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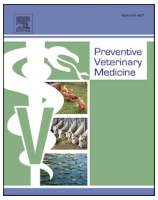

A systematic literature review and meta-analysis of risk factors for *Neospora caninum* seroprevalence in goats

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ABSTRACT

This meta-analysis aimed to estimate *N. caninum* seroprevalence in goats worldwide to determine the main risk factors for seropositivity that could be associated with parasite infection in herds. Four electronic databases were searched: PubMed, SciELO, Scopus and the VHL Regional Portal. Firstly, 367 articles were identified. After removing duplicates and non-eligible papers. A total of 36 articles were selected, which contained information concerning 22,234 goats, between 2004–2019. The combined seroprevalence of infection using a meta-analysis of the random effects model was 5.99 % (95 %, CI 4.38–7.83). The overall estimated *N. caninum* seroprevalence showed high heterogeneity, $I^2 = 97$ %. The present study showed that seropositive goats were 3.07 times more likely to abort (OR 3.07; 95 % CI 1.02–9.22) than seronegative animals. The presence of dogs on farms also increased the odds of *N. caninum* seropositivity (OR 1.40; 95 % CI 1.01–1.94). In addition, male animals had higher odds of being seropositive to neosporosis than females (OR 1.31; 95 % CI 1.00–1.71). *N. caninum* seroprevalence in goats is widely distributed worldwide, with the American continent having a higher proportion of seropositive animals.

1. Introduction

Neospora caninum is an Apicomplexa protozoan with worldwide distribution for which canines are the definitive host and homeothermic animals are intermediate hosts (Dubey et al., 2017). Neosporosis is one of the main causes of reproductive failure in ruminants and it has been estimated that the worldwide economic impact is approximately 1.3 billion dollars annually (Dubey et al., 2007; Reichel et al., 2013).

Neosporosis in goats is prevalent in several regions of the world, and seropositivity in a herd is commonly associated with miscarriage and neonatal mortality (Moreno et al., 2012; Mesquita et al., 2013). *N. caninum* seropositivity in goats is widely distributed worldwide and previous studies have shown that the seroprevalence of anti-*N caninum* antibodies ranges between 0.47 % and 26.65 % (Czopowicz et al., 2011; Tembue et al., 2011).

Sample calculation is an important tool for estimating seroprevalence in herds (Cameron and Baldock, 1998). Furthermore, seroprevalence associate with the potential risk factors is a way of understanding as the parasite maintained and spread among animals in the herd.

Some studies have associated *N. caninum* seropositivity in goats with certain risk factors, i.e. the presence of dogs, reproductive failures on farms and age. In addition, older animals appear to be more susceptible, as they have a longer duration of environmental exposure (Arraes-Santos et al., 2016; Gazzonis et al., 2016; Braz et al., 2018).

As there is no effective vaccine against *N. caninum*, epidemiological studies are essential for adopting biosecurity measures for herds (Dubey et al., 2007). This meta-analysis aimed to estimate the *N. caninum* seroprevalence in goats worldwide and identify the main risk factors for seropositivity that could be associated with parasite infection in herds.

2. Material and methods

2.1. Literature search strategy

This systematic review was structured according to the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (Moher et al., 2015). A thorough systematic review was carried out to identify the largest number of scientific

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articles reporting *N. caninum* seroprevalence in goats. For this, four electronic databases were consulted: PubMed, SciELO, Scopus and the VHL Regional Portal. The combination of terms used in the literary research were: '*Neospora caninum* AND goat', '*Neospora caninum* AND goat AND anti-*Neospora* antibodies', '*Neospora caninum* AND goat AND seroprevalence', '*Neospora caninum* AND goat AND risk factor' and '*Neospora caninum* AND goat AND seroprevalence AND risk factor'. For the selection of articles, there was no restriction on the year of publication and all articles that met the above criteria published until February 2020 were included.

The research results were imported into the free web-tool Rayyan for systematic reviews (Ouzzani et al., 2016) where two independent reviewers selected the papers in according to the pre-established criteria. When there was disagreement in the choice of articles, a third reviewer was consulted to resolve the situation. The inclusion criteria were: all articles that reported *N. caninum* seroprevalence in goats; that contained, in their methodology, calculation of the sample size of the study to define the seroprevalence found; and published in English, Portuguese or Spanish. Articles that did not meet these prerequisites were excluded. The following were also excluded: studies without a sample size calculation; experimental studies and reviews; studies with other species; studies with other diseases; theses and dissertations. Finally, a search for articles was performed in the reference lists of the included papers in order to find studies not indexed and found through the search items.

2.2. Data selection

Firstly, the articles were selected through the title and abstract. Where studies were present in more than one electronic database the duplicate article was deleted. The eligible papers were collected and the following information extracted: author; year of publication; type of study; continent; country; sample size; number of positive samples; diagnostic test; geographic location (latitude and longitude); and possible animal-related risk factors; sex; age ($\leq$ 1 year old or $>$ 1 year old); abortion; and presence of dogs. The data were organised in Microsoft Excel spreadsheets.

Articles that presented risk factor results only in the form of an odds ratio (OR) and did not have individualised risk factors were excluded from the meta-analysis of risk factors and these studies were only included in the overall meta-analysis of seroprevalence, as they had incomplete information concerning the number of positive animals, total number of the animals in the exposed or unexposed groups, or for evaluating the risk factors at herd level.

Studies that classified age ($<$ 1 year and $>$ 1 year; $<$ 1 year and $\geq$ 1 year; or in three or more categories that could not be standardised for $\leq$ 1 year old and $>$ 1 year old) were also excluded from the meta-analysis of risk factors.

Finally, the articles included in the meta-analysis of risk factors were standardised to allow a comparative assessment between the articles considering: age (adult vs young) – adult ($>$ 1 year old) and young ($\leq$ 1 year old); abortion (yes vs no); sex (male vs female); and presence of dogs (yes vs no).

2.3. Statistical analysis

The meta-analysis was performed using the R program, version 3.5.2 with RStudio (R Core Team, 2018) using the meta package (Schwarzer, 2007; Schwarzer et al., 2015). The random effects model was used for the meta-analysis (DerSimonian and Laird, 2015). The pooled seroprevalence estimate of *N. caninum* (at 95 % confidence intervals) was presented as a percentage ((number of seropositive animals / total of animals tested)*100) and the Freeman–Tukey double arcsine method was used to stabilise the variance using the formula:

$$\sin^{-1}\sqrt{\frac{x}{n+1}}+\sin^{-1}\sqrt{\frac{x+1}{n+1}}$$

Where:

x was the number of seropositive animals;

n was the total of animals tested.

The variance was calculated using the formula adapted by Barendregt et al. (2013) from that proposed by Freeman and Tukey (1950):

$$\mathrm{Var}=\frac{1}{n+0.5}$$

The risk factors for the studied variables were presented as odds ratios (OR) with a 95 % confidence interval. The command metaprop was used to estimate the pooled seroprevalence and the command metabin was used to estimate of the association between seroprevalence and possible risk factors: abortion, age, presence of dogs and sex.

