SYSTEMATIC REVIEW

Prevalence of zoonotic and non-zoonotic *Rickettsia* in horses: A systematic review and meta-analysis

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Abstract

In a broad sense, *Rickettsiae* are a group of microorganisms that can be transmitted mechanically or biologically to animals and humans. Rickettsioses are associated with hematic manifestations. Its prevalence in humans, dogs and other animals has been widely explored, but not in equine species.

To determine the prevalence of *Rickettsia* infection in horses.

A systematic review of the literature was carried out in five databases for the proportion of horses infected with *Rickettsia*, defined by molecular and immunological techniques. A meta-analysis was performed using a random-effects model to calculate the pooled prevalence and 95% confidence intervals (CI). The Cochran's Q test and the I^2 statistic were used to assess the between-study-heterogeneity. The pooled prevalence of *Rickettsia* in equines was 37.0% (95% CI: 26.0%-47.0%), with significant heterogeneity among studies (I^2 = 98.12%). In the subgroup analysis, the prevalence of *Rickettsia* in horses was found to be 24.0% (95%CI: 10.0%-41.0%) for IFI, 47.0% (95%CI: 30.0%-64.0%) for IFA, 14.0% (95%CI: 11.0%-17.0%) for IFAT and 39.0% (95%CI: 0.0%-95.0%) for PCR.

There was a high prevalence of *Rickettsia* among horses, with some of the species being zoonotic, with their corresponding implications for humans, which increasingly are in close contact with equines, particularly horses and their ticks, posing a risk for spillover and transmission.

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1. Introduction

Rickettsioses include a group of zoonotic bacterial diseases mainly transmitted by ticks [1,2], the *Rickettsia* genus has been classified into four groups, the typhus group (TG), which includes *Rickettsiae prowazekii,* which causes epidemic typhus, *Rickettsia typhi* that causes typhus endemic or murine, ancestral group (AG) made up of *Rickettsia canadensis* and *Rickettsia belliii* and the transitional group (TRG) that is made up of the species *Rickettsia australis*, *R. felis and R. akari;* Finally, the fourth group, which is better known as the spotted fever group (SFG) where around 20 species can be found that are transmitted by ticks [3,4], the last mentioned being *R. rickettsii* [5].

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Bacteria of the *Rickettsiae* genus are Gram-negative [6] and can infect animals such as canines, felines, and horses, among others, to humans. In the human body, this type of bacterium will seek to adapt, being highly pleomorphic and pleiotropic, making it a very resistant bacterium with rapid dissemination [7]; these accelerated processes are an essential factor to take into account to avoid transmission and subsequent death in humans, even so, studies on *Rickettsiae* in the area are scarce [3].

Infection in horses may be asymptomatic; that is, the animal can be infected and transmit the disease through its vectors and not present any clinical manifestations. Although there is an increase in IgG titers [8], the relationship between the appearance of fever and bacteremia could be related to the virulence of the strains and their infectious doses. Its diagnosis can be complex since its detection in the blood is problematic because it is a bacterium that multiplies inside the endothelial cells. Low numbers of these cells can be found in circulation during disease [9].

As we mentioned before, equines are usually asymptomatic animals against *Rickettsias* [10]; even so, in a clinical case carried out in the United States of America (USA), a horse was positive for *R. rickettsii* with the presentation of the following clinical signs: lethargy, tachycardia, tachypnea, fever, hyperemic mucous membranes, less than one-second capillary refill, anorexia, and muscle fasciculation; the clinical manifestations presented are strange to correlate, and are similar to those shown in infected humans [11], this information confirms the importance of maintaining control of the prevalence, to avoid further dissemination and even a mutation in the pathogenicity of the microorganism.

In general, rickettsioses in horses are poorly registered and underdiagnosed. These problems are highly linked to the lack of knowledge on the part of veterinarians and humans in terms of detection in humans, the scarcity of prediction and diagnosis methods and their similarity with other febrile diseases [12] and for horses, in some. Sometimes there is low availability of resources in marginalised areas for vector control [13], and as it is a disease that does not present apparent signs, it makes its prevention difficult and increases its spread [14].

According to the above and the intimate relationship that equines have with humans, facilitating multiple daily tasks, such as transportation and livestock work. Even so, they have not only been limited to work tasks; in the same way, we tame them for use in competitions, and now, they even travel and travel long distances between cities and countries, which would imply a potential source of infection if they are not taken appropriate preventive measures [15]. Therefore, the goal of the present study was to determine the prevalence of *Rickettsiae* in equines, particularly horses, through a systematic review with meta-analysis.

2. Methods

This systematic review was registered in the International Prospective Register of Systematic Reviews (PROSPERO) with code CDR420223691183. In addition, we followed the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) statement [16].

2.1. Databases and search strategy

We built the search strategy using MeSH terms and free terms ("*Rickettsia*" and "equine"). No language restriction was applied, and the date restriction was from January 1950. On August 2022, we ran the systematic search simultaneously through PubMed, LILACS, Scopus, Web of Science (Core Collection), and Embase. Likewise, a manual search was performed in Scielo and CNKI databases. The complete search strategy is attached as supplemental material (Supplementary Table S1).

2.2. Eligibility criteria

Our inclusion criteria were reported (i) observational studies, (ii) that reported the frequency of infections by *Rickettsia*, (iii) confirmed either by serological or molecular tests and (iv) in equines. We consider indirect immunofluorescence (IFI), immunofluorescence antibody test (IFAT or IFA) as possible serological tests and polymerase-chain reaction (PCR) as molecular tests. We excluded review articles, editorials, letters and conference abstracts.

2.3. Study selection process

Titles and abstracts first screened the retrieved results from the search strategy. The remaining references were reviewed in full text. When an article provided the same information on the same subjects, the information from both reports was combined to obtain complementary data, counting only as one study. Four authors independently performed all phases of the study selection process (DKB-A, AJR-M, JMO-M and KJC-B). Any conflict was resolved by consensus.

2.4. Data extraction and quality assessment

Four authors performed data extraction independently (JRU-B, EAH-B, VAB-Z and DKB-A). Extracted data were: author, publication date, publication type, design, country, and the total number of equines and infected equines evaluated by serological and molecular tests.

We used the adapted Newcastle Ottawa Scale for cross-sectional studies (NOS–C) [17] and the Joanna Briggs

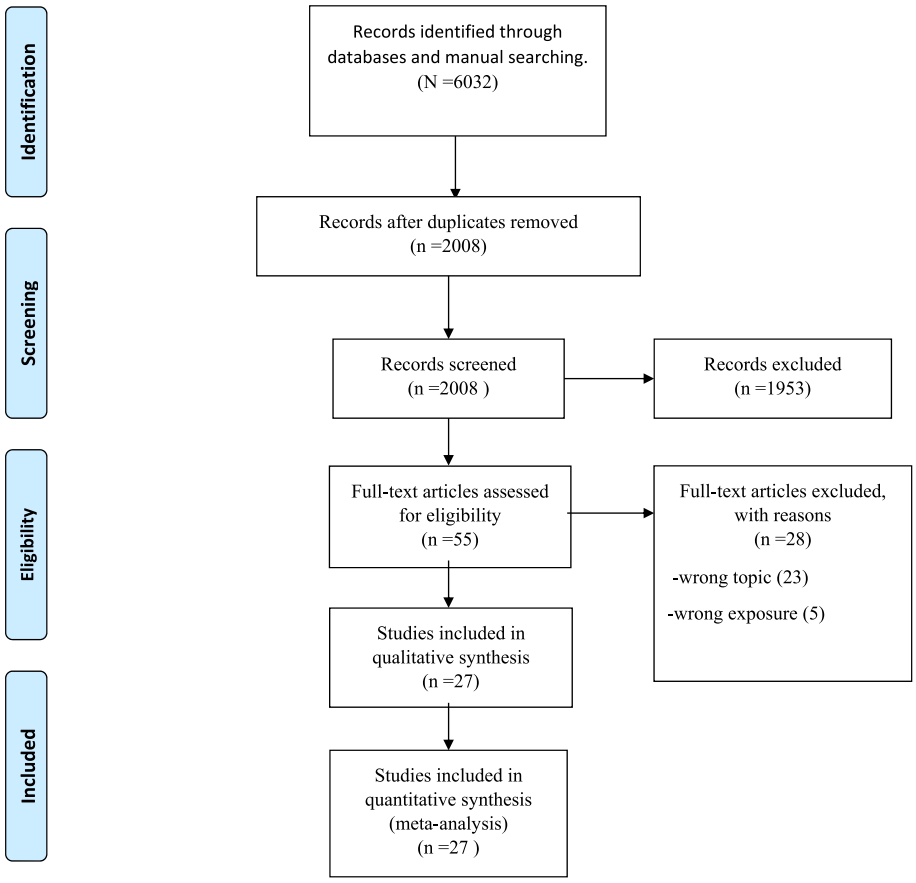

FIG. 1. PRISMA Flow Diagram.

