SYSTEMATIC REVIEW PROTOCOL FOR ANIMAL INTERVENTION STUDIES

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Item #	Section/Subsection/Item	Description	Check for approval
	A. General		
1.	Title of the review	**Factors associated with Visceral Leishmaniasis in dogs in the American continent: an update of existing systematic reviews and meta-analysis**	
2.	Authors (names, affiliations, contributions)	**Ms. Anna Gabryela Sousa Duarte, Post Graduate Student in Health Sciences, Universidade Federal de São João Del Rei, Campus Centro Oeste, Brazil. Mss. Sarah de Farias Lelis, Medical Student, Universidade Federal de São João Del Rei, Campus Centro Oeste, Brazil. Dr. Vinícius Silva Belo, Universidade Federal de São João Del Rei, Campus Centro Oeste, Brazil.**	
3.	Other contributors (names, affiliations, contributions)	-	
4.	Contact person + e-mail address	**Ms Anna Gabryela Sousa Duarte** **annagsd@hotmail.com**	
5.	Funding sources/sponsors	**There is no specific funding for this study.**	
6.	Conflicts of interest	**There are no conflicts of interest.**	
7.	Date and location of protocol registration	**July 15, 2020. Brazil.**	
8.	Registration number (if applicable)	-	
9.	Stage of review at time of registration	**Preliminary searches ticked as started.**	
	B. Objectives		
	Background		
10.	What is already known about this disease/model/intervention? Why is it important to do this review?	**Visceral Leishmaniasis (VL) is a disease with severe chronic evolution that, if left untreated, can lead to death in up to 90% of cases. VL is endemic in 76 countries and, of the cases recorded in Latin America, 90% occur in Brazil. Understanding the various variables present in the causality networks associated with the occurrence of VL in dogs is relevant for generating measures with greater potential for effectiveness. Since the measures recommended in Brazil to control the disease are not sufficient to reduce the incidence and the geographical expansion of cases, the study and continuous review of risk factors for VL may be relevant for more effective and effective actions. well-targeted are elaborated. In addition, the review of the methods used in the studies and the combination of their results will result in more**	

		consistent results regarding factors that are still poorly understood.	
	Research question		
11.	Specify the disease/health problem of interest	**Visceral Leishmaniasis.**	
12.	Specify the population/species studied	**Dogs of all breeds and ages, and both sexes submitted to different diagnostic methods for the detection of Leishmania infantum, dogs that manifested the disease clinically or the notification of cases by health services.**	
13.	Specify the intervention/exposure	**The present review will analyze socioeconomic, environmental and other factors potentially associated with infection by *Leishmania infantum* in dogs.**	
14.	Specify the control population	-	
15.	Specify the outcome measures	**The outcomes are related to *Leishmania infantum* infection in dogs verified by diagnostic methods; (serological and others), clinical cases (in case-control studies) and reported cases (in ecological studies).**	
16.	State your research question (based on items 11-15)	**What are the factors associated with Visceral Leishmaniasis in dogs in the American continent?**	
	C. Methods		
	Search and study identification		
17.	Identify literature databases to search (*e.g.* Pubmed, Embase, Web of science)	☐MEDLINE via PubMed ☐Web of Science ☐SCOPUS ☐EMBASE ☐Other, namely: Lilacs, Google Schoolar and CAPES Thesis Database ☐Specific journal(s), namely: **MEDLINE via Pubmed; Other namely: Lilacs, Google Schoolar and CAPES Thesis Database.**	
18.	Define electronic search strategies (*e.g.* use the step by step search guide[15] and animal search filters[20, 21])	When available, please add a supplementary file containing your search strategy: [insert file name] **MEDLINE via Pubmed: (Leishmaniasis, Visceral OR Leishmania infantum) AND (risk factors OR associated factors OR epidemiological studies OR immunology OR epidemiology).** **Lilacs: (visceral leishmaniasis OR leishmaniose visceral AND risk factors OR immunology)** **Google Scholar: leishmaniose visceral AND epidemiol*** **CAPES Thesis Database: Leishmaniose visceral** **The search strategies were based on MeSH.** **Using the suggested search strategies, the amount of results found was similar to that proposed.** **We researchers seek to balance the sensitivity and specificity of our searches.**	

