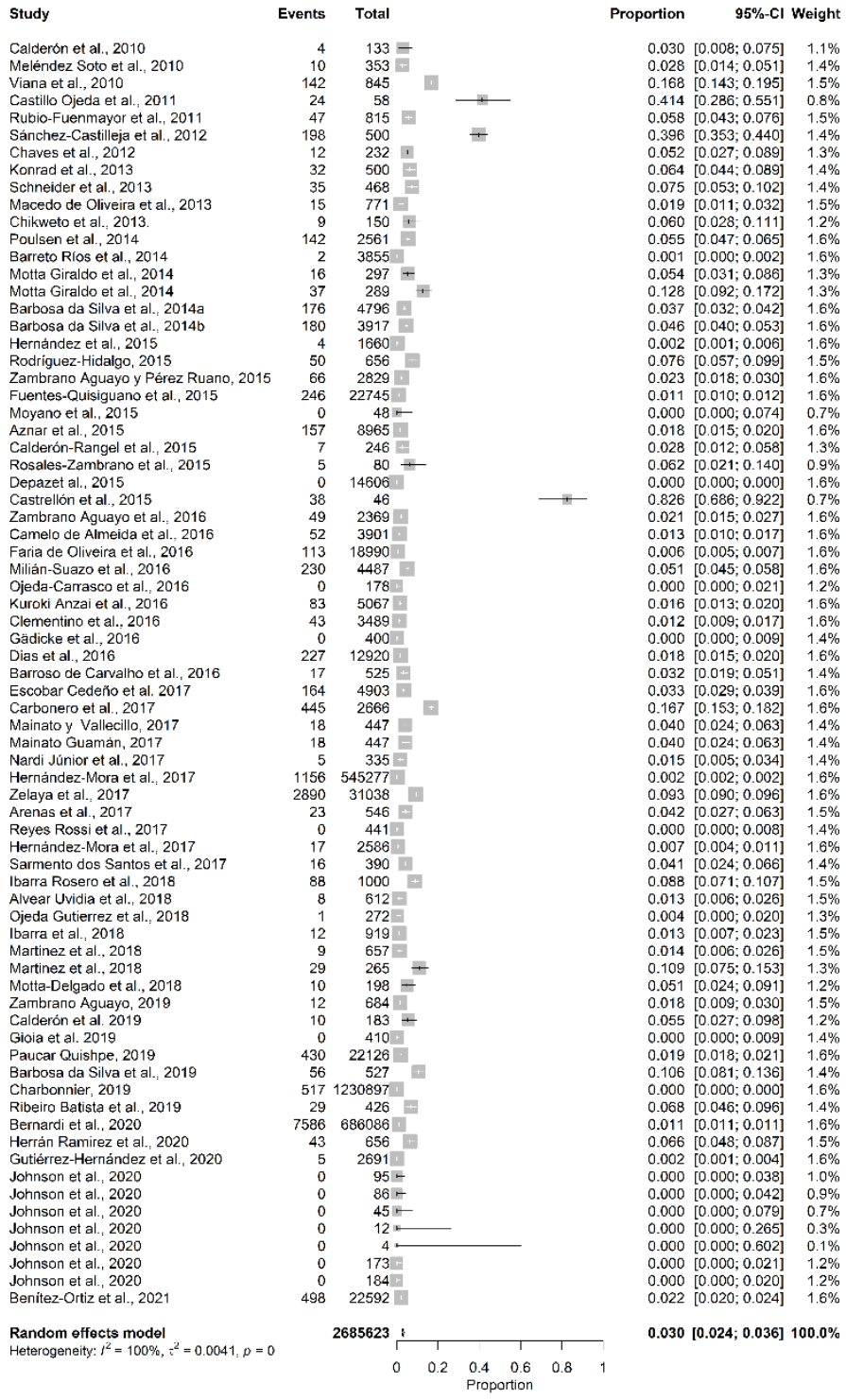

Figure 3. Tree diagram of the systematic review and meta-analysis based on the overall combined prevalence, according to the study records

An analysis of the Galbraith graph (Figure 4) showed the high heterogeneity level. The removal of atypical cases left very few studies to calculate the required estimations. This situation has been reported by other authors, and it is one of the major shortcomings of this type of studies (Adetunji *et al*., 2019).

