Feline herpesvirus (FHV-1) molecular prevalence comparing with others domestic cats' viruses: a systematic review protocol

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1. BACKGROUND

Feline herpesvirus (FHV-1) is an alphaherpesvirus that affects cats and causes mainly upper respiratory signs, but also ocular, oral, dermal, and neural signs[1]. Due to its elevated morbidity and, especially in kittens, high mortality it is recognized as an important clinical pathogen[2].

Considering that the infection or reactivation of this virus is commonly associated to immunosuppression[3] and stressful periods[4] and can concurrently occur to another infectious agents, carefully evaluation of the patient and exclusion of different diagnosis should be part of clinical inquiry[3,5,6].

Viral diseases diagnostic can be established by virus isolation, antibody immunofluorescent assay, antibody detection (serum neutralization assay or ELISA) or from acid nucleic identification, by polymerase chain reaction (PCR)[1].

PCR was created by the winner of the Chemistry Novel Prize, Kary Mullis[7], and over the years several techniques have been developed, such as conventional, *Nested,* and reverse transcriptase[8]. Currently, PCR panels are also being used by laboratories to investigate more than one pathogen simultaneously, providing more agents exclusion at a lower cost for the owner[9].

PCR test is used for infection screening, disease diagnosis, and to certify that an animal is "free of infection", when performed in conjunction with serology[10]. It is considering the gold standard for the diagnosis of viruses, being a more sensitive than virus isolation and

indirect immunofluorescence[2]. Furthermore, it can recognize carrier states, which helps in better understanding of pathogen self-sustain in a population[10].

Epidemiologic factors studies, whether correlated to the infectious agent itself, to the host or to the environment, can be used to perform disease risk assessment[10,11]. Besides, knowing these dynamics can facilitates the identification of outbreaks, establishes effective animal management, and improves preventive protocols, principally in high density population[12].

2. OBJECTIVES

2.1. General objective

To access the feline herpesvirus molecular prevalence comparing to others domestic cats' viruses.

2.2. Specific objectives

a) To access molecular prevalence from observational studies
b) To describe characteristics from selected studies
c) To verify correlation between studies variables and if they affect virus prevalence
d) To identify the heterogeneity and biases from selected studies
e) To perform a meta-analysis of synthesized data, if possible

3. METHODS

This research was approved by the Animal Science Postgraduate Program Director Board at Federal University of Goiás - UFG (23070.044013/2021-03) and this protocol, developed according to PRISMA-P checklist[13], will be registered on SYREAF (https://www.syreaf.org/).

3.1. Question

The question will be based on CoCoPop acronymous: condition, context, and population, as stated in JBI Manual for Evidence Synthesis[14]. So, the condition herpesvirus on feline population in global context will be describe.

1. Is the FHV-1 molecular prevalence higher than the others domestic cats' viruses?

2. What is the geographic distribution of the viruses based on the selected studies?

3.2. Eligibility criteria

3.2.1. Inclusion criteria

3.2.1.1. Population

Cats of every age, breed, and sex, neutered or not, from any ambient (street, shelters, houses, apartments, farms, and others), and with or without contactants, clinical signs or concomitant diseases.

3.2.1.2. Outcomes

Feline herpesvirus molecular prevalence and prevalence of others domestic cats' viruses.

3.2.1.3. Study design

Only observational studies will be evaluated.

3.2.1.4. Geographic scope

It will be a global review, so no geographic restriction will be made.

3.2.1.5. Language and duration

There will be no language and period restrictions for publication. However, translation tools, native or fluent speakers or specialized company will be used, if necessary.

3.2.2. Exclusion criteria

Papers whose data was overlapped with another included articles, without a clearly diagnostic method (PCR) for feline herpesvirus and without prevalence percentages (or positive events and sample size) for feline herspesvirus and at least one other virus, in the same article, will be excluded. Besides, review articles, book chapters, letter to the editor, correspondence and others that do not results in original data will be excluded.

3.3. Search strategies

A previous search was made to better understand the herpesvirus context and to verify the existence of primary studies to support the question. The terms used were generic to reach a maximum result: cats AND "feline herpesvirus" AND prevalence.

3.3.1 Study selection

After, a new search was made to select published feline herpesvirus studies as described below. The search results will be analyzed by two independent researchers (P.A.S and M.F.B.). First, the articles duplicity will be removed by Zotero 5.0.69.3 (Corporation for Digital Scholarship, USA) software. Then, title and abstract will be evaluated as stated in eligibility criteria. Later, the full text of selected articles will be read and reselected, if eligible. Disagreements between researchers on the selected articles will be solve with a discussion or a third person (V.M.B.D.M or B.S.V.).

3.3.1.1. Electronic databases

The included electronic databases were Embase, Pubmed, Scielo, Science Direct, Scopus and Web of Science. The search was conducted on November 16th and weekly mail alerts were created to identify new published articles that could be add on this systematic review.

3.3.1.2. Search terms

The search terms were design in consonance with electronic databases specificities, as described below:

Database	Search terms
Embase	(('cat'/exp OR 'cat disease'/exp OR 'pet animal'/exp) AND ('feline herpesvirus' OR 'herpes virus infections'/exp OR 'herpesviridae'/exp) AND ('prevalence'/exp))
Pubmed	((((cats[MeSH Terms]) OR (cat diseases[MeSH Terms]) OR (pets[MeSH Terms]) OR (kitten)) AND (("feline herpesvirus"[All fields]) OR ("Herpesviridae infections"[MeSH Terms]) OR ("Herpesviridae"[MeSH Terms])) AND (prevalence))

Scielo	((gatos OR cats OR chats) OR ("animais de estimação" OR pets OR mascotas OR "animaux de compagnie") OR ("doenças do gato" OR "cat diseases" OR "enfermedades de los gatos" OR "maladies des chats")) AND (("herpesvirus felino" OR "feline herpesvirus" OR "virus herpes felino" OR "herpèsvirus félin") OR (herpes OR herpès) OR (herpesviridae))
Science Direct	(((cat) OR (cats) OR ("cat disease") OR (pet) OR (kitten)) AND (("feline herpesvirus") OR ("Herpesviridae infections") OR ("Herpesviridae")) AND (prevalence))
Scopus	TITLE-ABS-KEY (((cat) OR (cats) OR ("cat disease") OR ("cat diseases") OR (pet) OR (pets) OR (kitten) OR (kittens)) AND (("feline herpesvirus") OR ("Herpesviridae infections") OR ("Herpesviridae")) AND (prevalence))
Web of Science	(((cat) OR (cats) OR ("cat disease") OR ("cat diseases") OR (pet) OR (pets) OR (kitten) OR (kittens)) AND (("feline herpesvirus") OR ("Herpesviridae infections") OR ("Herpesviridae")) AND (prevalence))

3.4. Data extraction

Data will be manually extracted from all included studies and organized in an electronic spreadsheet by year, authors, country of publication, study design, evaluated infectious agents and diagnostic methods used for the pathogen detection. Quantitative data as prevalence percentages, number of positive events and sample size will be extracted to answer the review question as well as the study objective, epidemiologic characteristics, vaccine status, clinical condition, clinical signs (or affected systems) and other pertinent results and conclusions.

3.5. Data synthesis and meta-analysis

If quantitative data synthesis is not applicable, qualitative synthesis will be conducted using narrative description, tables, and graphics. However, quantitative synthesis is expected and Review Manager – Revman 5.4.1 (The Cochrane Collaboration, USA) will be used to do it. Size effects will be expressed by odds ratio, considering 95% of confidence interval.

Heterogeneity will be evaluated by Chi^2, and its magnitude will be estimated by I^2. Heterogeneous results will be investigated by subgroups analysis. Non-reported bias will be access by funnel plot and its asymmetry will be tested using Egger's test. Potential outliers will be identified by visual inspection, and they will be temporarily excluded to evaluate its interference on general results.

3.6. Assessment of methodological quality

Joana Briggs Institute's tool (Critical Appraisal Checklist for Prevalence Studies)[15] will be used to assess methodological quality of the studies and risk of bias will be categorized according to "yes" answer percentages as high ($\leq$ 49%), moderate (50-69%), or low ($\geq$ 70%).

3.7. Systematic review products

The systematic review paper will contain protocol registration, Joana Briggs Institute (JBI) checklist, PRISMA flowchart, summary tables, and feline herpesvirus distribution map.

3.8. Amendments

Any protocol change will result in dated amendment with modification description and rationale.

3.9. Financial sources or other support for the review

This review will be financed by National Centre of Scientific and Technologic Development (CNPQ) and supported by the Pathology Department of Veterinary and Zootechnics School, Federal University of Goiás (Setor de Patologia Animal da Escola de Veterinária e Zootecnia da Universidade Federal de Goiás), Goiânia, Goiás, Brazil.

3.10. Conflict of Interest

There will be no conflict 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

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