		With the use of all terms in the Google Scholar and Lilacs databases, the number of publications was too large, so we opted for the search strategies described above.	
19.	Identify other sources for study identification	☐Reference lists of included studies ☐Books ☐Reference lists of relevant reviews ☐Conference proceedings, namely: ☐Contacting authors/ organisations, namely: ☐Other, namely:	
20.	Define search strategy for these other sources	**Two researchers will check the reference list.**	
	Study selection		
21.	Define screening phases (*e.g.* pre-screening based on title/abstract, full text screening, both)	**Pre-screening: All titles and abstracts of the articles found will be read and analyzed, initially excluding those considered irrelevant with regard to the proposed criteria.** **Screening: The studies that will be selected to be part of the systematic review will be read in full.**	
22.	Specify (a) the number of reviewers per screening phase and (b) how discrepancies will be resolved	**The studies will be selected by two researchers, in case of disagreement between the two researchers, the decision will be up to the third researcher.**	
	Define all inclusion and exclusion criteria based on:		
23.	Type of study (design)	**This is a systematic review study, with meta-analyze, which will update the results obtained in the following systematic review: "A systematic review and meta - analysis of the factors associated with Leishmania infantum infection in dogs in Brazil".**	
24.	Type of animals/population (*e.g.* age, gender, disease model)	Inclusion criteria: **Dogs of all breeds and ages, and both sexes submitted to different diagnostic methods for the detection of *Leishmania infantum*, dogs that manifested the disease clinically or the notification of cases by health services.** Exclusion criteria: **Dogs outside the American continent.**	
25.	Type of intervention (*e.g.* dosage, timing, frequency)	Inclusion criteria: - Exclusion criteria: -	
26.	Outcome measures	Inclusion criteria: **Diagnostic methods: serological; molecular; parasitological; clinical cases (in case-control studies) and reported cases (in ecological studies).** Exclusion criteria: -	
27.	Language restrictions	Inclusion criteria: **All languages.** Exclusion criteria: -	
28.	Publication date restrictions	Inclusion criteria: **From 2011 to 2020.** Exclusion criteria: **Before 2011.**	
29.	Other	Inclusion criteria: **Cross-sectional, cohort, case-control and ecological studies.** Exclusion criteria: **Review or descriptive studies, articles before 2011, studies that do not concern risk factors associated with visceral leishmaniasis in dogs in the**	

		American continent, studies with inconsistencies or flaws in the data presented.	
30.	Sort and prioritize your exclusion criteria per selection phase	Selection phase: search of articles 1. **Articles before 2011** Selection phase: selection by title and summary 1. **Not related to the risk factors associated with visceral leishmaniasis.** 2. **Not related to dogs.** 3. **Not carried out on the American continent.** 4. **Literature reviews and descriptive studies.** Selection phase: reading the full article 1. **Not related to the risk factors associated with visceral leishmaniasis.** 2. **Not related to dogs.** 3. **Not carried out on the American continent.** 4. **Literature reviews and descriptive studies.** 5. **Studies in which there are inconsistencies or flaws in the data presented will be excluded.**	
	Study characteristics to be extracted (for assessment of external validity, reporting quality)		
31.	Study ID (*e.g.* authors, year)	**Title; authors; place of execution; population; type of study; design used; groups(s) in which the study is classified; exposure and outcome variables; techniques used to measure outcomes; methods of data analysis; control or not of confounding factors; information necessary for the calculation of measures of effect for each variable or for possible conversions; main results obtained; conclusions and issues related to quality.**	
32.	Study design characteristics (*e.g.* experimental groups, number of animals)	**Number of dogs, case groups and control.**	
33.	Animal model characteristics (*e.g.* species, gender, disease induction)	**Sex, age, cohabitation of dogs with other animals, hair length, breed, place where the dog lives and access (or not) to the street.**	
34.	Intervention characteristics (*e.g.* intervention, timing, duration)	**Not applicable.**	
35.	Outcome measures	**Serological testes results including ELISA and IFAT, molecular tests and others.**	
36.	Other (*e.g.* drop-outs)	-	
	Assessment risk of bias (internal validity) or study quality		
37.	Specify (a) the number of reviewers assessing the risk of bias/study quality in each study and (b) how discrepancies will be resolved	**(a) Two researchers.** (b) **In cases of disagreement between the two researchers, the decision will be made by the third researcher.**	

