Occurrence of Rabies and other viral diseases that affect the CNS of cattle and equines: systematic literature review and meta-analysis

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1. BACKGROUND

The disease known as rabies (synonym: hydrophobia, rabies encephalitis) is a cosmopolitan viral anthropozoonosis, whose etiological agent is an enveloped RNA virus, belonging to the family *Rabdoviridae*, genus *Lyssavirus,* which is manifested mainly by neurological signs compatible with encephalitis in mammals and it has a lethality rate of approximately 100%[1]. For this reason, rabies causes a major economic impact on livestock in several countries to this day[1,2].

It is estimated that bovine rabies worldwide causes annual losses of hundreds of thousands of dollars, caused by the death of affected animals, the indirect costs of vaccinating millions of cattle and horses and the cost of post-exposure treatments for injured human beings. by animals suspected of carrying the disease[2].

Rabies can be transmitted to susceptible animals (mammals) when in contact with the saliva of infected individuals, including humans, by biting, scratching or licking the mucous membranes[1]. Because it affects humans and has a lethality rate of approximately 100%, rabies is a disease that requires continuous attention from municipal, state, federal and global health authorities[1,2].

According to the Pan American Health Organization (PAHO/WHO)[2], integration between medical care, epidemiological surveillance and the environment are essential for rabies control. For this reason, it is extremely important to notify cases and carry out epidemiological investigations into deaths of cattle and horses, so that veterinarians can carry out actions to prevent the disease in herds, rule out possible differential diagnoses, and agricultural defense agencies act to block a possible focus of the disease, in order to ensure the health of humans and susceptible animals, within the concept of one health[3].

In addition to the immunization of animals, epidemiological surveillance of rabies in Brazilian states is carried out by constant monitoring by agricultural defense agencies of notifications of suspected cases on rural properties, after the death of cattle and horses[3]. To confirm the occurrence, tissue samples are collected to be subjected to the Direct Immunofluorescence (IFD) technique and biological test (PB) for inoculation in mice or cultured cells[3,4, 5].

Despite the permanent practice of rabies surveillance by Brazilian agricultural defense agencies, it is also necessary to carefully evaluate epidemiological data of deaths of large herbivores on rural properties, as there is still underreporting of cases. The disclosure of the actual occurrence of cases reflects an important action in encouraging notifications that, combined with the conduct adopted by health bodies, can make rural producers aware of the need to vaccinate their herds as a prophylactic measure, with a view to reducing the incidence of rabies[3,4.5].

Even with all the surveillance work, there are still other viral diseases with neurological signs that affect cattle and horses, which can also lead to death and, thus, cause losses to rural producers and impact the production chain, including viral encephalomyelitis in horses (Eastern equine encephalitis virus, Western equine encephalitis virus and Vezenuelan equine encephalitis virus)[6], equine herpesvirus (EHV-1)[7], Saint Louis encephalitis (SLEV)[8], West Nile encephalitis (WNV)[9] and the herpetic menigoencephalitis in cattle (BoHV-1 and BoHV-5)[10].

Thus, considering that rabies possibly represents the main cause of death in large herbivores due to a viral disease with neurological manifestations[11,12] and that systematic reviews on rabies and other viral neurological diseases in horses and cattle are still incipient in the literature, we propose a systematic review with meta-analysis should be carried out to compare the prevalence of these viral neurological diseases in this population, in order to understand their real scope in Brazil and the world.

2. OBJECTIVES

2.1. General objective

To evaluate the global occurrence of rabies by comparing it to the prevalence of other neurological diseases of viral origin that affect cattle and horses, including equine viral encephalomyelitis (eastern equine encephalitis virus, western equine encephalitis virus and equine vezenuelan encephalitis virus), equine herpesvirus (EHV-1), Saint Louis encephalitis (SLEV), West Nile encephalitis (WNV) and bovine herpetic menigoencephalitis (BoHV-1 and BoHV-5).