Cochran's Q test was used to the heterogeneity between the studies and the I^2 statistic for evaluation of true variation due to heterogeneity (Cochran, 1954; Higgins et al., 2003; Borenstein et al., 2017). The I^2 shows the proportion of the variance, ranging from 0% to 100 % and observes the true size effect from all studies in the analysis (Borenstein et al., 2017). Subgroup meta-analysis and meta-regression were used to evaluate possible sources of heterogeneity. Subgroup analysis was done by continent: Africa, Central America, North America, South America, Asia and Europe. The raw prevalence data were used in the meta-regression and the results were presented in decimal numbers. Meta-regression was performed to determine whether the year of publication, longitude and latitude influenced the *N. caninum* seroprevalence in goats through the bubble plot from the metareg command of the R package.

Meta-regression was performed by the DerSimonian and Laird model equation:

$$\hat{\tau}^2=\frac{Q-(K-1)}{\sum_{k=1}^{K}w_k-\frac{\sum_{k=1}^{K}w_k^2}{\sum_{k=1}^{K}w_k}}$$

Where:

τ^2 was the additive (between-study) component of the variance;

k was amount of studies;

Q was the heterogeneity statistic test proposed by Cochran (1954).

w_k was a weighting factor for the *i*-th study, assuming a fixed model:

$$w_k=1/\hat{\sigma}_k^2$$

Where:

k was amount of studies;

σ was the treatment effect estimate (e.g. a log OR).

Possible publication bias regarding prevalence and risk factors was assessed using Begg's and Egger's tests in combination with a funnel plot and were visualised using funnel plots. Publication bias regarding subgroups and risk factors with at least ten articles was also evaluated (Sterne et al., 2011). In all analyses, a p-value less than 0.05 was considered statistically significant.

3. Results

3.1. Description of included studies

A PRISMA flow chart was created to briefly illustrate the selected studies included in the meta-analysis (Fig. 1). Firstly, 367 articles were pre-selected from the databases. After removing duplicates and non-eligible works, a total of 33 articles were selected. Review of the reference lists yielded three further articles. Finally, a total of 36 articles were eligible for systematic review and meta-analysis (Table 1).

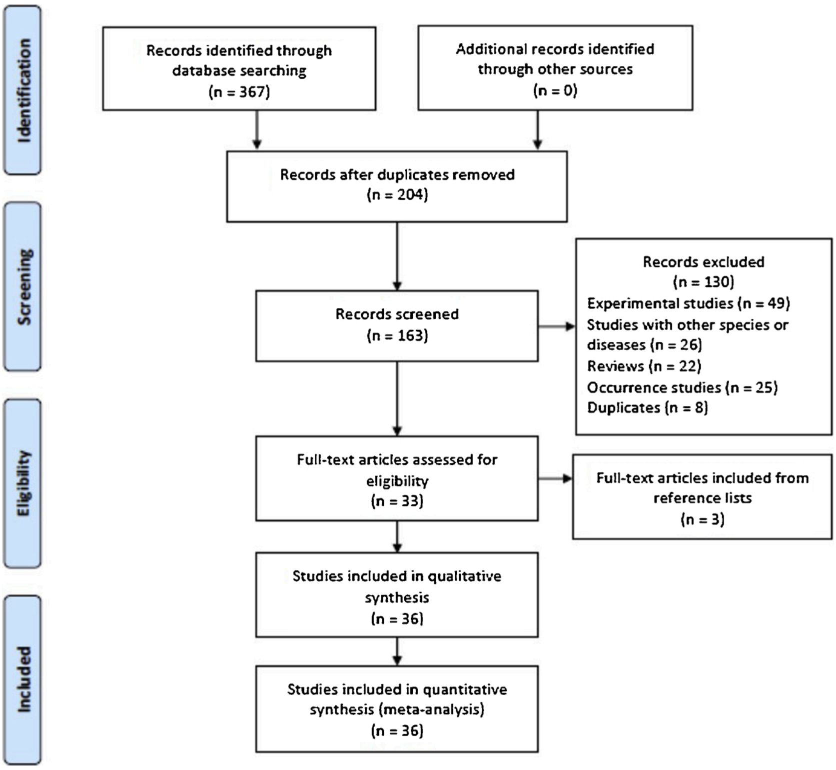


Fig. 1. PRISMA flowchart search strategy to select studies concerning *N. caninum* seroprevalence in goats.

Information concerning 22,234 goats, in these 36 selected articles, were from the period 2004–2019. This was used to determine the *N. caninum* seroprevalence in goats. Data were extracted from 19 locations, which were categorised into six continents, Africa (1), Central America (2), North America (1), South America (2), Asia (5) and Europe (8) (Table 1). The diagnostic methods described included the Enzyme-Linked Immunosorbent Assay (ELISA) (n = 20), Indirect Immunofluorescent Assay (IFAT) (n = 14) and *Neospora* agglutination test (NAT) (n = 2) (Fig. 2) (Table 1).

3.2. Seroprevalence

The pooled seroprevalence using the meta-analysis of the random effects model was 5.99 % (95 % CI 4.38–7.83) (Fig. 2). The overall estimated *N. caninum* seroprevalence showed a high heterogeneity (I^2 = 97 %). Subgroup analysis also showed a high heterogeneity in Asia (I^2 = 92 %), Europe (I^2 = 95 %) and South America (I^2 = 97 %) (Fig. 2). In the subgroup meta-analysis, the highest seroprevalence was found in the American continent, with 7.3 % (95 % CI 5.21–9.71) for Central America, 3.85 % (95 % CI 1.46–7.21) for North America and 8.78 % (95 % CI 5.85–12.23) for South America. In the other regions, the seroprevalence was 3.94 % (95 % CI 2.12–6.28) in Asia, 1.09 % (95 % CI 0.36–2.15) for Africa and 4.10 % (95 % CI 1.8–7.25) in Europe (Fig. 2).

Average neosporosis seroprevalence was reported in 18 countries and ranged from 0.47 % (Poland) to 11.60 % (Brazil) (Fig. 3). Seropositivity increased over the time period 2004–2019, but the meta-regression analysis was not statistically significant (p = 0.2041) (Fig. 4).

3.3. Risk factors

The systematic review identified six studies that reported an association between *N. caninum* seropositivity and the occurrence of abortion. The meta-analysis confirmed that infected goats are 3.07 times more susceptible to the occurrence of abortion (OR 3.07; 95 % CI 1.02–9.22; p = 0.0459) than seronegative animals (Fig. 5).

The age of the animals was collected from six articles and the results of the meta-analysis did not show a significant association between age and *N. caninum* seropositivity in goats (OR 1.14; 95 % CI 0.84–1.53; p = 0.3996) (Fig. 5).

Data on the association between *N. caninum* seropositive goats and the presence of dogs were extracted from four studies. The meta-analysis showed that the presence of dogs on farms increased the risk of *N. caninum* seropositivity in goats (OR 1.40; 95 % CI 1.01–1.94; p = 0.0462) (Fig. 5).

