

Global prevalence and zoonotic potential of cryptosporidiosis in camels (*Camelus dromedarius*): systematic meta-analysis

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Abstract

In this study, a meta-analysis on the prevalence and zoonotic significance of cryptosporidium infection in camels was performed. This study was completed following the instructions of PRISMA. Data were extracted afterward a complete search, and eligible articles were identified. The data were analyzed using a specific software program for meta-analysis, and the results included effect size, confidence intervals (CI), heterogeneity, and publication bias. A total of 4075 camels from 18 accepted studies were investigated for cryptosporidium infection. Of all, 287 camels were found positive for cryptosporidium infection, with a prevalence of 7.04%. The prevalence of cryptosporidiosis in camels varied significantly among countries ($P < 0.001$). Where the highest prevalence was recorded in Saudi Arabia (17.73), but the lowest prevalence was recorded in Algeria (3.17%). Zoonotic cryptosporidium spp. was recorded in five studies. Where *C. parvum* was isolated from both camels and contact humans in Algeria, China and Iran. At fixed and random effects, the Z-value was -34.44 (P -value = 0.00) and -9.60 (P -value = 0.000), correspondingly. The Q-value (241.64), I-squared (92.96), and P -value (0.000) are the outcome of heterogeneity. Also, the Tau-squared value was 1.02 with a SE of 0.49. The classic fail-safe N proposed that 5059 missing studies were required to conclude that the result of the study is significant ($P = 0.000$). The results of the present meta-analysis indicate the establishment of cryptosporidium infection in camels with zoonotic potential. Therefore, more attention should be paid to the prevention and control of this disease.

Keywords: camelidae, cryptosporidium, incidence, one health, review

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Introduction

Camels are members of the family *Camilidae* which includes the old-world camels, the new-world camels, and the Vicugna (Wilson and Reeder, 2005). There are two domesticated species within the Old-World camels: the single-humped dromedary, which is the most common, making up 95% and found in 47 countries and the double-humped Bactrian camels which are less common, living in the colder deserts of southern Russia and Asia (Sadek *et al.*, 2021). Camels' numbers have doubled in the last two decades, reaching about 39 million camels in 2021, most live in Africa, with fewer in Asia (George, 2024).

Several pathogens can infect camels, despite the previous belief regarding their resistance to infectious diseases (Balamurugan *et al.*, 2013; Ghanem *et al.*, 2009; Sadek *et al.*, 2021). Cryptosporidiosis, a common enteric disease of zoonotic importance, is caused by *Cryptosporidium* protozoa which are obligate unicellular parasites with diverse vertebrate hosts (Feng *et al.*, 2018; Pumipuntu and Piratae, 2018; Xiao and Feng, 2017). Around forty species and more than seventy *Cryptosporidium* genotypes have been recently identified in both humans and animals (Holubová *et al.*, 2020; Liang *et al.*, 2019). Infection is transmitted through direct contact with infected people and animals or through contaminated water or food by the fecal-oral route (Fayer *et al.*, 2000). Excystation of *Cryptosporidium* oocysts occurs after the host ingests the infective oocysts. Sporozoites are released and replicate in intestinal cells. After asexual and sexual reproduction, the sporulated oocysts are excreted in feces (Bouazid *et al.*, 2013). These oocysts resist environmental factors as they can survive for several months in an aquatic environment [10]. Due to the thick wall of sporulated oocysts, only a few chemical disinfectants are effective against them (Dillingham *et al.*, 2002). They can resist chlorine and monochloramin at levels frequently used to disinfect drinking water (Finch *et al.*, 1993). Four species of *Cryptosporidium* including *C. parvum*, *C. muris* and *C. andersoni*, have been identified in camels of which, *C. parvum* manifests in young camels with severe diarrhea, emaciation, varying degrees of dehydration and death may occur (Wernery and Kaaden, 2002).

Cryptosporidiosis symptoms often mimic many other enteric diseases; therefore, lab tests are required for accurate diagnosis. These tests involve microscopic examination of fecal smear to detect *Cryptosporidium* oocysts after staining with special stains like Modified Ziehl-Neelsen stain, fluorescent stain, or immunofluorescent stain (Garcia, 2021; Jex *et al.*, 2008). Several methods can be used for the qualitative detection of *Cryptosporidium* antigens in feces like enzyme-linked immunosorbent assay, a sensitive method (Radfar *et al.*, 2013), and lateral flow immunochromatographic assay, a rapid but less accurate method (Fleece *et al.*, 2016). For enhanced sensitivity, polymerase chain reaction (PCR) techniques can be used for the detection of *Cryptosporidium* DNA (Bouazid *et al.*, 2008).

Several epidemiological studies have investigated the prevalence of *Cryptosporidium* in camels in different countries. In Iran, using

microscopic examination, the prevalence of *Cryptosporidium* in one-humped camels ranged from 2%, 10%, and 16.9 % to 20.33% (Borji *et al.*, 2009; Nazifi *et al.*, 2010; Sazmand *et al.*, 2012b; Yakhchali and Moradi, 2012a). In Egypt, the prevalence of *Cryptosporidium* in one-humped camels was (3.37%) using microscopic examination (Saleh and Mahran, 2007). In Algeria, the prevalence of *Cryptosporidium* in one-humped camels was (7%) using PCR (Maxamhud *et al.*, 2023). Meanwhile in China, the prevalence of *Cryptosporidium* in Bactrian camels was 7.6% using nested-PCR (Cao *et al.*, 2020).