2.2. Specific objectives

a) Select, through a structured screening process, observational studies that compared the prevalence of rabies and other viral neurological diseases in cattle and horses;

b) Describe the characteristics of the selected studies;

c) Carry out meta-analysis to verify whether the prevalence of rabies in cattle and horses differs from that other neurological diseases of viral origin;

d) Identify population, environmental and methodological variables of studies that produce effect on the prevalence of viruses.

3. METHODS

This research was approved by the Animal Science Postgraduate Program Director Board at Federal University of Goiás - UFG and this protocol, developed

according to PRISMA-P checklist[10], will be registered on SYREAF (https://www.syreaf.org/).

As this is a systematic review of data on works already published on research platforms, this study does not require approval from the animal use ethics committee.

3.1. Question

The question will be based on CoCoPop acronymous: condition, context, and population, as stated in JBI Manual for Evidence Synthesis[11]. Thus, the condition of rabies and other viral neurological diseases in large herbivores (horses and cattle) will be described in a global context:

a) The occurrence of rabies is greater than that of other viral neurological diseases that do they affect cattle and horses?

3.2 Search for Reference in Literature

A search algorithm will be developed, in English, using the best descriptors and keywords related to the topic under study. To this end, we will consult the DECs and MeSH platforms to choose descriptors and select keywords commonly used in publications in the study area. Once this is done, we will begin building the search algorithm in the Medline/Pubmed database, by gradually introducing search terms in concept blocks, following the premises of the PICO strategy/method (population, intervention, comparison, outcome)[14]. Only terms whose introduction significantly alters the search results will remain in the search algorithm. Validation of the search algorithm will be done by identifying sentinel studies in the results obtained.

Once the search algorithm has been defined, its application will be carried out in the databases Medline, Scielo, Scopus, etc. The results obtained in all scientific databases will be exported to reference management software, where the study screening and eligibility process will be carried out, following the premises of the PRISMA group[15].

Initially, duplicate results will be automatically deleted in the manager software. Next, the titles, abstracts and full text will be sequentially read, leaving at the end of each stage only those studies that fully meet the eligibility criteria described below. At the end of this process, the causes of exclusion of studies that reached the full text reading stage, as well as the number of studies obtained in each of these stages, will be discriminated and will form the body of results of the systematic review. The synthesis of this entire process will be presented graphically through a flowchart.

3.3. Eligibility Criteria

a) Languages and study interval

Studies published in Portuguese, English, Spanish and Italian, over a period of 20 years.

b) Population

Primary studies will be included, published in the form of a full article in scientific journals, developed with cattle or horses, regardless of age, breed, sex and husbandry system, from any region of the world and environment, with or without contacts and with clinical signs and/or concomitant diseases.

c) Outcome of interest

Comparison between the prevalence of rabies and the prevalence of other viruses that cause neurological diseases in cattle and horses.

d)Types of study

Only observational studies will be selected.

e)Geographic scope

There will be no geographic restrictions, and a global review will be carried out.

3.4. Data Extraction and Analysis

Occurrence data (n sample and n of positives) for rabies and other viral neurological diseases will be extracted from the included studies and displayed in an electronic spreadsheet.[5]

Its formatting will be such that it will allow identification and grouping by study, continent/country/region of analysis, animal species and category, presence of contacts and clinical signs, assessed illness, diagnostic method, among other qualitative variables that may interfere in the prevalence of illnesses. This database will then be used for the general characterization of the studies included in the systematic review and, if possible, to carry out the meta-analysis, comparing the prevalence of rabies and other neurological illnesses of viral origin in the population of interest.

The effect size measure adopted in the meta-analysis will be the difference in risk/prevalence obtained in each study (prevalence of rabies in the population – prevalence of other neurological diseases in the population). Confidence intervals will be generated for each risk difference and the relative weight of each study in the meta-analysis will be determined based on the inverse variance method. From the relative weights, a weighted average of the risk difference will be calculated and considered as the overall result of the meta-analysis. The significance of the overall risk/prevalence difference will be tested using the Z test.