Twelve studies considered sex as a risk factor for *N. caninum* seropositivity in goats. The meta-analysis showed that male animals were more neosporosis seropositive than females (OR 1.31; 95 % CI 1.00–1.71; p = 0.0478) (Fig. 5).

According to the meta-regression, there was a significant relationship between geographic latitude and seroprevalence (p = 0.0032) (Fig. 6), although countries from higher latitudes had fewer reported seroprevalence studies. However, there was no effect of longitude on seroprevalence (p = 0.1994).

No apparent asymmetry in the funnel plot was observed and the absence of evidence of suspected publication bias was supported by Egger's statistical test in relation to sex as a risk factor, which was not significant (p = 0.6186) (Fig. 7). Similarly, there was no statistically significant effect of suspected publication bias for overall combined seroprevalence (p = 0.6589) (Fig. 8) or for combined seroprevalence in South America (p = 0.4061) (Fig. 9).

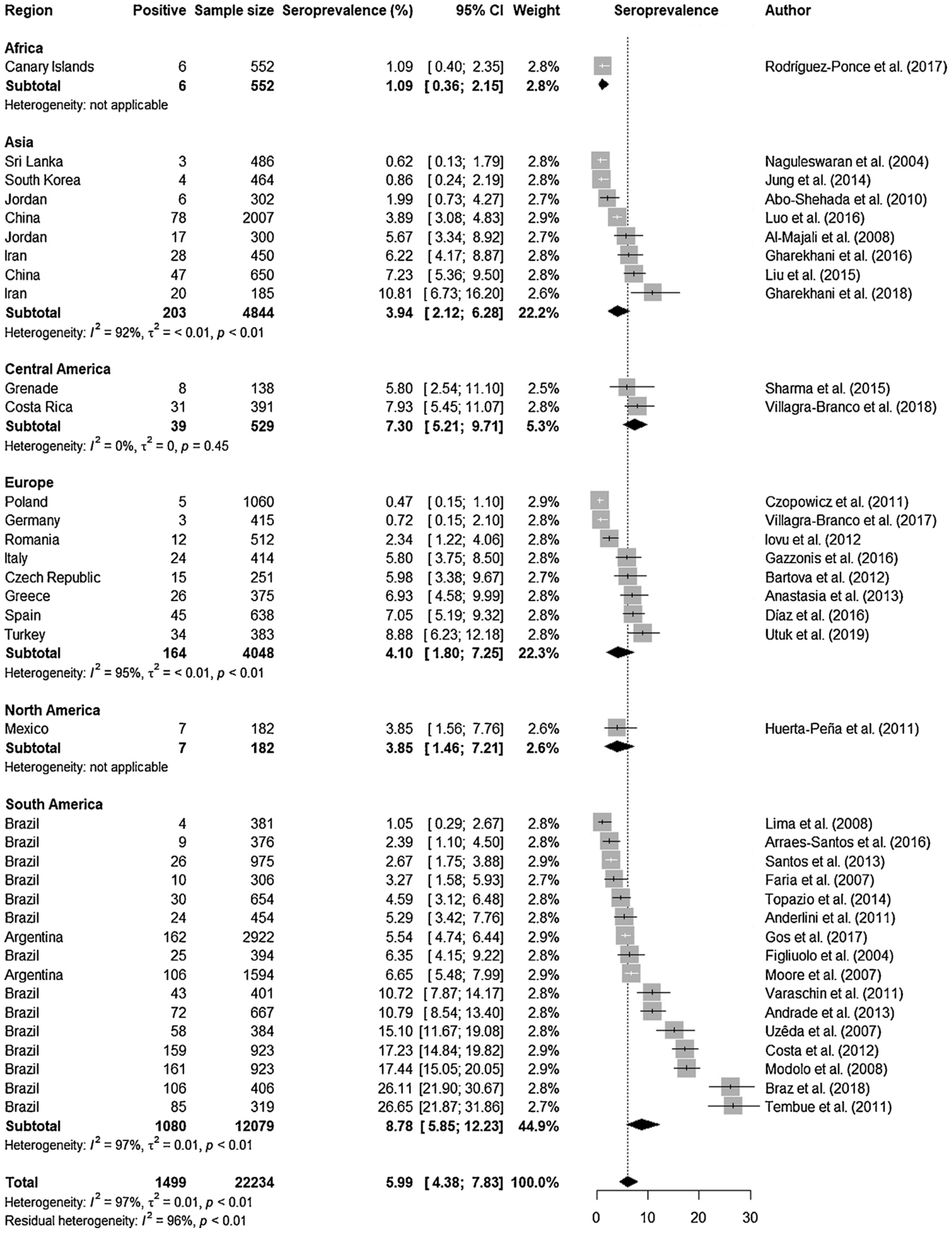
4. Discussion

This systematic review and meta-analysis evaluated 22,234 goats of different breeds, of both sexes and various ages from 18 countries. The results showed that there was a higher proportion of seropositive animals in the Americas than in other regions of the world.

The estimated seroprevalence in the Americas was 7.66 %; among which are the following highlights: Brazil had a satisfactory number of indexed studies (14 studies); two other indexed studies were from

Table 1
Summary of extracted data from all included studies.

Author	Study type	Region	Country	Sample size	Positive	Seroprevalence	Diagnostic test	Cut-off	Risk factors
Rodríguez-Ponce et al. (2017)	Cross-sectional	Africa	Canary Islands	552	6	1.09 %	ELISA		
Naguleswaran et al. (2004)	Cross-sectional	Asia	Sri Lanka	486	3	0.62%	ELISA		
Jung et al. (2014)	Cross-sectional	Asia	South Korea	464	4	0.86%	ELISA		
Abo-Shehada and Abu-Halaweh (2010)	Cross-sectional	Asia	Jordan	302	6	1.99%	ELISA		
Luo et al. (2016)	Cross-sectional	Asia	China	2007	78	3.89%	ELISA		Sex
Al-Majali et al. (2008)	Cross-sectional	Asia	Jordan	300	17	5.67%	ELISA		
Gharekhani et al. (2016)	Cross-sectional	Asia	Iran	450	28	6.22%	ELISA		Abortion, sex
Liu et al. (2015)	Cross-sectional	Asia	China	650	47	7.23%	ELISA		
Gharekhani et al. (2018)	Cross-sectional	Asia	Iran	185	20	10.81%	ELISA		Abortion, sex
Sharma et al. (2015)	Cross-sectional	Central America	Grenade	138	8	5.80%	ELISA		Sex
Villagra-Blanco et al. (2018)	Cross-sectional	Central America	Costa Rica	391	31	7.93%	ELISA		
Czopowicz et al. (2011)	Cross-sectional	Europe	Poland	1060	5	0.47 %	ELISA		
Villagra-Blanco et al. (2017)	Cross-sectional	Europe	Germany	415	3	0.72%	ELISA		
Iovu et al. (2012	Cross-sectional	Europe	Romania	512	12	2.34%	ELISA		
Gazzonis et al. (2016)	Cross-sectional	Europe	Italy	414	24	5.80%	ELISA		Presence of dogs, sex
Bartova and Sedlak (2012)	Cross-sectional	Europe	Czech Republic	251	15	5.98%	ELISA		
Anastasia et al. (2013)	Cross-sectional	Europe	Greece	375	26	6.93%	ELISA		
Díaz et al. (2016)	Cross-sectional	Europe	Spain	638	45	7.05%	ELISA		Age, sex
Utuk and Eski (2019)	Cross-sectional	Europe	Turkey	383	34	8.88%	ELISA		Abortion, presence of dogs, sex
Huerta-Pena et al. (2011)	Cross-sectional	North America	Mexico	182	7	3.85 %	ELISA		Abortion, presence of dogs
Lima et al. (2008)	Cross-sectional	South America	Brazil	381	4	1.05 %	IFAT	1:50	
Arraes-Santos et al. (2016)	Cross-sectional	South America	Brazil	376	9	2.39%	IFAT	1:50	Age, sex
Santos et al. (2013)	Cross-sectional	South America	Brazil	975	26	2.67%	IFAT	1:50	
Faria et al. (2007)	Cross-sectional	South America	Brazil	306	10	3.27%	IFAT	1:50	Sex
Topazio et al. (2014)	Cross-sectional	South America	Brazil	654	30	4.59%	IFAT	1:50	
Anderlini et al. (2011)	Cross-sectional	South America	Brazil	454	24	5.29%	IFAT	1:50	
Gos et al. (2017)	Cross-sectional	South America	Argentina	2922	162	5.54%	IFAT	1:100	
Figliuolo et al. (2004)	Cross-sectional	South America	Brazil	394	25	6.35%	IFAT	1:50	Age
Moore et al. (2007)	Cross-sectional	South America	Argentina	1594	106	6.65%	IFAT	1:50	Age, sex
Varaschin et al. (2011)	Cross-sectional	South America	Brazil	401	43	10.72%	IFAT	1:50	
Andrade et al. (2013)	Cross-sectional	South America	Brazil	667	72	10.79%	IFAT	1:50	
Uzêda et al. (2007)	Cross-sectional	South America	Brazil	384	58	15.10%	IFAT	1:100	
Costa et al. (2012)	Cross-sectional	South America	Brazil	923	159	17.23%	NAT	1:25	
Modolo et al. (2008)	Cross-sectional	South America	Brazil	923	161	17.44%	NAT	1:25	Abortion, presence of dogs, sex
Braz et al. (2018)	Cross-sectional	South America	Brazil	406	106	26.11%	IFAT	1:50	Abortion, age, sex
Tembue et al. (2011)	Cross-sectional	South America	Brazil	319	85	26.65 %	IFAT	1:50	Age



Region	Positive	Sample size	Seroprevalence (%)	95% CI	Weight	Author
Africa						
Canary Islands	6	552	1.09	[0.40; 2.35]	2.8%	Rodríguez-Ponce et al. (2017)
Subtotal	**6**	**552**	**1.09**	**[0.36; 2.15]**	**2.8%**	
Heterogeneity: not applicable						
Asia						
Sri Lanka	3	486	0.62	[0.13; 1.79]	2.8%	Naguleswaran et al. (2004)
South Korea	4	464	0.86	[0.24; 2.19]	2.8%	Jung et al. (2014)
Jordan	6	302	1.99	[0.73; 4.27]	2.7%	Abo-Shehada et al. (2010)
China	78	2007	3.89	[3.08; 4.83]	2.9%	Luo et al. (2016)
Jordan	17	300	5.67	[3.34; 8.92]	2.7%	Al-Majali et al. (2008)
Iran	28	450	6.22	[4.17; 8.87]	2.8%	Gharekhani et al. (2016)
China	47	650	7.23	[5.36; 9.50]	2.8%	Liu et al. (2015)
Iran	20	185	10.81	[6.73; 16.20]	2.6%	Gharekhani et al. (2018)
Subtotal	**203**	**4844**	**3.94**	**[2.12; 6.28]**	**22.2%**	
Heterogeneity: $I^2 = 92\%$, $\tau^2 = < 0.01$, $p < 0.01$						
Central America						
Grenade	8	138	5.80	[2.54; 11.10]	2.5%	Sharma et al. (2015)
Costa Rica	31	391	7.93	[5.45; 11.07]	2.8%	Villagra-Branco et al. (2018)
Subtotal	**39**	**529**	**7.30**	**[5.21; 9.71]**	**5.3%**	
Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, $p = 0.45$						
Europe						
Poland	5	1060	0.47	[0.15; 1.10]	2.9%	Czopowicz et al. (2011)
Germany	3	415	0.72	[0.15; 2.10]	2.8%	Villagra-Branco et al. (2017)
Romania	12	512	2.34	[1.22; 4.06]	2.8%	Iovu et al. (2012
Italy	24	414	5.80	[3.75; 8.50]	2.8%	Gazzonis et al. (2016)
Czech Republic	15	251	5.98	[3.38; 9.67]	2.7%	Bartova et al. (2012)
Greece	26	375	6.93	[4.58; 9.99]	2.8%	Anastasia et al. (2013)
Spain	45	638	7.05	[5.19; 9.32]	2.8%	Díaz et al. (2016)
Turkey	34	383	8.88	[6.23; 12.18]	2.8%	Utuk et al. (2019)
Subtotal	**164**	**4048**	**4.10**	**[1.80; 7.25]**	**22.3%**	
Heterogeneity: $I^2 = 95\%$, $\tau^2 = < 0.01$, $p < 0.01$						
North America						
Mexico	7	182	3.85	[1.56; 7.76]	2.6%	Huerta-Peña et al. (2011)
Subtotal	**7**	**182**	**3.85**	**[1.46; 7.21]**	**2.6%**	
Heterogeneity: not applicable						
South America						
Brazil	4	381	1.05	[0.29; 2.67]	2.8%	Lima et al. (2008)
Brazil	9	376	2.39	[1.10; 4.50]	2.8%	Arraes-Santos et al. (2016)
Brazil	26	975	2.67	[1.75; 3.88]	2.9%	Santos et al. (2013)
Brazil	10	306	3.27	[1.58; 5.93]	2.7%	Faria et al. (2007)
Brazil	30	654	4.59	[3.12; 6.48]	2.8%	Topazio et al. (2014)
Brazil	24	454	5.29	[3.42; 7.76]	2.8%	Anderlini et al. (2011)
Argentina	162	2922	5.54	[4.74; 6.44]	2.9%	Gos et al. (2017)
Brazil	25	394	6.35	[4.15; 9.22]	2.8%	Figliuolo et al. (2004)
Argentina	106	1594	6.65	[5.48; 7.99]	2.9%	Moore et al. (2007)
Brazil	43	401	10.72	[7.87; 14.17]	2.8%	Varaschin et al. (2011)
Brazil	72	667	10.79	[8.54; 13.40]	2.8%	Andrade et al. (2013)
Brazil	58	384	15.10	[11.67; 19.08]	2.8%	Uzêda et al. (2007)
Brazil	159	923	17.23	[14.84; 19.82]	2.9%	Costa et al. (2012)
Brazil	161	923	17.44	[15.05; 20.05]	2.9%	Modolo et al. (2008)
Brazil	106	406	26.11	[21.90; 30.67]	2.8%	Braz et al. (2018)
Brazil	85	319	26.65	[21.87; 31.86]	2.7%	Tembue et al. (2011)
Subtotal	**1080**	**12079**	**8.78**	**[5.85; 12.23]**	**44.9%**	
Heterogeneity: $I^2 = 97\%$, $\tau^2 = 0.01$, $p < 0.01$						
Total	**1499**	**22234**	**5.99**	**[4.38; 7.83]**	**100.0%**	
Heterogeneity: $I^2 = 97\%$, $\tau^2 = 0.01$, $p < 0.01$						
Residual heterogeneity: $I^2 = 96\%$, $p < 0.01$						

