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	Molecular and serological surveys of canine distemper virus: a cross-sectional study and meta-analysis	
2.	Authors (names, affiliations, contributions)	Vivaldo Gomes da Costa[1], Marielena Vogel Saivish[2], Roger Luiz Rodrigues[2], Rebeca F de Lima e Silva[2], Marcos Lázaro Moreli[2], Ricardo Henrique Krüger[1] [1]Department of Cell Biology, University of Brasília (UnB) [2]Virology Laboratory, Federal University of Goias (UFG)	
3.	Other contributors (names, affiliations, contributions)	-	
4.	Contact person + e-mail address	Vivaldo Gomes da Costa Department of Cell Biology, University of Brasília, Asa Norte, Brasília-DF, Brazil. E-mail: vivaldo14@gmail.com or vivbiom@gmail.com	
5.	Funding sources/sponsors		
6.	Conflicts of interest	None	
7.	Date and location of protocol registration	**December 2018**	
8.	Registration number (if applicable)	**Update: Items 1, 2, 7, 8, 9, 22, 38**	
9.	Stage of review at time of registration	Review stage: Started / Completed Preliminary searches: Yes / Yes Piloting of the study selection process: Yes / Yes Formal screening of search results against eligibility criteria: Yes / Yes Data extraction: Yes / No Risk of bias (quality) assessment: Yes / No Data analysis: Yes / No	
	B. Objectives		
	Background		
10.	What is already known about this disease/model/intervention? Why is it important to do this review?	Canine distemper virus (CDV), *Morbillivirus* genus, poses a serious threat to the health of several members of family *Canidae*, among wich is the domestic dog (Canis lupus familiaris). This virus is the etiological agent of one of the most important viral diseases in dogs [1,2]. Canine distemper (CD) is a disease that has little specific clinical signs, and it is easy to confuse with other pathogens [3]. In this way, laboratory diagnostic methods play an important role in confirming the disease [4]. Therefore, series of CDV seroepidemiologic studies over years may provide the baseline evidence for appropriate surveillance strategies against CD in places of occurrence of the diseases. The absence of a database hinders primary animal health care prevention. In addition, the most studies evaluating CDV	

		infection in the dog population have small samples, and were conducted using different detection methods. Finally, the understanding of CDV frequency will be useful for monitoring changes in CDV distribution in different regions of world.	
	Research question		
11.	Specify the disease/health problem of interest	What are the frequency parameters of canine distemper virus (CDV) infections in domestic dogs around the world? What is the current state of knowledge on the epidemiology of CDV? Therefore, review question(s) are to perform a review systematic and meta-analysis to determine the frequency parameters of CDV infections in dogs with their biological samples tested by different diagnostic methods.	
12.	Specify the population/species studied	Canis lupus familiaris/domestic dog.	
13.	Specify the intervention/exposure	Level of CDV infection (IgM and amplicons) in the world using serological and molecular diagnostic methods.	
14.	Specify the control population	-	
15.	Specify the outcome measures	IgM serological marker for detection of acute CDV infection; detection of molecular markers of CDV genes (N, P and L genes).	
16.	State your research question (based on items 11-15)	1. To determine the CDV's frequency in domestic dogs in different countries of the world. 2. To determine CDV's frequency in domestic dog in different continents. 3. To determine CDV's frequency in domestic dog according to the diagnostic method and type of biological sample used. 4. To determine the global status of CDV's frequency with synthesis of polled data and thema update.	
	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: Google Scholar, SciELO, Science Direct ☐ Specific journal(s), namely:	
18.	Define electronic search strategies (*e.g.* use the step by step search guide[15] and animal search filters[20, 21])	The data search included a combination of the following keywords: "canine distemper virus", "viruses in dogs", "Canine distemper". These terms will be combined using the connectives "AND" with "domestic dogs" or "viruses"	
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	-	
	Study selection		
21.	Define screening phases (*e.g.* pre-screening based on title/abstract, full text screening, both)	1. Pre-screening based on title and abstract 2. Full-text screening simultaneously performed with data extraction	
22.	Specify (a) the number of reviewers per screening phase and (b) how discrepancies will be resolved	(a) Two per stage (b) For discrepancy, it was resolved after discussion.	
	Define all inclusion and exclusion criteria based on:		
23.	Type of study (design)	Inclusion criteria: Original articles published in journals (papers); with studies analysing molecular and serological surveys of CDV in domestic dogs. Exclusion criteria: review articles; duplicated articles (i.e., same data published in journal); personal opinions; book chapters, editorials and conference abstracts; studies in vitro; serostatus in CD confirmed animals; Non-dog seroprevalence studies (i.e., fox, wild dogs).	
24.	Type of animals/population (*e.g.* age, gender, disease model)	Inclusion criteria: All domestic dogs of any age and sex. Exclusion criteria: Other animals	
25.	Type of intervention (*e.g.* dosage, timing, frequency)	Inclusion criteria: - Exclusion criteria: -	
26.	Outcome measures	Inclusion criteria: All outcomes related to CDV detection Exclusion criteria: Non CDV related outcomes	
27.	Language restrictions	Inclusion criteria: -English language Exclusion criteria: - Other language	
28.	Publication date restrictions	No restriction.	
29.	Other	Inclusion criteria: - Exclusion criteria: -	
30.	Sort and prioritize your exclusion criteria per selection phase	Selection phase: Stage 1 (screening on basis of title and abstract) 1. Not a primary research article (review, comment, editorial, conference communication, letter to the editor) 2. Study in other animals (status serologic and molecular in non-domestic dogs). Selection phase: Stage 2 (full text screening) 1. Criteria above 2. Incomplete or confusing data on the level of CDV infection in dogs suspected of canine distemper.	
	Study characteristics to be extracted (for assessment of external validity, reporting quality)		
31.	Study ID (*e.g.* authors, year)	Authors, year, DOI, full title, journal name	
32.	Study design characteristics (*e.g.* experimental groups, number of animals)	1. Observational studies with samples from dogs clinically suspected of distemper. 2. Number of animals regarding with the following subgroups will be extracted: type of exams used; types of biological material; origin of samples; gender; age and data on CVD vaccination.	
33.	Animal model characteristics (*e.g.* species, gender, disease induction)	Specie: canis lupus familiaris, male and females of different age groups.	
34.	Intervention characteristics (*e.g.*	-	

	intervention, timing, duration)		
35.	Outcome measures	Frequency will be estimated by the number of cases (CDV infection) divided by the total number of sample from domestic dog suspected to have canine distemper, and expressed as a percentage.	
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) Three reviewers (b) Resolved by discussion with third investigator	
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: For the study quality analysis, modified Joanna Briggs Institute [5] appraisal checklist will be evaluated. In addition, the quality evaluation of the studies referred to the modified method of quality evaluation of the studies referring to the methodology of participant selection, laboratory tests and outcome variables.	
	Collection of outcome data		
39.	For each outcome measure, define the type of data to be extracted (*e.g.* continuous/dichotomous, unit of measurement)	The primary outcome will be the proportion of CDV infection in dogs clinically suspected of canine distemper. The crude and the weight frequency estimates are expected to be dichotomous. Thus, proportion of positive CDV infection will be extracted to calculate a global incidence/frequency of CDV, and a confidence interval (CI) of 95% will be used whenever possible.	
40.	Methods for data extraction/retrieval (*e.g.* first extraction from graphs using a digital screen ruler, then contacting authors)	1. From text 2. From graphs 3. If necessary, the authors of the article may be contacted	
41.	Specify (a) the number of reviewers extracting data and (b) how discrepancies will be resolved	(A) Three authors (VGC, MVS and RLR) independently extracting data. (B) Each disagreement will be resolved with discussion, or reviewed by another researcher.	
	Data analysis/synthesis		
42.	Specify (per outcome measure) how you are planning to combine/compare the data (*e.g.* descriptive summary, meta-analysis)	Data will be compared using both descriptive summary and meta-analysis.	
43.	Specify (per outcome measure) how it will be decided whether a meta-analysis will be performed	Summary estimates will be provided when 2 or more comparisons are available. Thus, meta-analysis will be performed using STATA IC/64 version 13.1 software (Stata Corporation, College Station, Texas, USA). Subgroup analysis will be conducted to diagnose the heterogeneity	

		based on the diagnostic method, age, degree of clinical classification, sample size, gender, types of biological samples, data on CVD vaccination and place of study.	
	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)	Categorical variables will be summarized by frequencies/percentages. Thus, a quantitative synthesis will be conducted using random or fixed effects model in according the distribution of effect sizes and relevant source of error. The available data will be aggregate in tables for dichotomous variables with the goals to calculate the pooled Frequency in percentage. In this case, will be calculated the confidence interval (CI) of 95%, which will be calculated using the standard formula for a proportion: p±1.96*sqrt[p*(100-p)/n]. If possible, we will use the risk ratio to analyze the frequency of the incidence of CDV according to the diagnostic method, age, degree of clinical classification, sample size, gender, types of biological samples, place of study and data on CVD vaccination. In addition, the forest plot graph will be generated for better synthesis and understanding of the results obtained.	
45.	The statistical model of analysis (*e.g.* random or fixed effects model)	Random or fixed-effects models	
46.	The statistical methods to assess heterogeneity (*e.g.* I^2, Q)	Heterogeneity will be assessed using I^2 and τ^2 heterogeneity values	
47.	Which study characteristics will be examined as potential source of heterogeneity (subgroup analysis)	- Study site; - Age (puppy versus old age); - Gender (Female versus male); - Diagnostic method (ELISA, Immunofluorescence, Immunochromatographic, PCR) - Types of biological samples (blood, feces, saliva); - Degree of clinical classification (neurological, gastrointestinal); - Sample size (large and small); - Data on CVD vaccination.	
48.	Any sensitivity analyses you propose to perform	If there is heterogeneity (using I-squared statistic, p value < 0.05) sensitivity analyses will be performed to identify the associated cofactors, such as the origin of the studies, type of diagnostic method, biological sample analyzed, among others.	
49.	Other details meta-analysis (*e.g.* correction for multiple testing, correction for multiple use of control group)	In cases where the lower limit of the 95% CI is negative, we set the value to zero to avoid negative frequency.	
50.	The method for assessment of publication bias	Potential publication bias (small-study effect) will be assessed by using visual inspection of funnel plot, and objectively by using Egger's/begger's statistical tests.	
Final approval by (names, affiliations):		1. Vivaldo Gomes da Costa, UnB 2. Marielena Vogel Saivish, UFG 3. Roger Luiz Rodrigues, UFG	Date: 28 Nov 2018

4. Marcos Lázaro Moreli, UFG

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