A meta-analysis is an epidemiological study designed to systematically assess the results of previous investigations to reach a conclusion about this research topic (Haidich, 2010). It includes a combined and quantitative review of a large, frequently complex, and occasionally apparently conflicting body of literature (Moher *et al.*, 2010). Additionally, the results of the meta-analysis may provide a more accurate estimation of the effect of risk factors or treatment for specific diseases or other outcomes than any individual study participating in the pooled analysis (Moher *et al.*, 2009). Therefore, the objective of the present study was to conduct a systematic meta-analysis on the global prevalence and zoonotic significance of cryptosporidiosis in old-world camels.

Materials and Methods

Ethical approval: According to the guidelines of Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA), this study was conducted. Consequently, it is not necessary to have approval from the ethical committee for animal use in scientific research.

Selected studies and reference camels: The present meta-analysis included all published studies describing the prevalence of cryptosporidiosis in camels using different techniques. All camels examined have no characteristic clinical signs.

Selection criteria:

Inclusion

- Only acceptable papers are in English.
- All publications on cryptosporidiosis in old-world camels.
- A reputable journal publication
- Case-control and cross-sectional studies
- Studies on the prevalence of cryptosporidiosis in old-world camels were involved.
- Studies implying the prevalence using any diagnostic technique.

Exclusion

- Techniques for identifying cryptosporidiosis in camels other than prevalence.
- Arabic-language publications or languages other than English.
- Preprint and review articles.

Study selection: The objective of this study was to search all publications that had been written about the prevalence of cryptosporidiosis in camels. We searched PubMed, Web of Science, Sage, BESCO, Ovid, CABI, Scopus, databases. The combination of the following search terms was used: ("CAMELS" "CRYPTOSPORIDIOSIS") (title and abstract) ("CRYPTOSPORIDIOSIS ") (title/abstract) AND ("CAMELS") (title / abstract) AND ("PREVALANCE"

"INCIDENCE") (title/ abstract). Preliminary screening of the articles was based on the title and abstract from the earliest data available by May 2024. This procedure was supplemented by manual searching, Google Scholar searching, expert recommendations, and citation reviews. Database outputs were integrated using EndNote software. The standard identification, selection, and eligibility criteria of the selected studies are shown in Figure 1.

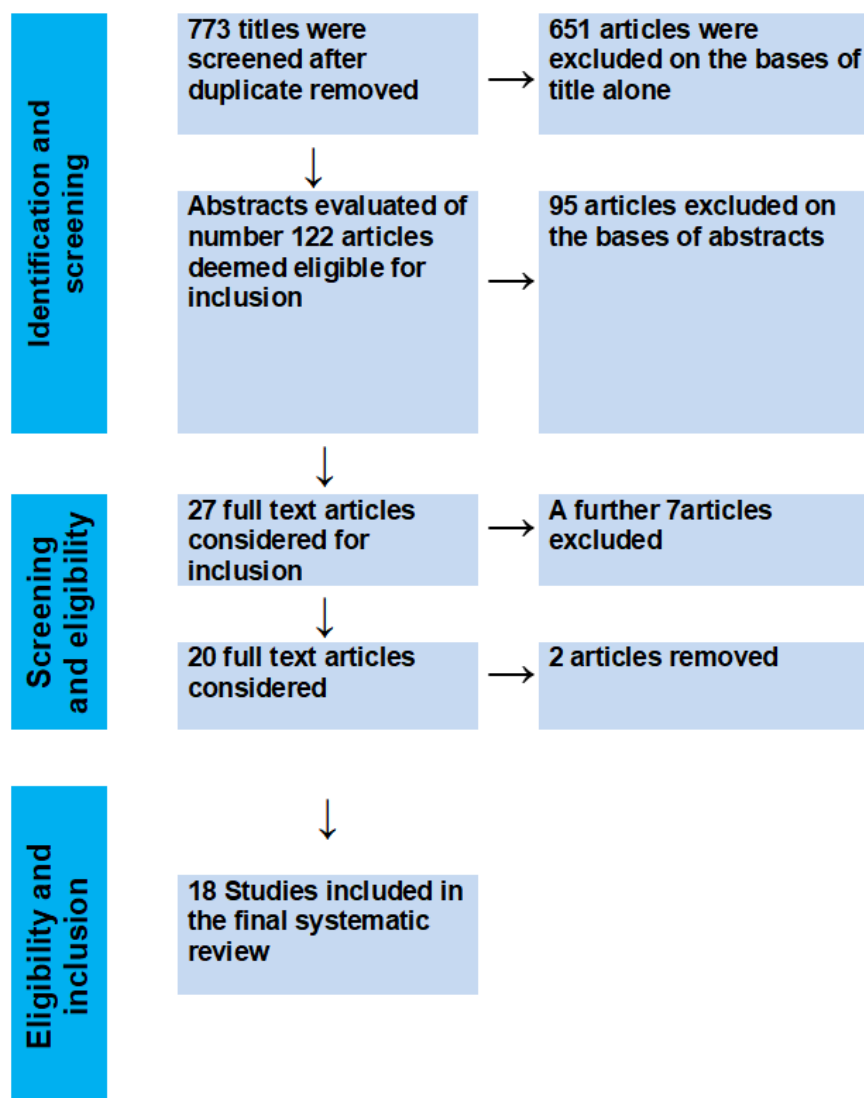


Figure 1 Histopathological examination of kidney tissue of Nile tilapia fish. (a) control kidney showed distinct and normal sized

Data extraction and analysis: The data extracted included the year of publication, study area, diagnostic method, sample size, cryptosporidium spp., and positive cases with summary statistics (Table 1).