Fig. 2. Forest plot comparison of *N. caninum* seropositivity in goats from 36 studies. The black dot point is the estimate and the horizontal line is the 95 % CL for seroprevalence plotted for each study. Each column shows the discriminated studies according to the region/country; number of seropositive animals; sample size; seroprevalence %; 95 % CL; study weight in the overall meta-analysis; seroprevalence in forest plot; authors. The black diamond at the bottom of each continent is the estimated average *N. caninum* seroprevalence in goats.

Argentina; with only one indexed study each from Mexico, Costa Rica and Granada. Some American countries such as the USA, Mexico, Peru, Argentina and Bolivia, which have goat populations greater than one million (FAO, 2018) presented indexed studies with limited or absent seroprevalence data.

Europe's seroprevalence was 4.1 %, however, there were few indexed studies from traditional countries in goat farming and with a considerable goat population such as Turkey, Greece and Spain, while indexed studies from France and Russia presented limited or absent seroprevalence data.

In Asia, eight indexed studies with an average seroprevalence of 3.94 % were found. Only two indexed studies were from China, the country with the largest goat population in the world (FAO, 2018). Other countries that also have the large goat population such as Iran had indexed articles containing limited data regarding seroprevalence information and India, Pakistan and Nepal had not presented indexed studies containing seroprevalence data.

Africa has more than 40 % of the world goat population (FAO, 2018), but it was the most deficient continent in indexed studies on neosporosis seroprevalence in goats, with just one indexed article from the Canary Islands. In this meta-analysis, we identified that many countries with a representative goat population did not have indexed studies with data on *N. caninum* seroprevalence in goats within the four main databases or when they had indexed articles, they had limited data on seroprevalence. This absence of information does not mean that these countries are areas free of *N. caninum* seropositivity in goats. Probably, the goat population may be infected and seroprevalence data were not in indexed articles, thus limiting researchers' access to this information. Failure to access data concerning seroprevalence generates the impossibility of estimating seroprevalence and risk factors from these countries in this study. We emphasise the need for more indexed studies concerning neosporosis seroprevalence in goats in these countries, mainly in the African continent and if possible, considering the main risk factors found in this meta-analysis.

There was an increase in neosporosis seroprevalence in goats over the years (Fig. 4); however, without a statistically significant difference (p = 0.2041). Therefore, this variation may be related to an increase in the number of studies carried out in recent years. The highest

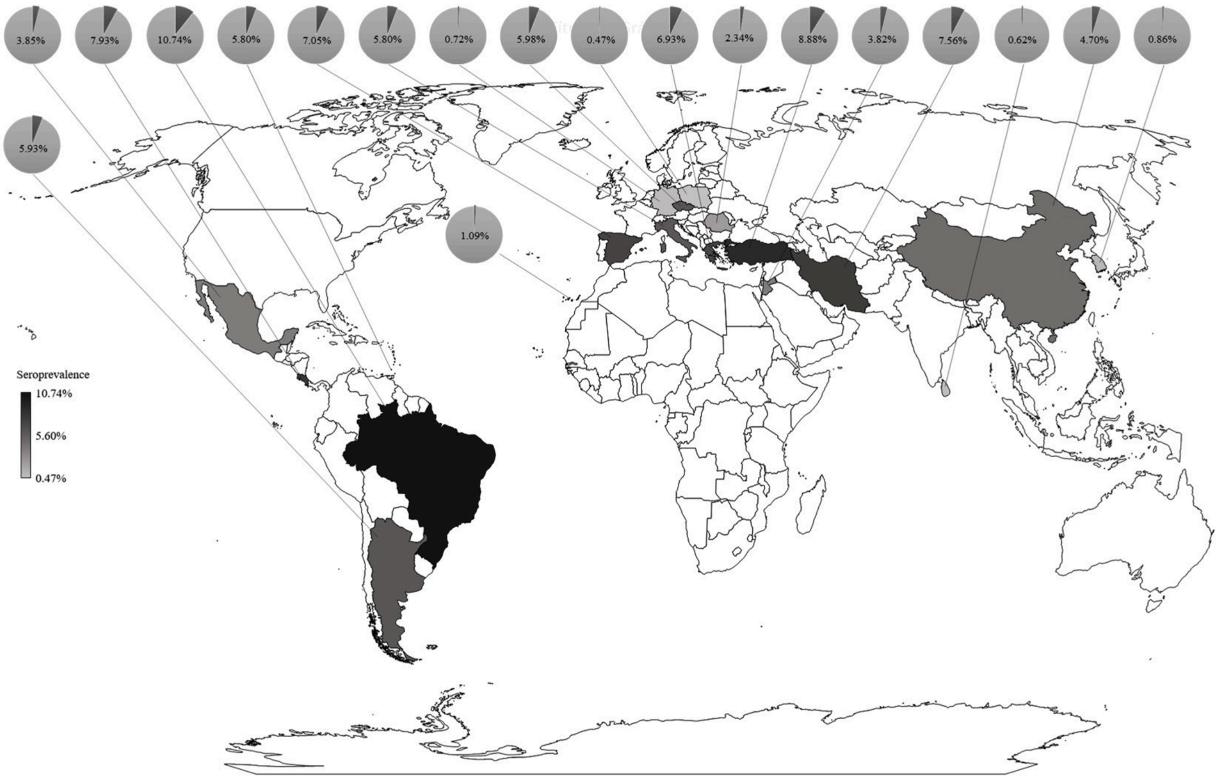


Fig. 3. World map showing the *N. caninum* seroprevalence in goats from the various countries. The pie graphs show the seroprevalence rates for *N. caninum* estimated according to the articles published in the indexing databases from each country.