Institute checklist for Case Series (JBICC-S) [18]. In both scales, a score of 7 or more stars was considered a low risk of bias, while a score of 6 or fewer stars was considered a high risk of bias.

2.5. Data analysis

We used the STATA v 17.0 © for statistical analysis. A random effects model (Dersimonian and Laird) was used to calculate the pooled prevalence and 95% confidence interval (95%CI). We calculated the 95%CI for the proportions of the individual studies using the Clopper-Pearson Method. The Freeman-Tukey Double Arcsine transformation was used as the variance stabiliser. The Cochran's Q test and the I^2 statistic were used to assess the between-study heterogeneity. Values equal to or greater than 60% were categorised as high heterogeneity for the I^2 statistic, and a p-value <0.05 was a sign of heterogeneity in Cochran's Q test. In addition, we carried out a subgroup analysis according to the method of *Rickettsiae* infection diagnosis and a sensitivity analysis excluding studies with a high risk of bias.

2.6. Publication bias

Publication bias was not performed because there is no evidence that proportions adjust correctly to funnel plots or Egger's tests [19,20].

3. Results

3.1. Study selection

The systematic search yielded 6032 records; after removing 2008 duplicates, 4024 records remained. Screening by titles and abstracts left 55 studies for full-text review. An assessment of full texts found 27 studies that complied with all eligibility criteria [11,13,15,21–44]. PRISMA flow diagram summarises the study selection process (Fig. 1).

3.1. Study characteristics

Characteristics from all included studies are summarised in Table 1. A total of 27 studies with a total of 4829 animals were

TABLE 1. Characteristics of the included studies of *Rickettsia* infection in *Equus caballus*. (IFI, indirect immunofluorescence; IFAT or IFA, immunofluorescence antibody test; PCR, polymerase-chain reaction)

Author	Year	Country, state (or province)	Method	Species of *Rickettsia*	Total number of animals	Total of animals detected with *Rickettsia*	%
De Lemos E et al. [25]	1996	Brazil, Sao paulo	IFA	*R. rickettsii*	20	10	50.00
Horta M et al. [33]	2004	Brazil, Sao paulo	IFA	*R. rickettsii*	22	17	77.27
Vianna M et al. [43]	2008	Brazil, Minas Gerais	IFA	*R. rickettsii*	11	11	100.00
Toledo RS et al. [40]	2009	Brazil, Paraná	IFA	*R. rickettsii*	26	10	38.46
Hidalgo M et al. [32]	2009	Colombia, Villeta	IFI	*R. rickettsii*	159	26	16.35
Batista F et al. [21]	2010	Brazil, Paraná	IFA	*R. rickettsii* *R. parkeri*	71	6	8.45
Tamekuni K et al. [39]	2010	Brazil, Paraná	IFA	*R. rickettsii* *R. parkeri*	273	20	7.33
Silveira I et al. [38]	2012	Brazil, Pauliceia	IFA	*R. rickettsii* *R. parkeri* *R. amblyommii* *R. bellii*	140	35	25.00
Alves A et al. [15]	2014	Brazil, Pantatal	IFI	*R. rickettsii* *R. parkeri* *R. amblyommii* *R. bellii* *R. rhipicephali*	547	337	61.61
Souza C et al. [13]	2016	Brazil, Sao paulo	IFI	*R. rickettsii* *R. parkeri* *R. bellii*	504	183	36.31
De Toledo Vieira F et al. [44]	2018	Brazil, Espirito Santo	IFA	*R. bellii*	10	2	20.00
Tyrrell J et al. [41]	2019	Brazil and Nicaragua	PCR	*R. felis*	90	2	2.22
Ebani V et al. [27]	2019	Italy, Central Italy	IFI	*R. rickettsii*	479	91	19.00
De Oliveira P et al. [26]	2019	Brazil, Bahia	IFI	*R. rickettsii* *R. parkeri* *R. amblyommii* *R. bellii*	69	17	24.64
Li J et al. [34]	2019	China, Xinjiang	PCR	*Rickettsia* spp.	200	163	81.50
Costa S et al. [24]	2021	Brazil, Bahia	IFA	*Rickettsia* spp.	569	190	33.39
De Oliveira FM et al. [29]	2010	Brazil, Southern Brazil	IFA	*R. rickettsii* *R. parkeri*	75	75	100.00
Fuehrer H et al. [30]	2020	Portugal, Lisbon	IFAT	*Rickettsia helvetica*	479	63	13.15
Gazeta G et al. [31]	2009	Brazil, Río Janeiro	PCR	*Rickettsia* spp.	34	15	44.12
Bermúdez C et al. [22]	2010	Panamá, Coclé	IFA	*R. rickettsii* *R. parkeri* *R.amblyommii* *R. belii* *R. rhipicephali*	20	14	70.00
Sangioni L et al. [37]	2005	Brazil, Sao paulo	IFA	*R. rickettsii*	79	17	21.52
Milagres B et al. [36]	2010	Brazil, Minas Gerais	IFA	*R. rickettsii* *R.amblyommii* *R. belii* *R. rhipicephali*	108	26	24.07
Faccini-Martínez A et al. [28]	2017	Colombia, Villeta	IFA	*R. rickettsii*	74	25	33.78
Moraes-Filho J et al. [35]	2008	Brazil, Sao Paulo	IFI	*R. rickettsii*	363	64	17.63
Riveros-Pinilla D et al. [11]	2015	Colombia, Orinoquía	IFI	*Rickettsia* spp.	246	7	2.85
Cordeiro M et al. [23]	2015	Brazil, Río de Janeiro	IFA	*R. rickettsii* *R. parkeri* *Rickettsia spp.* *R. rhipicephali*	42	35	83.33
Ueno T et al. [42]	2020	Brazil, Sao paulo	IFAT	*R. rickettsii*	62	14	22.58

included from studies published between 1996 and 2021. Most were studies from Brazil (77%), Colombia (10%), China (3%), Italy (3%), Panama (3%), and Portugal (3%).

The NOS and JBICC-S were used for the quality assessment of the studies (see Supplementary Table S2). It was identified that two studies had a high risk of bias and 25 studies had a low risk of bias.

A total of 2367 horses (7 studies) were evaluated for IFI. Infection by *Rickettsia rickettsii* was assessed in six of them, *R. parkeri* in three of them, *R. bellii* in three of them, and *Rickettsia amblyommii* in two of them. Also, *Rickettsia rhipicephali* in one and *Rickettsia* spp. in another.

A total of 1540 horses (15 studies) were evaluated for IFA, in which *Rickettsia rickettsii* infection was assessed in 14 of them,

R. parkeri in six of them, *R. bellii* in four of them, *Rickettsia amblyommii* in three of them, *Rickettsia rhipicephali* in three of them, and *Rickettsia spp*. in two of them.

A total of 541 horses (2 studies) were evaluated for IFAT, in which *Rickettsia helvetica* infection was assessed in one of them and *Rickettsia rickettsii* in another.

A total of 324 horses (3 studies) were evaluated using PCR, in which *Rickettsia felis* infection was assessed in one of them and *Rickettsia* spp. in two of them.

3.2. Proportion of infection by *Rickettsia* in horses

The pooled prevalence of *Rickettsia* in horses was 37.0% (95% CI: 26.0%-47.0%), with significant heterogeneity among studies (I^2 = 98.12%) (Fig. 2). In the subgroup analysis (Fig. 3), the prevalence of *Rickettsia* in horses was found to be 24.0% (95% CI: 10.0%-41.0%) for IFI, 47.0% (95% CI: 30.0%-64.0%) for IFA, 14.0% (95% CI: 11.0%-17.0%) for IFAT and 39.0% (95% CI: 0.0%-95.0%) for PCR. In the sensitivity analysis (Fig. 4), after removing studies with a high risk of bias, a prevalence of 37.0% (95% CI: 26.0%-48.0%) was found, with no decrease in heterogeneity (I^2 = 98.26%).

4. Discussion

Vector-borne and zoonotic diseases remain a significant public health problem, especially in tropical and subtropical countries [45–47]. In the case of tick-borne diseases, these are more neglected than mosquito- or *Aedes*-borne infections [48–50]. Rickettsiosis is a zoonosis transmitted by ticks; this includes a group of bacterial diseases which are classified into four groups, typhus group (GT), ancestral group (GA), transitional group (GTR) and spotted fever group (GFM) [3]. *Rickettsia* may infect a broad number of animal hosts and the human, then participating in possible zoonotic cycles in different ecoepidemiological settings.

The pathogen is acquired through the tick vector, which must come into contact with the equine and transmit the disease through the bite [51]. In the same way, if a healthy tick bites a previously infected equine, it will become infected and start a new cycle of spread to more animals and humans [13]. Once the animal is infected, the infection will go unnoticed; however, in a clinical case study in the United States, clinical findings associated with the symptoms of *Rickettsia* infection were found. Human disease is usually much more lethal and pathogenic; the signs and symptoms can vary according to evolution [52]. Therefore, it is crucial to maintain transmission and spread control to avoid clinical and epidemiological consequences and complications [53].

In this meta-analysis we found that the prevalence of *Rickettsia* in equines was 37.0% (95% CI: 26.0%-47.0%), being higher with IFA, 47.0% (95% CI: 30.0%-64.0%); and 39.0% (95% CI: 0.0%-95.0%) using PCR. Then, such results represent important implications, and would be consider high values. Even more, eight (Table 1) studies reported more than 50% of prevalence. The largest study (n = 569) reported 33% [24]. Unfortunately,

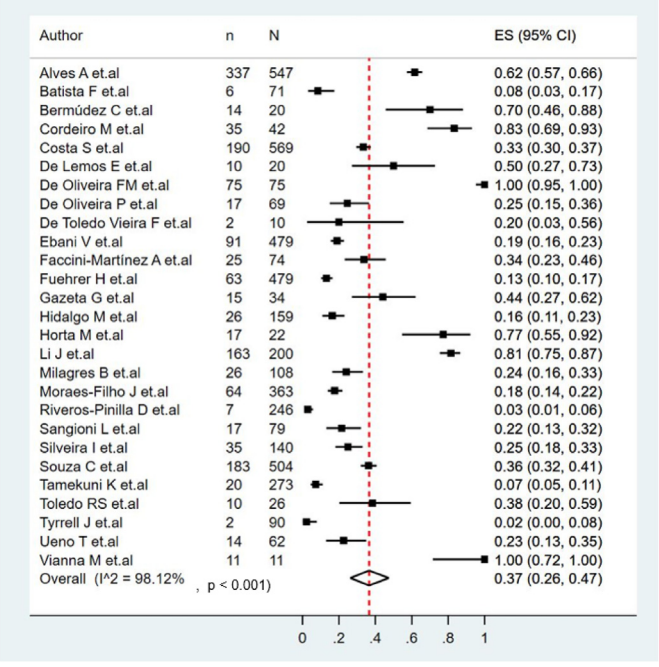

FIG. 2. Prevalence of *Rickettsia* in horses (n: events; N: total of participants).

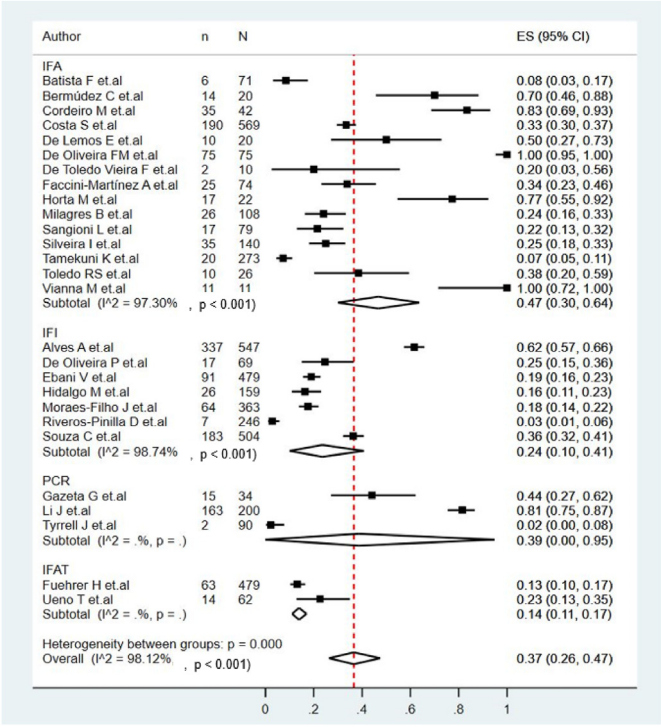

FIG. 3. Subgroup analysis according to serological/molecular tests (n: events; N: total of participants).

there are no studies showing which prevalence will become relevant to human populations. In future studies this should be assessed. Additionally correlational studies would assess the association between the incidence rates of equine rickettsiosis and human disease.