Data analyses: First, the prevalence of cryptosporidiosis was calculated for the total examined camels in accepted studies. The Chi-square test was used to assess significant variation among countries (GraphPad Prism for Windows version 9, USA). Commercial Meta-Analysis software was used (Comprehensive Meta-Analysis software version 2, Biostat, Englewood, NJ, USA). In both random and

fixed effects models, effect size, 95% confidence intervals, variance, heterogeneity, relative weight, and publication bias were the main tests. Effect size was expressed by both *P*-value and standardized *Z*-statistic. Cochran's *Q* test was conducted to assess the heterogeneity and the *I*² statistic was used to reveal the proportion of heterogeneity (Duffield *et al.*, 2008). To assess the degree of publication bias, a funnel plot was generated (Higgins *et al.*, 2011). Egger's linear regression intercept (Egger *et al.*, 1997) and Begg-Mazumdar rank correlation tests were also applied (Begg and Mazumdar, 1994).

Table 1 Descriptive data regarding cryptosporidiosis in camels.

	Author	Samples	Positive	%	Technique	Country	Cryptosporidium species	Zoonotic implication
1	(Saleh and Mahran, 2007)	1097	37	3.37	Modified Ziehl-Neelsen	Egypt	<i>C. muris</i>	
2	(Borji et al., 2009)	306	6	1.9	Modified Ziehl-Neelsen	Mashhad, Iran	Cryptosporidium spp	
3	(Razawi et al., 2009)	103	39	37.9	Modified Ziehl-Neelsen	Isfahan Province, center of Iran	Cryptosporidium spp	
4	(Nazifi et al., 2010)	65	11	16.9	Modified Ziehl-Neelsen	Qeshm Island, southern Iran	<i>Cryptosporidium parvum</i>	Zoonotic
5	(Yakhchali and Moradi, 2012b)	170	17	10	Modified Ziehl-Neelsen	Iran	Cryptosporidium spp.	
6	(Sazmand et al., 2012a)	300	61	20.3	Modified Ziehl-Neelsen	Iran	Cryptosporidium spp.	
7	(Radfar et al., 2013)	85	2	2.4	Modified Ziehl-Neelsen	Kerman province of Iran	Cryptosporidium spp.	
8	(AL-Megrin, 2015)	49	9	18.4	Modified Ziehl-Neelsen	Riyadh region, Central of Saudi Arabia	Cryptosporidium spp.	
9	(Baroudi et al., 2018)	39	2	5.12	PCR	Algeria	<i>C. parvum</i>	Zoonotic
10	(Laatamna et al., 2018)	149	8	8.9	Modified Ziehl-Neelsen	Algeria	Cryptosporidium spp.	
11	(El-Alfy et al., 2019)	101	6	5.94	PCR	Egypt	Cryptosporidium spp.	
12	(Bouragba et al., 2020)	717	13	1.81	Modified Ziehl-Neelsen	Algeria	Cryptosporidium spp.	
13	(Cao et al., 2020)	476	36	7.6	PCR	Northwestern China	<i>C. andersoni</i> (n = 24) <i>C. parvum</i> (n = 6) <i>C. occultus</i> (n = 2) <i>C. ubiquitum</i> (n = 2) <i>C. hominis</i> (n = 1) <i>14C. bovis</i> (n = 1)	Zoonotic
14	(El Hassan et al., 2020)	92	16	17.39	Ag-ELISA	Eastern Province of Saudi Arabia	Cryptosporidium spp.	
15	(Maxamhud et al., 2023)	63	5	7.93	PCR and qPCR	Algeria	<i>C. parvum</i> (3) <i>C. bovis</i> (2)	Zoonotic
16	(Elmahallawy et al., 2023)	102	3	2.9	PCR	Egypt	<i>C. parvum</i> <i>C. bovis</i>	
17	(Ouchene and Khelifi-Touhami, 2023)	40	4	10	PCR	Oued Souf in southern Algeria	Cryptosporidium spp.	
18	(Salama et al., 2023)	121	12	10.14	PCR	Egypt	<i>C. parvum</i>	Zoonotic

Results

A total of 773 articles were detected from database search. Finally, 18 acceptable studies were incorporated in the present meta-analysis (**Table 1, Figure 1**). A total of 4075 camels from 18 accepted studies were investigated for cryptosporidium infection. Of all, 287 camels were found positive for cryptosporidium infection, with a prevalence of 7.04%. The prevalence of cryptosporidiosis in camels varied significantly among countries ($P < 0.001$). Where the highest prevalence was recorded in Saudi Arabia (17.73), but the lowest prevalence was recorded in Algeria (3.17%). Zoonotic cryptosporidium spp. was recorded in five studies. Where *C. parvum* was isolated from both camels and contact humans in Algeria, China and Iran (Table 1).