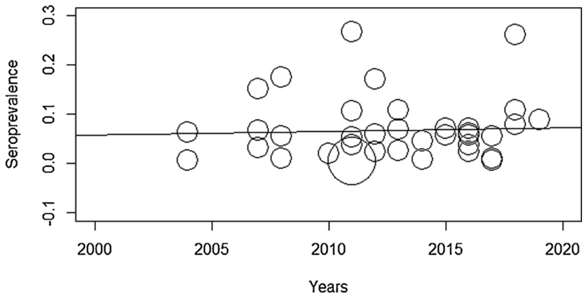


Fig. 4. Meta-regression plot of study publication year against *N. caninum* seroprevalence in goats (percentage of seropositivity on the y-axis) (n = 36 studies, p = 0.2041). The circles represent the individual studies. The continuous line represents the regression line. The year of publication is plotted on the horizontal axis. The prevalence of *N. caninum* in plotted numbers is plotted on the vertical axis.

seroprevalences were found in Central and South American countries compared to countries in other continents (Fig. 2), while a statistically significant effect was observed in relation to latitude (p = 0.032). According to Dubey (2007), high temperatures may favour the survival and sporulation of oocysts in the environment, increasing the risk of eventual infection. These variations in seroprevalence, in different continents and mainly in relation to latitude, may be related to factors such as climatic conditions, differences in the nutritional and health management of animals, in addition to the adoption of biosafety measures or there may still be some differences due to the use of different techniques in serological diagnosis (Dubey et al., 2007).

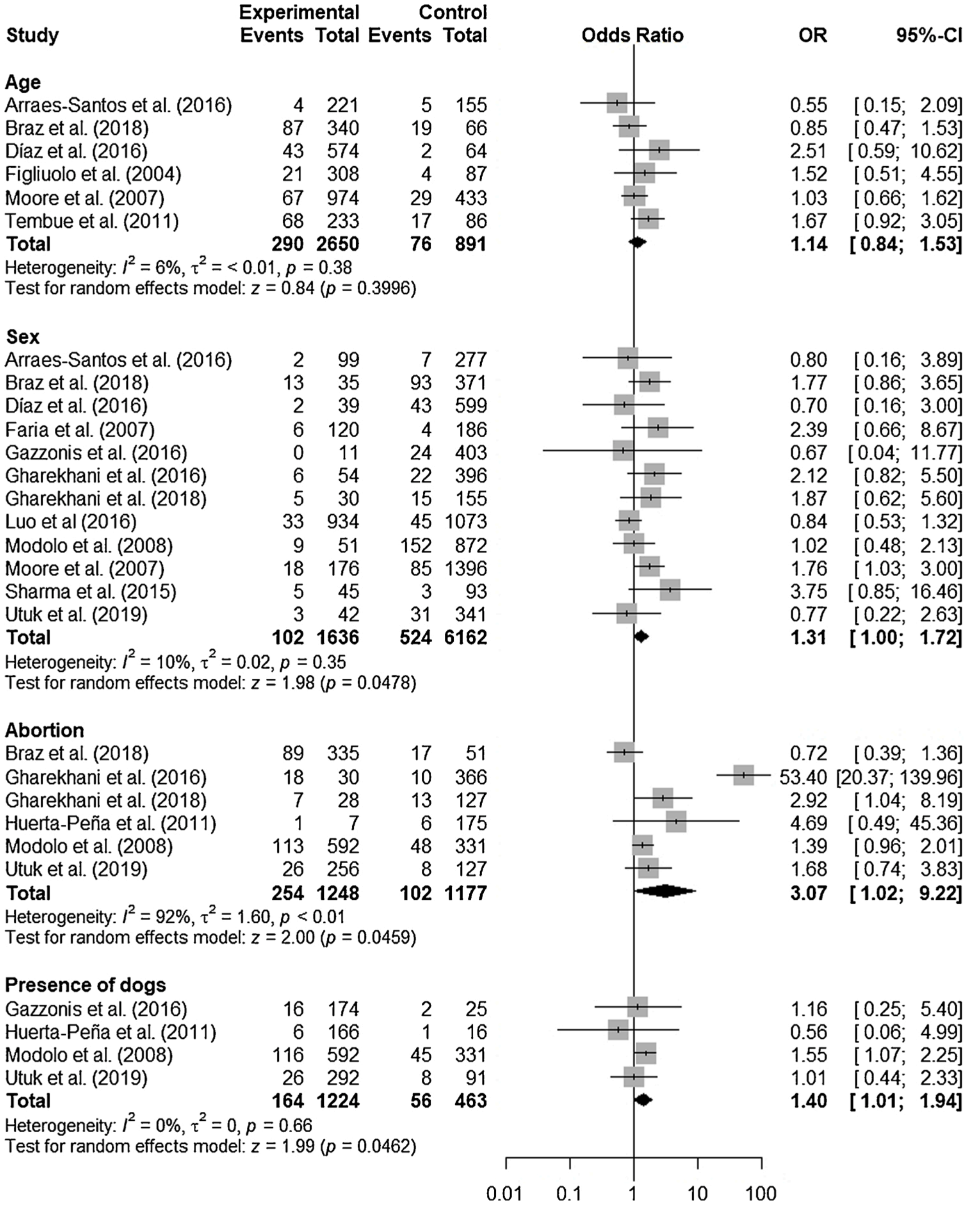
The low neosporosis seroprevalence in goats in European and Asian countries may be related to climatic factors, production systems, the use of local breeds, better hygienic–sanitary conditions and nutritional management practices (Al-Majali et al., 2008; Jung et al., 2014; Díaz et al., 2016; Gazzonis et al., 2016; Luo et al., 2016; Villagra-Blanco et al., 2017).

The great variation in seroprevalence in South America (1.05%–26.65%) has also been reported in other articles (Lima et al., 2008; Tembue et al., 2011). These results may be related to goat production systems, which are extensive production systems with a low technological level. The higher seroprevalence in the Brazilian goat population has been reported mainly in relation to family production systems in which the nutritional and sanitary management is precarious, in addition to concomitant risk factors, such as the presence of dogs. (Uzêda et al., 2007; Modolo et al., 2008; Tembue et al., 2011; Costa et al., 2012; Santos et al., 2013; IBGE, 2017; Braz et al., 2018).

The high heterogeneity of seroprevalence estimated between countries and continents indicates that there is clear evidence that *N. caninum* seroprevalence in goats varies from one population to another and may be related to the particular characteristics of each region, such as climatic characteristics, production systems of each population from where the study originated.

Previous studies have already shown that there is a relationship between abortion and *N. caninum* seropositivity in goats (Mesquita et al., 2013; Unzaga et al., 2014; Porto et al., 2016). In this meta-analysis an association between *N. caninum* seroprevalence in goats wherein seropositive goats had more than three times the risk of abortion compared to seronegative goats (p = 0.0478) was observed (Fig. 5). This result corroborates that found by Gharekhani et al. (2018) and Varaschin et al. (2011), in which seropositive goats had almost four times greater risk of abortion compared to seronegative goats.