Heterogeneity between studies will be tested using the Chi^2 test, expressed in general (Tau^2) and also excluding the sampling error component (I^2). In the case of significant heterogeneity, the database will be divided and re-analyzed into subgroups, in an attempt to verify the influence of the study location, animal species, diagnostic method and other qualitative/methodological variables on the difference in risk/prevalence of illnesses.

At all stages, a 5% ($p \leq 0.05$) level of significance will be adopted.

3.5. Data extraction

Quantitative and qualitative data will be extracted from the selected articles and will include year of study and authors, region of research, sample size, study design and evaluation of infectious agents and diagnostic methods used to detect the pathogen. Additional data on epidemiology, clinical condition (asymptomatic and symptomatic) of the animals, affected systems based on clinical signs, anatomopathological findings and prevalence percentages, number of positive events and sample size will be extracted to answer the question, as well as the objective of the study, epidemiological characteristics, vaccination status and other pertinent results and conclusions.

3.6. Data synthesis and meta-analysis

If quantitative synthesis is not possible, a qualitative synthesis will be carried out based on a narrative presentation containing tables and graphs for standardization and better exposure of the results. However, it is expected that quantitative synthesis will be carried out. Thus, effect sizes will be calculated based on the odds ratio (for dichotomous outcomes) and the difference in means (for continuous outcomes), considering the 95% confidence interval (CI). Heterogeneity will be assessed using I^2, and heterogeneous results will be investigated by subgroup analysis. Unreported biases will be accessed through the funnel plot and their asymmetry will be tested using the Egger test. Potential Outliers will be identified by visual inspection and will be temporarily excluded to assess their interference with the overall result.

3.7. Assessment of the methodological quality of the included studies

The Joanna Briggs Institute's critical appraisal tool will be used for use in systematic reviews: “Critical appraisal checklist for studies reporting prevalence data”[14]. The risk of bias in the study will be based on the frequency of “yes” answers to the questions on the list, being categorized as “high” (up to 49%), “moderate” (between 50-(69%) or “low” (above 70%).

3.8. Risk of bias

The risk of publication bias will be assessed visually, through the distribution of risk/prevalence differences in the funnel graph.

3.9. Systematic review products

A redação final da revisão sistemática conterá tabelas resumidas com os resultados, fluxograma PRISMA do processo, mapas de distribuição da raiva e das demais enfermidades neurológicas de origem viral dos herbívoros, registro de protocolo e lista de verificação PRISMA[15].

3.10. Amendments

If there is a need to make any changes to the protocol, a dated amendment will be made available with a description and reason for the modification.

3.11. Conflicts of Interest

There will be no conflicts of interest.

4. TIMELINE OF THE REVIEW PROCESS

Stage	Started	Completed
Literature review and team selection	Yes	Yes
Pilot project and adjustments	Yes	Yes
Electronic database search	Yes	Yes
Data selection	No	No
Data extraction	No	No
Quality appraisal	No	No
Synthesis	No	No
Meta-analysis	No	No

5. EXPECTED RESULTS AND IMPACTS

The analysis of the epidemiological characteristics of rabies in herbivores can help optimize specific behaviors and strategies, aiming to reduce cases and plan new environmental education strategies, which will inform the population about the risks, prevention and control of rabies, thus reducing the number of animals affected and the economic losses that rabies causes when there are affected animals in herds.

The differential diagnosis of other neurological viruses that affect cattle and horses will help producers to adopt more effective control measures, in order to reduce losses and losses in the production of their herds.

Therefore, this study is expected to verify whether the occurrence of diseases caused by the rabies virus and other neurological viruses that affect cattle and horses are different, identifying factors that may interfere with this condition such as geographic location, breeding/production systems, diagnostic method and others, so that strategies to combat diseases can be planned in a more objective and effective way

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