Regarding the diagnostic techniques, Modified Ziehl-Neelsen was used in 10 studies with a prevalence

of 6.67 % (203/3041). However, PCR was used in seven studies with a prevalence of 7.21% (68/942). ELISA was used only in one study with an infection rate of 17.39% (16/92). There was a significant variation between the results of ELISA and both PCR and Modified Ziehl-Neelsen ($P < 0.01$). However, the results of PCR and Modified Ziehl-Neelsen did not vary significantly.

Meta-analysis: The effect size of the prevalence of cryptosporidium infection at the random and fixed effects are presented in **Table 2**. The Z-value was -34.44 ($P = 0.00$) and -9.60 ($P = 0.000$) at fixed and random effects, respectively. To illustrate the degree of heterogeneity, a forest plot was constructed. The result of event rate, logit event rate, and relative weight on both fixed and random effects are shown in Figures 2-4. The I-squared (92.96), Q-value (241.64), and P-value (0.000) are the results of heterogeneity. Also, the Tau-

squared value was 1.02 with a SE of 0.49 (**Table 3**). Variables of publication bias were presented in Figures 5 and 6.

Egger's linear regression test did not imply a publication bias, and its outcomes were intercepted (-2.32), 95% CI (-6.65 to 2.0), t-value (1.13) and P-value (0.1).

The classic fail-safe N proposed suggests that 5059 missing studies were required to conclude that the result of the study is significant ($P = 0.000$). In addition, in observed studies, Orwin's fail-safe N proposes a -2.2-event rate, but in missing studies, it proposes a 0.00 mean event rate.

Table 2 Results of meta-analysis regarding the effect size for 18 studies on the prevalence of cryptosporidiosis in camels.

Model	Effect size and 95% Confidence Interval (CI)				Test of null (2-Tail)	
	Number of studies	Point estimate	Lower limit	Upper limit	Z-value	P-value
Fixed	18	-2.20	- 2.32	-2.07	-34.44	0.00
Random	18	-2.45	-2.96	-1.95	-9.60	0.00

Table 3 Results of heterogeneity for 18 studies on the prevalence of cryptosporidiosis in camels.

Model	Heterogeneity					Tau-squared	
	Number of studies	Q-value	df (Q)	P-value	I ²	Tau ²	SE
Fixed	18	241.642	17	0.000	92.96	1.03	0.49
Random	18	-	-	-	-	-	-

DF: degree of freedom

I²: I-squared

Tau²: Tau-squared

SE: Standard Error

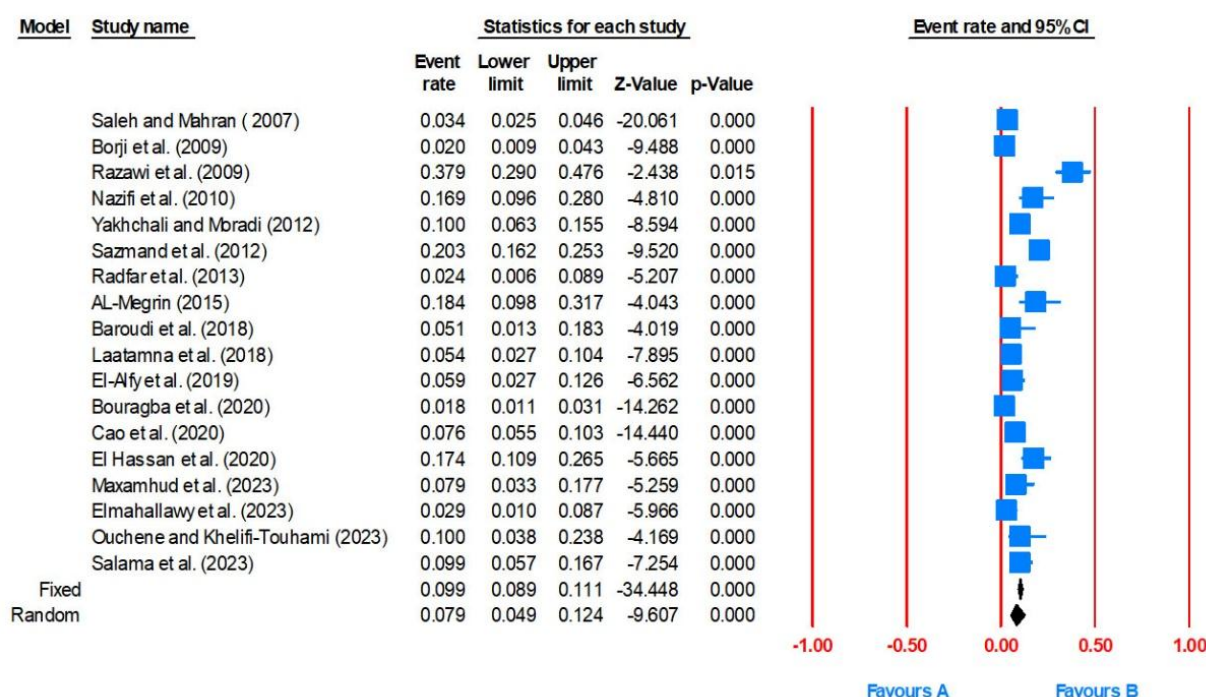


Figure 2 Forest Plot on the prevalence of cryptosporidiosis in camels shows the event rate, 95% confidence interval, Z- value, P- value, and relative weight on both fixed and random models of 20 observed studies.

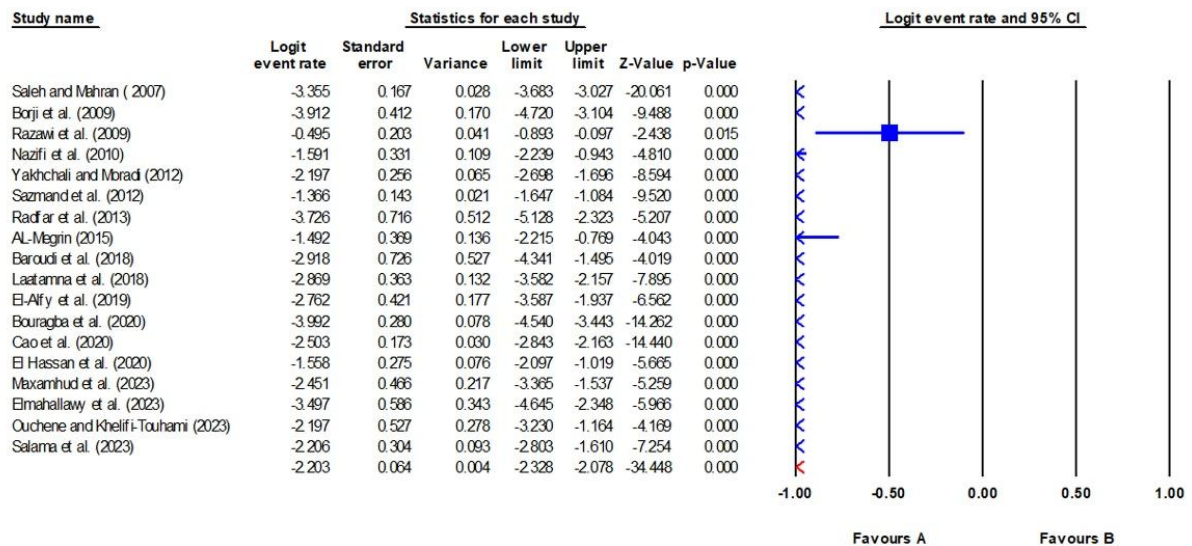


Figure 3 Forest Plot of the prevalence of cryptosporidiosis in camels shows the logit event rate, 95% C, standard error, and variance on both fixed and random models of 20 observed studies.

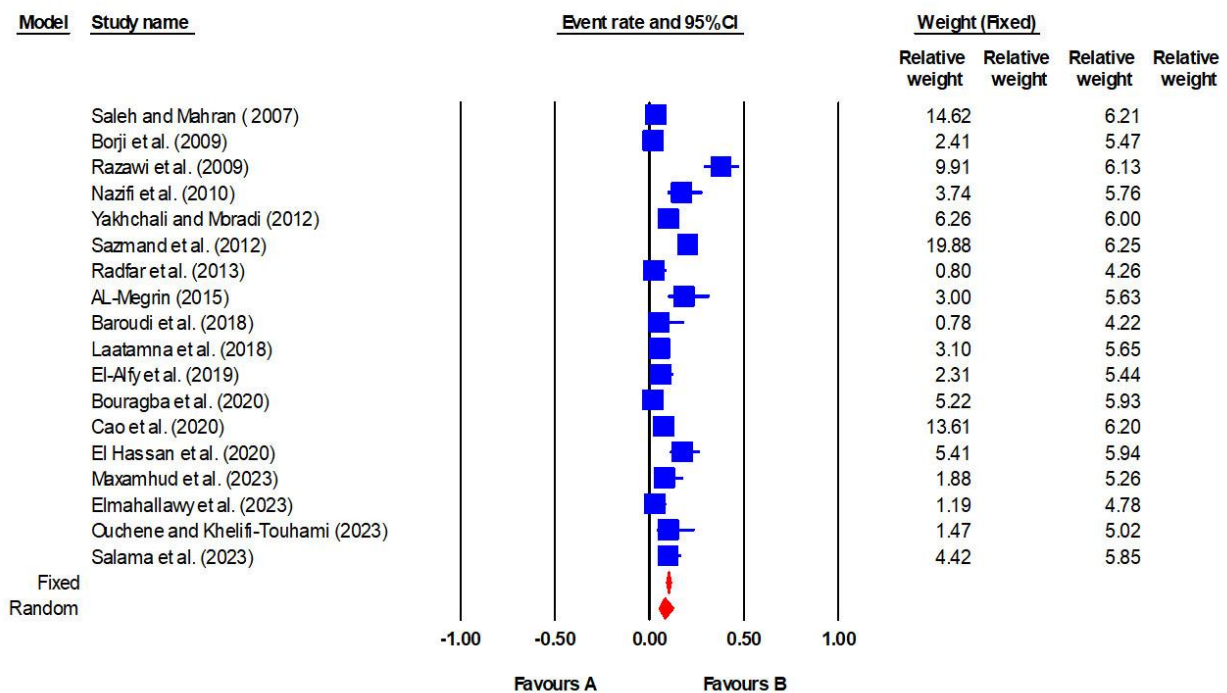


Figure 4 Forest Plot of the prevalence of cryptosporidiosis in camels shows the weight on both fixed and random models of 20 observed studies.

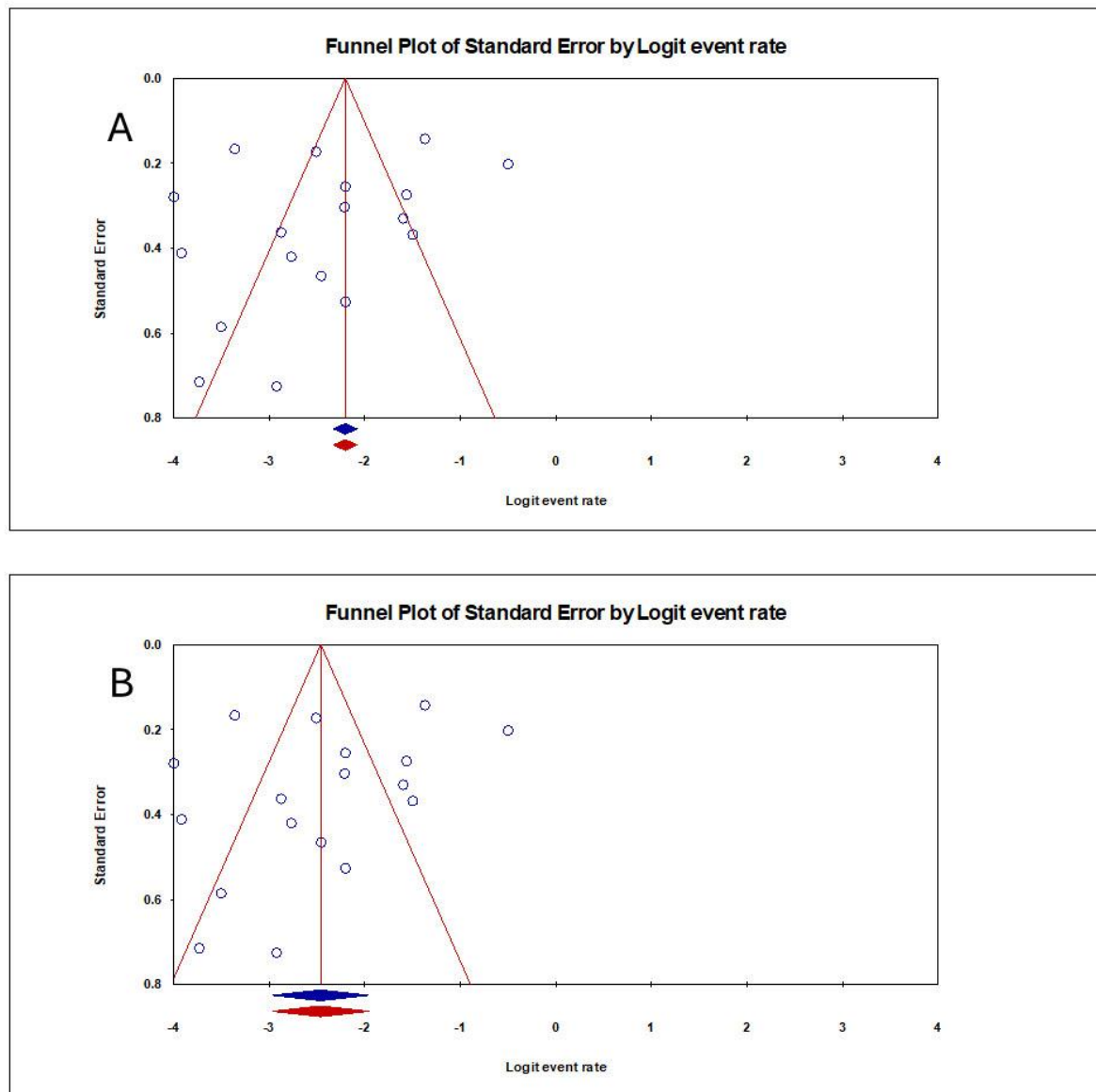


Figure 5 Funnel plot of the prevalence of cryptosporidiosis in camels shows standard error by logit event rate on fixed (A) and random (B) models of 20 observed and imputed studies.

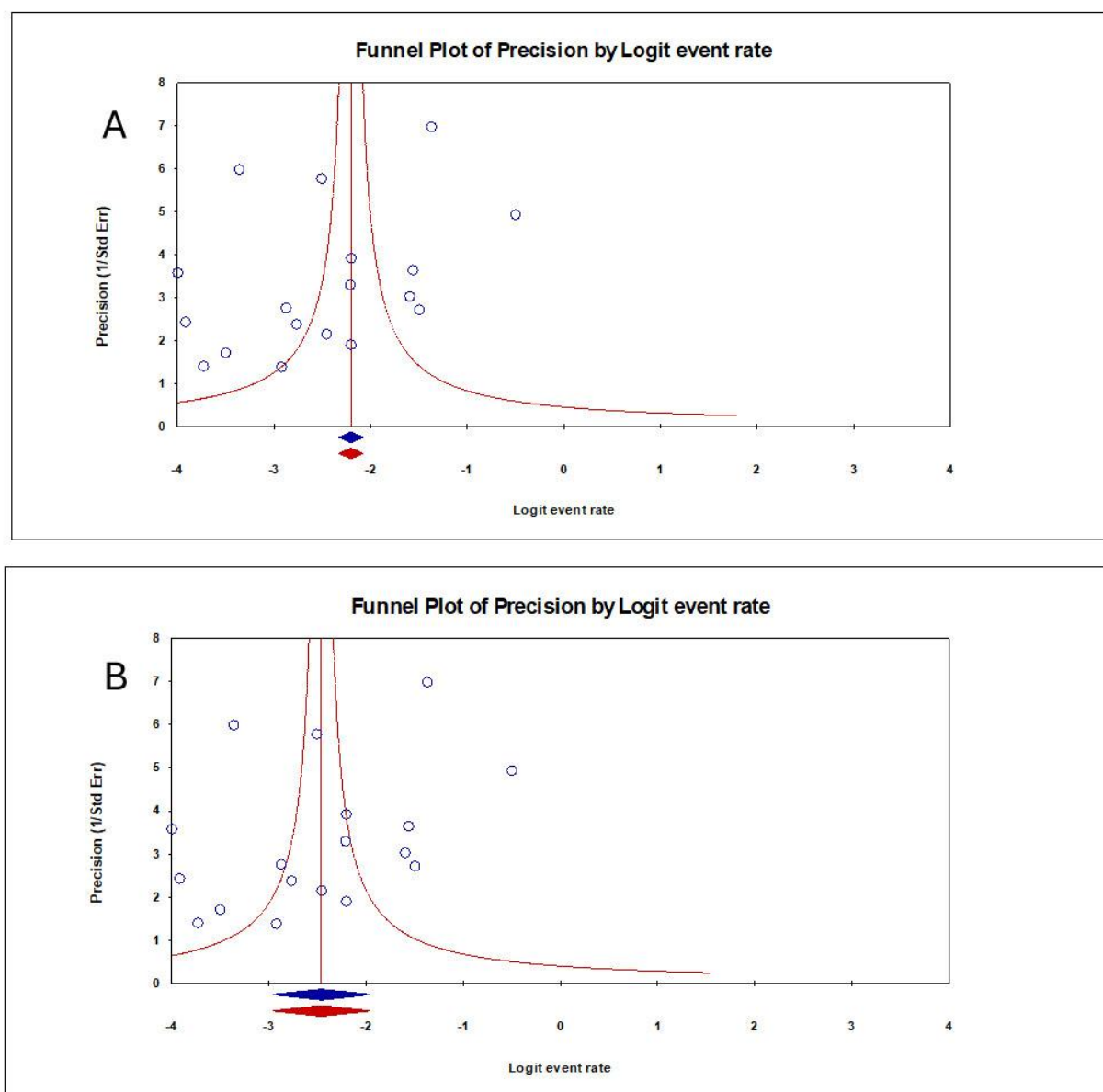


Figure 6 Funnel plot of the prevalence of cryptosporidiosis in camels shows precision by logit event rate on fixed (A) and random (B) model of 20 observed and imputed studies.

Discussion

The objective of the meta-analysis was to get a conclusion on the global prevalence and zoonotic significance of cryptosporidiosis in camels (*Camelus dromedarius*). In this study, a prevalence of 7.04% was recorded for cryptosporidium infection with variations in infection rates in different countries. This variation may be attributed to climatic conditions, management, and other contributing factors. The effects of season on the prevalence of cryptosporidiosis have been controversial. In calves and cattle, the prevalence was higher in winter (Mohammed *et al.*, 1999). However, other studies found no effect of season on the prevalence of the infection (Becher *et al.*, 2004). It was stated that there is no age correlation for cryptosporidiosis in camels (Sazmand *et al.*, 2012a). Additionally, in wild animal, the infection rate has not been found to depend on the age of animals (Torres *et al.*, 2000). In other animal species, age, climate and

management were found to affect prevalence of cryptosporidiosis (El-Khodery and Osman, 2008).

In the present results, the prevalence of the disease is nearly the same when either PCR or modified Zhiel-Neelsen was used. But, the prevalence was significantly higher when ELISA was used. Regarding the diagnostic techniques, although modified zhiel-Neelsen techniques are an old traditional, it has been found to provide the same specificity and slightly lower sensitivity for the identification of cryptosporidium oocysts (Tahvildar-Biderouni and Salehi, 2014). Therefore, the diagnostic technique has a low effect on the prevalence and consequently the results of the meta-analysis. On the other hand, it has been found that different types of ELISA have less sensitivity and specificity PCR for diagnosis of cryptosporidium in animals (Danišová *et al.*, 2018). In the present meta-analysis, only one study in which ELISA was used to diagnose cryptosporidiosis in camels. This single study may have a negligible effect on the accurate evaluation of the infection rate.

C. parvum, *C. muris*, and *C. andersoni* are the species that infect camelids (Fayer et al., 1991; Wang et al., 2008). Clinically, cryptosporidiosis may show acute or chronic signs. Chronic cryptosporidiosis has been identified in Bactrian camels with signs of chronic diarrhea and weight loss (Fayer et al., 1991). *C. parvum* is considered as major public health risk (Zhu et al., 2019). In the present meta-analysis, five studies recorded zoonotic cryptosporidium spp. in both camels and human (Baroudi et al., 2018; Cao et al., 2020; Nazifi et al., 2010; Maxamhud et al., 2023). However, we cannot rule out the presence of zoonotic *Cryptosporidium* spp. in other studies, as the diagnostic techniques used were not sufficient to detect the subtype of the parasite. This explanation is supported by the molecular detection of zoonotic *C. parvum* (subtype IIaA17G2R1) in newborn camel calves in Australia (Zahedi et al., 2018).

Based on the findings of the meta-analysis, the results of the large study (Sazmand et al., 2012a) provided high relative weight (19.88 %), whereas small studies (Ouchene and Khelifi-Touhami, 2023), and (Elmahallawy et al., 2023) provided approximately 1.47 % and 1.19%, respectively. It is known that the common effect can be assessed by large studies but not by small studies. Studies with small sample sizes had a negligible effect on the total value. The present meta-analysis provided a Z-value of -34.44 ($P = 0.00$), and -9.60 ($P = 0.000$). The Z-value here does not add to the results, as it is not the effect size but only indicates the data distribution (Hak et al., 2016).

Regarding heterogeneity, Q-statistic and I^2 for this study were 241.64 and 99.96, respectively (P -value < 0.00). The Q-statistic includes the observed dispersion, while the null hypothesis for heterogeneity proposes that the studies assign a common effect size. Consequently, it is assumed that the degrees of freedom are equal to the Q-statistic (Thompson, 1994). However, if Q-statistic provides no effect size dispersion, I^2 and tau-squared can provide alternative good interpretation (Schulz et al., 1995).

The I^2 concludes that the definite differences in effect sizes for 99 % of the variance among the studies and only 1 % of the observed variation can be predicted by means of random error. The tau-squared value for camel cryptosporidiosis was 92.96, which is the variance among studies and is utilized to calculate weights. It has been stated that the I^2 can be used successfully to measure the level of heterogeneity in meta-analysis (Huedo-Medina et al., 2006).

Heterogeneity analysis usually proves how the effect width varies among studies. This statistical test explains the difference among studies due to differences between the studies or to sampling errors (Borenstein et al., 2021; Hedges and Olkin, 1985). Considering heterogeneity, the null hypothesis is that the effect will be zero for both fixed and random effects. Hedges' g/standard error for the relevant model is usually used to determine the z-value, which is used to check the null hypothesis (Higgins JP, 2019). It has also been stated that the p-value is not an effect size, and therefore, is not a measure of the magnitude of heterogeneity. In this case, a low p-value indicates that there is probably some (unidentified) degree of heterogeneity (Duffield et al., 2008).

Regarding publication bias, studies with small sample sizes, inadequate power, no obvious difference between groups, and a higher incidence of complications are supposed to have a detrimental effect on the overall effect or introduce bias by increasing the average effect size (Joober et al., 2012). Thus, detecting publication bias is an important issue as such bias may lead to inaccurate conclusions in systematic meta-analyses (Sutton et al., 2000). Funnel plot is often used in meta-analysis to detect the presence of heterogeneity and/or publication bias. In this plot, the effect size is usually shown against standard errors or precision (J. Light and B. Pillemer, 1986). In the present study, as the funnel plot was asymmetric, and there was a distinction among studies with lower and higher accuracy, there was no indication of publication bias. Moreover, the results of the Egger's linear regression test confirm the absence of publication bias (intercept (-2.32), 95% CI (-6.65 to 2.0), t-value (1.13), df = 16.00. The 1-tailed P -value was (0.27), and the 2-tailed P -value was 0.1). It has been stated that in meta-analysis, the weighted regression slope is expected to be zero in the absence of publication bias (Rothstein HR, 2005). If the Begg and Mazumdar rank correlation test has a strong correlation, this indicates the presence of publication bias (Begg and Mazumdar, 1994). In the present study, Kendall's tau with continuity correction was -0.58, with a 1-tailed P -value of 0.18 and 2-tailed P -value of 0.36. This finding provided the Egger regression test results, with no indication of publication bias. Egger's regression test is a statistical tool for measuring funnel plot asymmetry through the standardized effect sizes on their precision; in the absence of publication bias, the regression intercept is expected to be zero (Egger et al., 1997).

The trim and fill test is an additional test that evaluates the total effect size and tests publication bias (Duval and Tweedie, 2000). A repetitive procedure was used to exclude small studies at the margin ends of the positive end of the funnel plot. The trimming and filling processes were repeated until the funnel plot was symmetric with regard to the effect size (Duval, 2005). The results of the present 18 studies indicated an adjusted correlation of -2.32 to -2.07.

The Fail-safe N test suggests that 5059 missing studies were required to conclude the result of study is significant ($p = 0.000$). The present result is supported by the findings of the previous study (Rosenthal, 1979). Calculation of the number of missing studies is possible in the meta-analysis to conclude if the p-value is significant. In addition, in observed studies, Orwin's fail-safe N proposes a -2.2-event rate, but in missing studies, it proposes a 0.00 mean event rate. Even though they are usually used in meta-analysis applications, these tests may have different types of errors (Peters et al., 2006, 2007; Rücker et al., 2008; Sterne et al., 2000; Terrin et al., 2003).

In conclusion, the results of the present meta-analysis indicate the establishment of cryptosporidium infection in camels with presence of zoonotic species. Therefore, more attention should be paid to the prevention and control of this disease. Molecular identification of cryptosporidium spp. is essential to identify the zoonotic potential.

Conflicts of interest: Authors declare that there was no conflict of interest.

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