The spread of oocysts in the environment by infected dogs is an important risk factor for neosporosis (Dijkstra et al., 2002; Bartova and Sedlak, 2012). In the present study, the presence of dogs was shown to be significantly associated with neosporosis seroprevalence in goats (p = 0.0462). These finding corroborate the results of Abo-Shehada and Abu-Halaweh (2010) and Liu et al. (2015) who reported that the presence of cats and dogs, the access of dogs to the pasture, water and feed



Study	Experimental Events	Experimental Total	Control Events	Control Total	OR	95%-CI
Age						
Arraes-Santos et al. (2016)	4	221	5	155	0.55	[0.15; 2.09]
Braz et al. (2018)	87	340	19	66	0.85	[0.47; 1.53]
Díaz et al. (2016)	43	574	2	64	2.51	[0.59; 10.62]
Figliuolo et al. (2004)	21	308	4	87	1.52	[0.51; 4.55]
Moore et al. (2007)	67	974	29	433	1.03	[0.66; 1.62]
Tembue et al. (2011)	68	233	17	86	1.67	[0.92; 3.05]
Total	**290**	**2650**	**76**	**891**	**1.14**	**[0.84; 1.53]**
Heterogeneity: $I^2 = 6\%$, $\tau^2 = < 0.01$, $p = 0.38$						
Test for random effects model: $z = 0.84$ ($p = 0.3996$)						
Sex						
Arraes-Santos et al. (2016)	2	99	7	277	0.80	[0.16; 3.89]
Braz et al. (2018)	13	35	93	371	1.77	[0.86; 3.65]
Díaz et al. (2016)	2	39	43	599	0.70	[0.16; 3.00]
Faria et al. (2007)	6	120	4	186	2.39	[0.66; 8.67]
Gazzonis et al. (2016)	0	11	24	403	0.67	[0.04; 11.77]
Gharekhani et al. (2016)	6	54	22	396	2.12	[0.82; 5.50]
Gharekhani et al. (2018)	5	30	15	155	1.87	[0.62; 5.60]
Luo et al (2016)	33	934	45	1073	0.84	[0.53; 1.32]
Modolo et al. (2008)	9	51	152	872	1.02	[0.48; 2.13]
Moore et al. (2007)	18	176	85	1396	1.76	[1.03; 3.00]
Sharma et al. (2015)	5	45	3	93	3.75	[0.85; 16.46]
Utuk et al. (2019)	3	42	31	341	0.77	[0.22; 2.63]
Total	**102**	**1636**	**524**	**6162**	**1.31**	**[1.00; 1.72]**
Heterogeneity: $I^2 = 10\%$, $\tau^2 = 0.02$, $p = 0.35$						
Test for random effects model: $z = 1.98$ ($p = 0.0478$)						
Abortion						
Braz et al. (2018)	89	335	17	51	0.72	[0.39; 1.36]
Gharekhani et al. (2016)	18	30	10	366	53.40	[20.37; 139.96]
Gharekhani et al. (2018)	7	28	13	127	2.92	[1.04; 8.19]
Huerta-Peña et al. (2011)	1	7	6	175	4.69	[0.49; 45.36]
Modolo et al. (2008)	113	592	48	331	1.39	[0.96; 2.01]
Utuk et al. (2019)	26	256	8	127	1.68	[0.74; 3.83]
Total	**254**	**1248**	**102**	**1177**	**3.07**	**[1.02; 9.22]**
Heterogeneity: $I^2 = 92\%$, $\tau^2 = 1.60$, $p < 0.01$						
Test for random effects model: $z = 2.00$ ($p = 0.0459$)						
Presence of dogs						
Gazzonis et al. (2016)	16	174	2	25	1.16	[0.25; 5.40]
Huerta-Peña et al. (2011)	6	166	1	16	0.56	[0.06; 4.99]
Modolo et al. (2008)	116	592	45	331	1.55	[1.07; 2.25]
Utuk et al. (2019)	26	292	8	91	1.01	[0.44; 2.33]
Total	**164**	**1224**	**56**	**463**	**1.40**	**[1.01; 1.94]**
Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, $p = 0.66$						
Test for random effects model: $z = 1.99$ ($p = 0.0462$)						

Fig. 5. Forest plot comparison of *N. caninum* seroprevalence in goats from 28 studies. The black dot point is the estimate and the horizontal line is the 95 % CL for seroprevalence plotted from each study. Each column shows the discriminated studies according to the authors/risk factors: age (adult vs young, respectively ≤ 1 year and > 1 year); sex (male vs female); abortion history (yes vs no), presence of dogs (yes vs no); experimental control with number of seropositive animals and total of animals from each risk factor divided into the risk factor parameters; odds ratio; OR – study weight in the overall meta-analysis; 95 % CL. The black diamond at the bottom of each risk factor is the estimated average *N. caninum* seroprevalence.

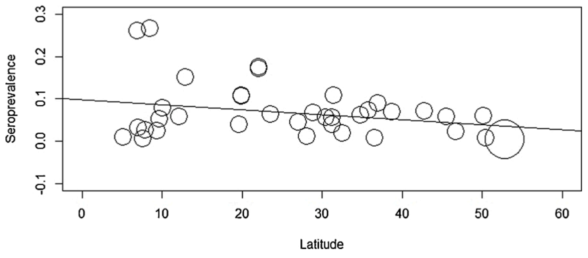


Fig. 6. Meta-regression plot of latitude of the studied region against the *N. caninum* seroprevalence in goats (percentage of seropositivity on the y-axis) (n = 36 studies, p = 0.0032). The circles represent the individual studies. The continuous line represents the regression line. The latitude is plotted on the horizontal axis. The prevalence of *N. caninum* in plotted numbers is plotted on the vertical axis.

sources of ruminants, and the hygiene on farms increased the seroprevalence in the herd. Consequently, it is of vital importance to control the dog population as a tool to reduce the spread of the parasite in the environment and hence, reduce seroprevalence (Dubey et al., 2007).

Sex, when analysed as a risk factor (OR 1.31; 95 % CI 1–1.72; p = 0.0478), indicates that males had greater neosporosis seropositivity than females; this difference was also reported by Moore et al. (2007) and Sun et al. (2020). No publication bias effect was evaluated in the studies that used sex as a risk factor for *N. caninum* seroprevalence in goats (Fig. 7), and the explanations for the greater *N. caninum* seropositivity for males were not elucidated in the literature. Several studies did not report a significant association between seroprevalence and sex (Arraes-Santos et al., 2016; Díaz et al., 2016; Gazzonis et al., 2016; Luo et al., 2016; Gharekhani et al., 2018) or when showing a statistical significance, the studies did not describe the possible related causes (Faria et al., 2007). Additional studies are needed to clarify the real mechanisms and factors involved in the relationship between seropositivity and sex.