For the laboratory diagnosis, specific difficulties may arise since its detection in the blood is complex because it is a bacterium that multiplies within the endothelial cells. These cells can be found in circulation during an illness [52]. Therefore, there are various diagnostic methods; at the time of

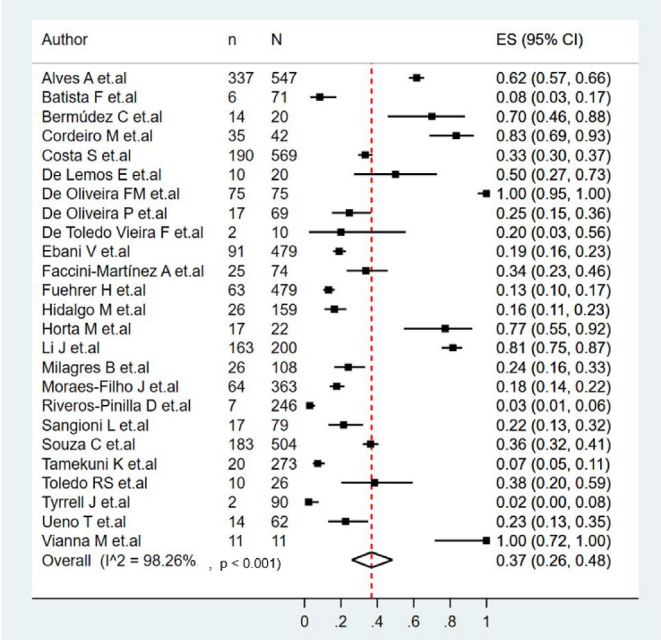

FIG. 4. Sensitivity analysis according to the risk of bias (n: events; N: total of participants).

evaluation, the indirect immunofluorescence test (IFI) is used, which is performed using isolated *Rickettsia* antigens. This method is among the most accurate for diagnosing *Rickettsia* infection since, according to the data analysed in previous investigations using the real-time PCR method, its detection in the blood is problematic because it is a bacterium that multiplies within the endothelial cells [54]. Nevertheless, the future of confirmation is focused on genome sequencing and metagenomics [55,56]. Reports on the use of next-generation sequencing (NGS) and metagenomics to diagnose *Rickettsia* spp. Infection have been increasing. Despite offering several potential advantages in the diagnosis and surveillance of disease, genomic approaches are currently only limited to reference and research laboratories [57].

Once the results were analysed, it was found that the IIF test was the most used method for the detection of *Rickettsiae*; however, 324 horses were evaluated by PCR, which, as mentioned above, is not a highly reliable test, so some animals may turn out to be false negatives or false positives [52]. Therefore, generating a correlation of the diagnostic procedures, we conclude that it is of particular importance to approach the method that, to the current investigations, presents the highest percentage of reliability to obtain the results of the study in a more precise and safe way in future studies [58].

The prevalence of *Rickettsia* in horses is underdiagnosed and poorly studied; currently, we do not have a comprehensive information database to explore the global prevalence level, but the data is enough to report significant findings. Among the *Rickettsia* studied, the highest incidence are*: R. rickettsii, R. parkeri, R. bellii, R. amblyiommi, R. rhipicephali, R. felis and R. helvetica*, ranked from highest to lowest prevalence. *Rickettsia rickettsii*, from the group of spotted fevers, has the most significant impact and is classified among the groups as the most important, and even lethal, for humans [59], which can not only infect horses but can also be transmitted to domestic animals such as canines and exotic animals such as capybaras, wild rodents and some marsupials [60]. Regarding the reported *Rickettsia* species in horses (Table 1), three of them are clearly pathogenic for humans. *Rickettsia rickettsii* (known as both Rocky Mountain spotted fever and Brazilian spotted fever etiological agent), *R. parkeri* (causing the American Boutonneuse fever) vectorized by the Gulf Coast tick (*Amblyomma maculatum*) or Lone Star tick (*A. americanum*), and *R. felis* (causing the flea-borne spotted fever), are present in humans and horses (Table 1). Additionally, *Rickettsia helvetica*, presente in horses, has been sporadically reported as a pathogen in humans [61,62]. Then, these four species of *Rickettsia* in horses may be considered zoonotic and should be considered under the umbrella of OneHealth. When bitten by the *Amblyomma cajennense* tick in South America, these would help maintain and explain areas of high endemicity for this infection in human populations [63].