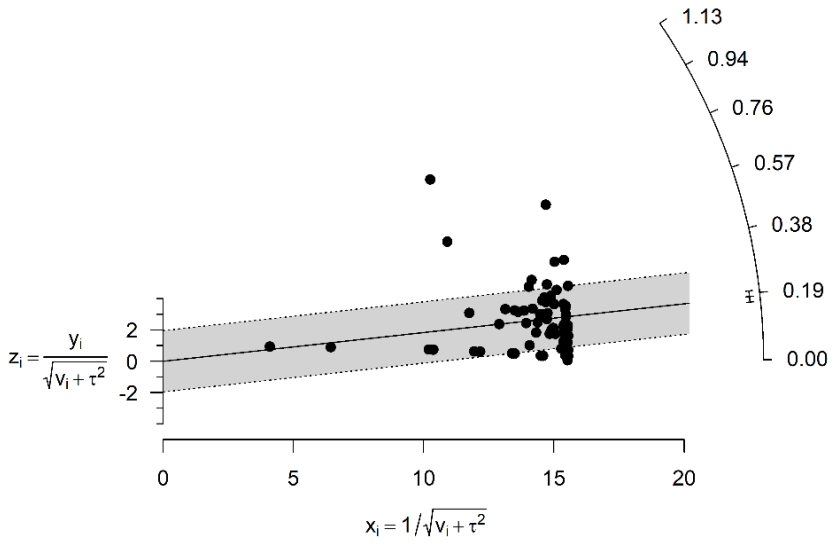

Figure 4. Galbraith graph for the analysis of the studies included

The prevalence estimated in the individual studies ranged between 0.0% and 82.6%, with an overall combined prevalence of 3.0% (CI 95%: 2,4-3,6), which indicates that, despite all the measures taken in the countries, such as vaccination, removal of the positive reactors, and epidemiological surveillance, the disease is still a sanitary problem. This result coincides with the reports made in Mexico (Ordóñez-Velázquez *et al*., 2021), in which, despite the vaccination campaign and information spreading, 71.12% of the national territory the disease is active. This scenario was linked to the lack of compliance with the measures set up in the control program.

Similar reports have been made in other areas, namely Ethiopia, where the combined prevalence was determined at 3.0 (Asmare *et al*., 2014; Tesfaye *et al*., 2021). Meanwhile, in Iran, high combined prevalence of the disease (34.4%) was reported in cattle (Moosazadeh *et al*., 2016).

The meta-analysis of the subgroup revealed a combined prevalence in South America, of 3.1% (IC 95%: 2.6 3.7), and Central America and the Caribbean (3.0) CI 95%: 0.2 7.6) (Table 4). However, following an evaluation of the multivariate meta-regression (Table 7), no differences of

combined prevalence were confirmed in the areas studied, similar to previous reports (Cárdenas Contreras, 2018).

Table 4. Comparison of combined individual prevalence of brucellosis in cattle and bubaline, in Central America and the Caribbean, and South America

Regions	Prevalence (CI 95%)	I2	Q	Heterogeneity test	
				GL	P
Central America and the Caribbean	0.030 (0.002 - 0.076)	99.7%	4862.77	15	0.000
South America	0.031 (0.026 - 0.037)	99.7%	20750.48	56	0.000
Overall	**0.030 (0.024 - 0.036)**	**99.8%**	**30409.47**	**72**	**0.000**

Legend: CI: Confidence interval, GL: Freedom level, I2: Inverse variance index, Q: Cochrane Q statistics, P: P-valor

Higher combined prevalence was observed in the buffaloes (5.2%) (IC 95%: 3.4 7.4); and in cattle (2.7%) (IC 95%: 2.1 3.3) (Table 5).

Table 5. Subgroup analysis by comparing the combined individual prevalence of brucellosis in the different species

Species	Prevalence (CI 95%)	I2	Q	Heterogeneity test	
				GL	P
Cattle	0.027 (0.021 - 0.033)	99.8%	29231.85	61	0.000
Bubaline	0.052 (0.034 - 0.074)	95.3%	214.17	10	0.000
Overall	**0.030 (0.024 - 0.036)**	**99.8%**	**30409.47**	**72**	**0.000**

Legend: CI: Confidence interval, GL: Freedom level, I2: Inverse variance index, Q: Cochrane Q statistics, P: P-valor

Other authors (Martínez *et al*., 2018) noted that this situation may be related to the fact that buffaloes, generally, have been included in the control and eradication programs of the disease in the countries belonging to the areas studied more recently, so they have greater prevalence in bubaline than cattle. This behavior may also be associated with differences in the efficacy of the existing vaccines, between cattle and bubaline, as the immune response to vaccination is not well known in the latter.

Although there are reports about the higher buffalo resistance to the disease (Fosgate *et al*., 2011), the contact between cattle and bubaline herds, either due to mixed raising or by the presence of free-living buffaloes without veterinary control, led to an increase of the population, which posed risks to the control and eradication of the disease (Barbosa da Silva *et al*., 2014b), and indicated the need for special development attention in terms of meat and milk output.

In the 2010-2016 period, higher combined prevalence was observed (4.3%) (IC 95%: 3,2-5,6); in the 2017-2021, period, 2.0% (IC 95%: 1,3-2,7) (Table 6).

Table 6. Subgroup analysis by comparing the combined individual prevalence of brucellosis in cattle and bubaline in the time period studied

Periods	Prevalence (CI 95%)	I2	Q	Heterogeneity test	
				GL	P
2010 2016	0.043 (0.032 - 0.056)	98.9%	3318.95	36	0.000
2017 2021	0.020 (0.013 - 0.027)	99.9%	25229.96	35	0.000
Overall	0.030 (0.024 - 0.036)	99.8%	30409.47	72	0.000

Legend: CI: Confidence interval, GL: Freedom level, I2: Inverse variance index, Q: Cochrane Q statistics, P: P-valor

This reduction in the combined prevalence of the disease may be associated with the presence of trade restrictions for countries with active Brucella spp. infections (Carbonero *et al*., 2017), which has set the alarms of many of the countries from the studied areas, concerning the programs for the control of this disease, especially, those dedicated to cattle or by-products, such as in Mexico and South America.

Previous research has reported that in countries where brucellosis is endemic, there has been a declining tendency toward a reduction of prevalence in the 1996-2014 period. In Central America and South America there have been reports of highly affected areas due to the disease, globally (Cárdenas Contreras, 2018).

Despite the control programs set up, in Central America and the Caribbean and South America, the disease has become endemic in most of the 40 countries (Cárdenas Contreras, 2018). Though there has been a general decline of the combined prevalence of the disease in the last five years, it continues to be elevated, indicating the need to implement more steps to control it.

The analysis of multivariate meta-regression revealed that the variables studied were significant ($P<0.01$) in the period and animal species studied (Table 7).

Table 7. Results of the individual multivariate meta-regression analysis

Variables	Categories	Coefficient (CI 95%)	P
Region	Central America and the Caribbean	1 (ref)	
	South America	-0.01 (-0.05 - 0.02)	0.4648
Species	Cattle	1 (ref)	
	Bubaline	0.06 (0.01 - 0.1)	0.0099
Period	2010 2016	1 (ref)	
	2017 2021	-0.04 (-0.07 - -0.01)	0.005

Based on the systematic review and the meta-analysis of the results, this study found a rationale for the design of sanitary policies, and for the recommendation of new research studies (Mirnejad *et al*., 2017). This study led to the combination of greater combined prevalence of the disease in buffaloes, along with a decline observed in the last five years, and the absence of the disease in the last five years in the the two areas included.

The downside of this investigatoin was the concentration of studies in four countries only, and the scarce research on the evaluation of the prevalence of the disease in buffaloes, which should be considered for further studies.

CONCLUSIONS

The combined prevalence of the disease was 3.0%, higher in buffaloes, though decreasing for the last five years and the existence of no differences between the two geographical areas in the study.

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AUTHOR CONTRIBUTION STATEMENT

Research conception and design: CAZM, MDZA, GANS, MMRZ, OFR, MPR; data analysis and interpretation: CAZM, MDZA, GANS, MMRZ, OFR, MPR; redaction of themanuscript: CAZM, MDZA, GANS, MMRZ, OFR, MPR.

CONFLICT OF INTERESTS

The authors of this paper confirm the absence of no conflict of interests.