In this meta-analysis, there was no significant association between age and neosporosis seroprevalence in goats (p = 0.3996) (Fig. 5). This is supported by previous studies demonstrating that there were no statistical differences in relation to seroprevalence between different ages (Moore et al., 2007; Iovu et al., 2012; Gazzonis et al., 2016; Braz et al., 2018). Although age was not found to have a statistically significant

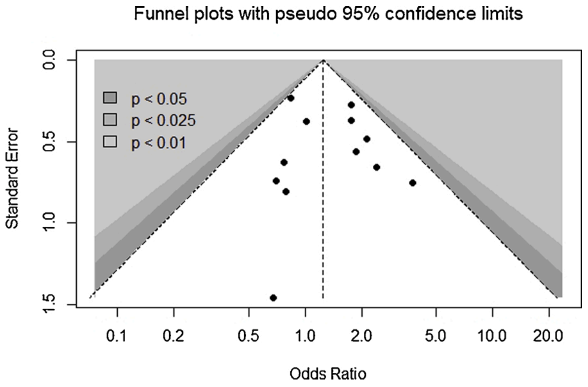


Fig. 7. Funnel plot measuring the odds ratio of *N. caninum* seroprevalence in goats with 95 % CL using the Freeman–Tukey double arcsine method to stabilise the variance differences on the x-axis, standard error on the y-axis from the 12 studies that classified the sex as a risk factor for *N. caninum* seroprevalence in goats. Individual studies are represented by black dots. The dashed external lines indicate the triangular region where 95 % CL of the studies are expected, and the central vertical line is the axis of the general effect.

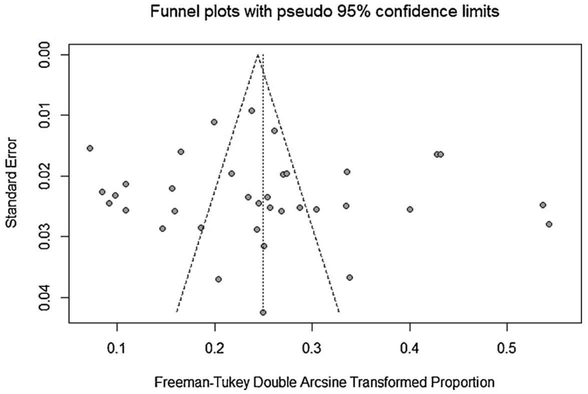


Fig. 8. Funnel plot measuring the odds ratio of *N. caninum* seroprevalence in goats with 95 % CL which was transformed using the Freeman–Tukey double arcsine method to stabilise the variance differences on the x-axis, standard error on the y-axis of the animals (in relation to the total sample) from 36 studies of *N. caninum* seroprevalence in goats. Individual studies are represented by black dots. The dashed external lines indicate the triangular region where 95 % CL of the studies are expected, and the central vertical line is the axis of the general effect. All values were $p > 0.05$ (Egger's test), indicating that there is no evidence of significant publication bias.

effect on seroprevalence, these studies suggest that the infection route is different between young and adult animals. In adult animals, the literature reports that horizontal transmission is probably the most common route of infection as the environments can be contaminated with sporulated oocysts, and the adult animals are exposed to contaminated feed or water for longer periods (Tembue et al., 2011; Sun et al., 2020). The vertical route is the main route of transmission in young animals, which is speculated as being due to the shorter time of exposure to environments with sporulated oocysts, but the possibility of horizontal transmission due to the immunity of young animals should not yet be fully effective. Therefore, age should be considered a risk factor.

There was no effect of publication bias in the data analysed and extracted from indexed articles, as shown in the funnel graphs of overall seroprevalence and seroprevalence in South America (Figs. 8 and 9). However, additional research has not been carried out into other national and regional databases from countries without studies indexed in the main databases, and this may be a limitation of the present study.

Among the variables evaluated, there is a need for further studies concerning seroprevalence and risk factors for *N. caninum* in goats,

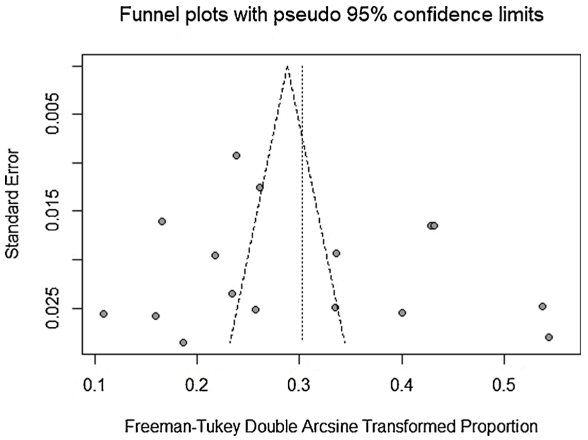


Fig. 9. Funnel plot measuring the odds ratio of *N. caninum* seroprevalence in goats with 95 % CL which was transformed using the Freeman–Tukey double arcsine method to stabilise the variance differences on the x-axis, standard error on the y-axis from 16 studies of *N. caninum* seroprevalence in goats in South America. Individual studies are represented by black dots. The dashed external lines indicate the triangular region where 95 % CL of the studies are expected, and the central vertical line is the axis of the general effect. All values were $p > 0.05$ (Egger's test), indicating that there is no evidence of significant publication bias.

exercising caution when assessing latitude, as some studies attribute a reduction in seroprevalence to climatic conditions (Díaz et al., 2016; Luo et al., 2016; Villagra-Blanco et al., 2017). Possibly, there is a combined effect of risk factors such as the presence of dogs, sex of animals evaluated, management practices and abortions, as well as particular climatic issues in higher latitudes.

In addition to the risk factors discussed in this meta-analysis, the high level of heterogeneity among all prevalence studies may be related to variables that have been associated with increased *N. caninum* seroprevalence in goats, such as the types of productive systems, grazing together with other ruminant species and the presence of wild animals, such as birds, rodents, canines and felines (Huang et al., 2004; Al-Majali et al., 2008; Santos et al., 2013; Gazzonis et al., 2016; Barros et al., 2018).

The extensive search for studies carried out in four databases of worldwide importance in order not to omit important studies on the topic, including only studies that describe the calculation of sample size in their methodology, in addition to investigating possible causes of heterogeneity through meta-regression and subgroup analysis (Crowther et al., 2010), allowing a better understanding of the variations between studies, were strengths of the present study. According to Crowther et al. (2010), comprehensive research generally improves the quality of a review and the inclusion of articles with similar study designs can reduce research bias. As a weakness, we can mention the lack of information on seroprevalence in countries with a large population of goats. We emphasise that searches were not carried out in regional databases of countries with no prevalence or in the grey literature.

5. Conclusion

N. caninum seroprevalence in goats is widely distributed throughout the world, in which the American continent presents a higher proportion of seropositive goats. Seropositive goats showed an association with abortion, presence of dogs and sex. Studies concerning seroprevalence and risk factors for caprine neosporosis were reported in a few articles, also missing articles from countries of the world's largest caprine population, both into the main database researched. The largest number of indexed studies were reported from South America, specifically Brazil, which allowed the estimated seroprevalence in that country to be more accurate.

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Declaration of Competing Interest

None.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.prevetmed.2020.105176.

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