This disease is widely distributed, and a geographic area's morbidity depends on endemic foci, as occurs in the Rocky Mountains of the United States of America. Therefore, in this country, this disease is notifiable [64], but as discussed before, rickettsioses are not notifiable in many other countries, e.g. Latin America, despite being highly prevalent [65–67].

Here, it is of paramount importance to stop to carry out a deeper and more detailed analysis; we cannot go unnoticed globalisation, exports, imports, and equine transport between cities or countries, are a focus of spread worldwide [68], over the years we have been able to verify how the expansion of markets can be beneficial for countries, even so, it brings with it different problems as has been experienced with other epidemics and over the years with the transmission of emerging and re-emerging diseases, between continents [69]. Environmental aspects, also play a key role in these cycles, then a OneHealth approach for rickettsiosis is critical, as is related to environmental health, animal health and human health at the same time [70–72].

As we mentioned before, there are not enough studies to prove infection with clinical findings in horses; it is of the utmost importance to further evaluate the published clinical case with the presence of symptoms that we mentioned above since this could represent epidemiological relevance, and clinical in terms of possible greater pathogenicity of the bacteria [73]. Then, there is a need to develop clinical studies in equines and horses, to understand better the clinical consequences of such studies.

Humans are closely related to horses, representing an essential point for presenting this pathology [74]. Therefore, it is pertinent to continue working at the epidemiological and prevalence level regarding *Rickettsias*, taking into account its lethal factors, zoonoses and its variety of domestic [75] and wild-type amplifiers that can generate a greater spread of the disease [76].

4.1. Limitations

Our study has several limitations. First, many studies included do not present a large population, so this should be considered in future research. Secondly, it would have been interesting to carry out more subgroups or sensitivity analyses that could explain the high heterogeneity found, such as horse breed, *Rickettsia* species, and rearing hygiene condition, among others, because our subgroups and sensitivity analyses that we used did not improve heterogeneity. Likewise, some studies with small sample sizes and non-probabilistic sampling were included, which could exaggerate the representation in the weighting in the random effects method, distorting the confidence interval

estimates. Thirdly, most included studies were conducted in the Americas, particularly in South America, so it would be essential to carry out more studies in other continents to see some variation due to the different sociodemographic and economic realities. Additionally, it is important to mention that better serological tests are needed, for example the use of Western-blot or PRNT would be useful in this setting. An initial screening approach with serological tests is useful, but further molecular and genomic confirmation would be required, especially to identify genus and species.

5. Conclusions

In conclusion, the prevalence of *Rickettsiae* in equines, particularly horses, is high. However, more studies are needed, given their epidemiological implications, as many of the *Rickettsia* species are zoonotic. Given that, adequate control in horses is required to avoid zoonotic transmission to humans.

As mentioned above, currently, the number of studies on the subject is scarce, so it is relevant to maintain control of the frequency of the disease and its prevalence levels [73]. To generate even more explicit arguments and answers about this pathology, we must open up the field of research more and develop different exclusive databases with the information of interest; in this way, control and subsequent studies on the subject will be easier, as expected.

Credit author statement

D. Katterine Bonilla-Aldana: Conceptualization, Investigation, Formal analysis and Writing – original draft. Karen Johana Castaño-Betancourt: Conceptualization, Investigation, Formal analysis and Writing – original draft. Juan Manuel Ortega-Martínez: Conceptualization, Investigation, Formal analysis and Writing – original draft. Juan R. Ulloque-Badaracco: Methodology, Formal analysis and Writing – original draft. Enrique A. Hernandez-Bustamante: Methodology, Formal analysis and Writing – original draft.Vicente A. Benites-Zapata: Methodology, Writing – review & editing, Visualization and Supervision. Alfonso J. Rodriguez-Morales: Conceptualization, Investigation, Writing – review & editing, Visualization and Supervision.

Declaration of competing interest

The authors declare no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.nmni.2022.101068.

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