38.	Define criteria to assess (a) the internal validity of included studies (*e.g.* selection, performance, detection and attrition bias) and/or (b) other study quality measures (*e.g.* reporting quality, power)	☐By use of SYRCLE's Risk of Bias tool[4] ☐By use of SYRCLE's Risk of Bias tool, adapted as follows: ☐By use of CAMARADES' study quality checklist, e.g [22] ☐By use of CAMARADES' study quality checklist, adapted as follows: ☐Other criteria, namely: **The main limitations of the studies, as well as the susceptibility to bias, will be analyzed using the tool "Strengthening the Reporting of Observational Studies in Epidemiology" (STROBE) Newcastle-Ottawa Quality Assessment Scale questions will also be consulted to assess the quality of case-control and cohort studies and Fischer and Getis's book to assess the quality of ecological studies.**	
	Collection of outcome data		
39.	For each outcome measure, define the type of data to be extracted (*e.g.* continuous/dichotomous, unit of measurement)	**Serological tests result including IFAT and ELISA, molecular tests and others. The result will be extracted in a dichotomous way (positive or negative) from the data provided by each study.**	
40.	Methods for data extraction/retrieval (*e.g.* first extraction from graphs using a digital screen ruler, then contacting authors)	**Data extraction will be performed in an Excel spreadsheet. In studies where information is not available, we will contact the authors.**	
41.	Specify (a) the number of reviewers extracting data and (b) how discrepancies will be resolved	**(a) Two researchers.** **(b) In cases of disagreement between the two researchers, the decision will be made by the third researcher.**	
	Data analysis/synthesis		
42.	Specify (per outcome measure) how you are planning to combine/compare the data (*e.g.* descriptive summary, meta-analysis)	**Each association between a variable and the outcome will be considered a separate and independent meta-analysis.**	
43.	Specify (per outcome measure) how it will be decided whether a meta-analysis will be performed	**A single measure of effect will be chosen for each meta-analysis. The choice will depend mainly on how the associations were tested in the primary studies. When the numerical diversity of data from primary studies prevents them from being combined statistically, meta-analysis methods for combinations of p values will be used.**	
	If a meta-analysis seems feasible/sensible, specify (for each outcome measure):		
44.	The effect measure to be used (*e.g.* mean difference, standardized mean difference, risk ratio, odds ratio)	**The results of the studies, except ecological ones, will be described using Odds Ratio (OR) and their confidence intervals (CI). In cases where the studies portray information about statistical significance, direction of association and sample size, the OR will be estimated by reverse computation.**	
45.	The statistical model of analysis (*e.g.* random or fixed effects model)	**Whenever a summary measure is obtained, the random effects model will be used to combine the data.**	
46.	The statistical methods to assess heterogeneity (*e.g.* I^2, Q)	**The Q test will be used to analyze the occurrence of heterogeneity in the sizes of the effects of the studies. The I^2 statistic will be calculated to determine which**	

		proportion of the observed variance represents a real dispersion in the size of the effects. Subgroup analyzes may also be carried out to identify factors that explain the identified heterogeneities.	
47.	Which study characteristics will be examined as potential source of heterogeneity (subgroup analysis)	**Subgroup analyzes will be performed to sex, age, cohabitation of dogs with chickens or other domestic fowl, cohabitation of dogs with other mammals. The following groups will be considered: type of study (i. cross-sectional; ii. cohort; iii. case-control), method for measure the result (i. serological; ii. others; iii. clinical case), hair length of coat (i. short hair; ii. long hair), breed of dog (i. mixed; ii. purebred), restriction of movement of dog (i. domestic-restricted; ii. peri-domestic restricted), and adjustment for confusion (i. yes; ii. no).**	
48.	Any sensitivity analyses you propose to perform	-	
49.	Other details meta-analysis (*e.g.* correction for multiple testing, correction for multiple use of control group)	-	
50.	The method for assessment of publication bias	**The investigation of the existence of publication bias among the studies selected for each meta-analysis will be carried out using the funnel plot, the Egger test and the "Durval and Tweedie's Trim and Fill" statistics.**	
Final approval by (names, affiliations):			Date: