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Review

Global prevalence of *Cryptosporidium* spp. in cats: A systematic review and meta-analysis

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ABSTRACT

The One-Health approach highlights that the health of human populations is closely connected to the health of animals and their shared environment. Cryptosporidiosis is an opportunistic zoonotic disease considering as global public health concern. Cats are considered as one of potential host for transmitting the *Cryptosporidium* spp. infection to humans. A random-effects meta-analysis model was used to estimate the overall and the subgroup-pooled prevalence of *Cryptosporidium* spp. across studies, and the variance between studies (heterogeneity) were quantified by I^2 index. Eighty articles (including 92 datasets), from 29 countries met eligibility criteria for analysis. The pooled global prevalence (95% CI) of *Cryptosporidium* spp. in cats was 6% (4–8%), being highest in Africa 14% (0–91%) and lowest in South and Central America 4% (3–7%) countries. Considering the detection methods, the pooled prevalence was estimated to be 26% (1–67%) using serological detection methods, 6% (3–10%) using coproantigen detection methods, 5% (3–7%) using molecular detection methods, and 4% (3–7%) using microscopic detection methods. The highest prevalence of *Cryptosporidium* spp. was found in stray cats 10% (5–17%), while pet (domestic) cats 4% (3–7%) had the lowest prevalence. These results emphasize the role of cats as reservoir hosts for human-infecting *Cryptosporidium* spp. Prevention and control of this zoonosis in cats should receive greater attention by health officials and health policymakers, especially in countries where risk factors and prevalence are highest.

1. Introduction

Cryptosporidium spp. are considered as an opportunistic zoonotic parasite that affects a wide range of animals including humans. The parasite primarily infects the gastrointestinal epithelium of hosts and causes diarrheal disease (Nime et al., 1976; Xiao and Cama, 2018). The first case of human cryptosporidiosis was reported by Nime et al. (1976) in a child with severe acute self-limited enterocolitis during 1970s. The infection is often self-limited among immunocompetent persons; while, cryptosporidiosis in elderly people, malnourished subjects, and patients with immunodeficiency can lead to severe consequences, even death if left untreated (Gambhir et al., 2003; Wang et al., 2018). Based on Khalil et al. (2018) cryptosporidiosis is ranked as the fifth leading cause of diarrhea-related mortality in children under 5 years in 2016. This acute infection caused over 48.000 deaths and 4.2 million disability-adjusted life-years (DALYs) worldwide (Khalil et al., 2018). The pooled global prevalence of *Cryptosporidium* spp. infec-

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tion in HIV-positive patients were determined at 14.0% (95% CI: 13.0–15.0%) using meta-analysis approach (Wang et al., 2018).

During the past years, the role of cats in the spread and transfer of *Cryptosporidium* spp. oocysts has been investigated (Sykes, 2013). Cats as a part of human companion providing some benefits in relation to mental health and physical well-being of the population (McConnell et al., 2011). Based on formal reports, the global number of cats is estimated approximately 700 million (220 million pets and 480 million stray cats) (https://www.carocat.eu), (Rostami et al., 2020a, 2020b). It is worth to mention that the reported populations of cats worldwide is probably underestimated and the real number is significantly higher, due to lack of registration (https://www.carocat.eu) (Rostami et al., 2020a, 2020b). Evidence suggests that pet owners have a better well-being status, with less visits to the physician, consume fewer drugs and have lower cholesterol levels than non-pet owners (Barker and Wolen, 2008; Beck and Meyers, 1996). Pets provide several important benefits in to humans, there are also associated with health hazards. Besides the risk of bites, scratches and allergies as the common health hazards, cats may harbor a diverse range of zoonotic parasitic infections. Thus, close contact with these pets are considered as a risk factor (Chalkowski et al., 2019; Dubey et al., 2020; Ramírez-Ocampo et al., 2017; Robertson and Thompson, 2002; Rostami et al., 2020a, 2020b).

Several studies have demonstrated the prevalence of *Cryptosporidium* spp. infection in cats. However, there is a lack of a comprehensive global estimation of the prevalence of *Cryptosporidium* spp. in the cat population. Considering the public health concern related to cats as a potential source of *Cryptosporidium* spp. infection, this meta-analysis paper provides the first comprehensive review to evaluate the pooled global prevalence of *Cryptosporidium* spp. and the related risk factors in cats.

2. Methodology

In the current systematic review and meta-analysis, we have followed the standard protocol of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) to design, report and interpretation of our results (Moher et al., 2015).

2.1. Search strategy

The authors systematically explored four international databases (PubMed, Web of Science, Scopus, and Google scholar) for peer-reviewed articles, released online between January 1st, 1990 and 30 May 2020, to find all publicly accessible papers that reported the prevalence of *Cryptosporidium* spp. in cats worldwide. A combination of the following search terms was applied in our literature searches as follows: “Intestinal Parasites” OR “Coccidian” OR “Opportunistic protozoa” OR “*Cryptosporidium*” OR “Cryptosporidiosis” AND “Prevalence” OR “Epidemiology” OR “Frequency” AND “Cat” OR “Feline” OR “Kitten”. The authors also reviewed the references of the included articles, in order to identify further studies that might have been missed.

2.2. Eligibility criteria, study selection, and data extraction

In the first step, all published records retrieved were imported into the Endnote (version X7) reference management program and duplicate citations were removed. Then, two authors independently, reviewed the records according to the titles/abstracts and excluded irrelevant papers in relation to the aim of the review. The abstracts of all remaining citations were imported into a Microsoft Word file for further assessments in terms of inclusion criteria. Afterwards, the full-texts of all potential eligible studies were downloaded through online resources and their relevance was evaluated according to inclusion and exclusion criteria. Final eligibility and inclusion criteria were appraised and any discrepancies were resolved through discussion with the principal investigator. The papers were included in the current systematic review, should present all of the following criteria: 1) peer-reviewed original research papers, brief reports or letters to the editors which reported the prevalence of *Cryptosporidium* spp. in cats; 2) published online or indexed in four international databases (PubMed, Web of Science, Scopus, and Google scholar) from 1st January 1990 up to 30 May 2020; 3) the papers with full-text or abstract in English without geographical limitation; 4) precise information was available on the total sample size and positive samples; 5) those articles that employed at least one of the following methods, including microscopy, molecular, or coproantigen detection in feces and/or serology detection in serum samples. Papers were excluded papers if they didn't meet the all the above criteria or if they were narrative reviews, systematic reviews, editorials, and case reports. The data extraction was performed independently by two trained investigators and recorded using a Microsoft Excel template (2016 version; Microsoft, Redmond, WA, USA) in a blinded manner. The extracted data was carefully rechecked for accuracy. Any disagreement or inconsistency the principle investigator was consulted and resolved to reach a decision. The Microsoft Excel software template included the following variables, study characteristics (the first author's last name, publication year, study period, continent, country, and city), geographic locations (latitude and longitude), climatic conditions (mean annual rainfall, mean relative humidity, and mean annual temperature), the diagnostic methods (microscopy, molecular, coproantigen and serological methods), type of cats (pet or stray), total sample size, positive samples. If available, the data about age, gender, and the presence or absence of diarrhea were also extracted. With respect to molecular methods, the genes type of each study along with the identified species were extracted. In this study, we used several data sources to define the geographical and climatic status of different cities and areas studied (https://www.timeanddate.com/, https://en.climate-data.org/, and https://gps-coordinates.org/) (Rostami et al., 2020a, 2020b). Since there were several types of cats in the studies included, we divided cats into: (1) pet (domestic) animals: “pet, household, sheltered or domestic”; (2) stray animals: “stray, free-roaming or feral”; (3) unknown animals: “It is not clear whether the cats are domestic or stray”.

2.3. Study quality assessment

The Joanna Briggs Institute (JBI) checklist was used for quality assessment of the included articles (Institute, 2014). This checklist contains ten questions with four options including, Yes, No, Unclear, and Not applicable. Briefly, a study can be awarded a maximum of one star for each numbered item. The papers with a total score of 4–6 and 7–10 points were specified as the moderate and high quality, respectively. Based on the obtained score, the authors have decided to include (4–10 points) and exclude (≤3 points) the papers.

2.4. Meta-analysis

In this paper, all analysis procedures were performed using the random-effects (RE) model to estimate the prevalence of *Cryptosporidium* spp. in cats worldwide, as described recently (Taghipour et al., 2020a, 2020b, 2020c, 2020d; Taghipour et al., 2021;). The global and regional prevalence rate of *Cryptosporidium* spp. was computed by 95% confidence interval [CI] in the context of continents and countries. Heterogeneity between publications was calculated using the t^2 and I^2 statistics and the values of $<50\%$, 50%–80%, and $>80\%$ were specified as low, moderate, and high heterogeneity, respectively (Higgins et al., 2003; Taghipour et al., 2020c). The analyses of subgroups to assess the source of heterogeneity between the selected papers were done based on geographical latitude and longitude, continent, country, climatic variables (mean relative humidity, annual temperature and annual precipitation), type of cats, age group, gender, and type of diagnostic

method(s). Moreover, due to different sensitivities and specificities of diagnostic methods, we assumed that our results would be "apparent" prevalence rates, and did not represent true prevalence rates. We also used the funnel plot to check the probability of publication bias during the analysis (Egger et al., 1997; Zhang et al., 2017). We applied the Meta package (Schwarzer, 2007) for R software version 3.5.1 for the statistical analyses and a *P*-value of <0.05 was considered as significant.

3. Results

3.1. Characteristics of studies

As shown in Fig. 1, the systematic search yielded 4201 relevant articles; after removing duplicates and/or non-eligible papers, 80 publications containing 92 datasets were eligible for the systematic review and meta-analysis. The main characteristics of each study along with the references are listed in Supplementary Table 1. The results of quality assessment according to JBI for eligible studies are presented in Supplementary Table 1. All the included articles were of acceptable quality. These studies (92 datasets) provided data on 23,588 cats from 29 countries from five continents. In total, 31 datasets were available for America (9782 cats), 29 for Europe (6875 cats), 21 for Asia (4635 cats), eight for Oceania (2082 cats), and three for Africa (214 cats). Only one study was found for Greece, Russia, Slovakia, Poland, Netherlands, Norway, and Austria from Europe; Colombia and Costa Rica from America; Indonesia from Asia, Egypt, Kenya, and Nigeria from Africa. The countries with the highest number of formal reports were USA (15 datasets), Brazil (11 datasets), and Australia (8 datasets). *Cryptosporidium* spp. prevalence in cat populations in all 29 individual countries is listed in Table 1. Considering the diagnostic methods, 49 datasets used microscopic detection methods, 21 datasets used molecular detection methods, 17 datasets used coproantigen detection methods and five datasets used serological detection methods (Table 2). To identify potential publication bias, we used an asymmetry in funnel plot test. This test indicated that there was a significant publication bias in eligible studies ($t = 4.05$, df = 90, *P*-value = 0.0001, Supplementary Fig. 1).

3.2. Global and regional prevalence rates of Cryptosporidium spp. in cats

The pooled global prevalence of *Cryptosporidium* spp. in cats was 6% (95% CI, 4–8%; 1126/23,588), with a high heterogeneity among studies ($I^2 = 96\%$) (Table 1). With regard to continents, the prevalences were: 14% (0–91%; 54/214) in Africa; 6% (3–11%; 496/6875) in the Europe; 6% (3–9%; 190/4635) in Asia; 5% (1–14%; 72/2082) in Oceania; and 4% (3–7%; 314/9782) in America. In terms of countries, Costa Rica (14%; 1/7) in America; Scotland (38%; 211/493) in Europe; Kenya (41%; 42/103) in Africa; Iraq (13%; 40/363) in Asia exhibited some of the highest prevalence rates. In contrast, Russia (1%; 15/1261) in Europe, Canada (1%; 17/1537) in America, Indonesia (2%; 13/532) in Asia, and Nigeria (0%; 0/52) in Africa had the lowest prevalence of *Cryptosporidium* spp. in cats (Table 1).

3.3. Prevalence rates according to type of cat, age, gender, and diarrhea status

About type of cat, the highest prevalence of *Cryptosporidium* spp. was found in stray cats 10% (95% CI: 5–17%; 152/2293); while pet (domestic) cats 4% (95% CI: 3–7%; 683/15,871) had the lowest prevalence (Table 2). Eighteen datasets have reported the prevalence of *Cryptosporidium* spp. based on cat age. In subgroup analysis, the pooled *Cryptosporidium* spp. was estimated 7% (95%CI: 4–12%; 93/2304) and 3% (95% CI: 1–6%; 111/3660) in cats aged ≤12 months and > 12 months, respectively. A positive association was observed

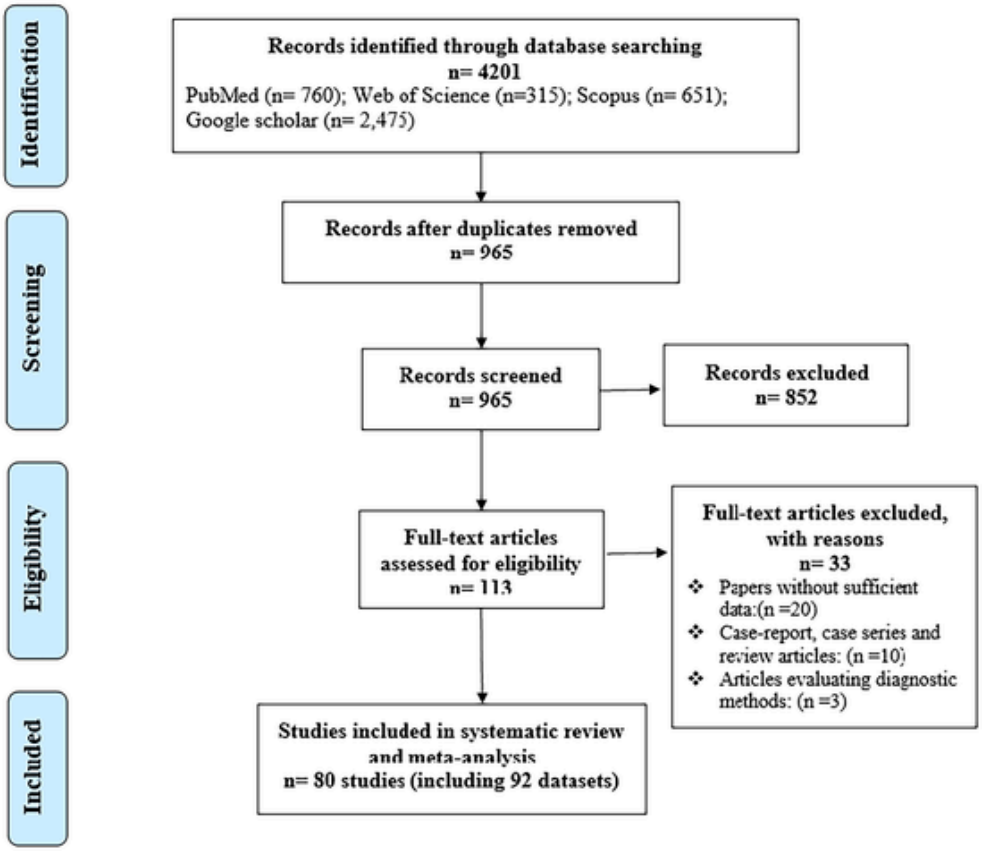

Fig. 1. PRISMA flow diagram describing included/excluded studies.

Table 1
Global, regional and national pooled prevalence of *Cryptosporidium* infection in cats.

Continent/country	Number of datasets	Total samples (n)	Infected samples (n)	Pooled prevalence (95% CI)	Heterogeneity		
					I^2%	t^2	*P*-value
Global	**92**	**23,588**	**1126**	**6 (4–8)**	**96**	**0.02**	**0**
Europe	**29**	**6875**	**496**	**6 (3–11)**	**98**	**0.04**	***P* < 0.01**
Italy	5	932	60	3 (0–17)	97	0.03	*P* < 0.01
Germany	4	1122	54	7 (3–33)	96	0.04	*P* < 0.01
Spain	3	149	8	5 (1–12)	0	0.0007	*P* = 0.64
Czech Republic	3	388	72	15 (0–78)	98	0.07	*P* < 0.01
UK	3	1557	38	3 (0–45)	97	0.04	*P* < 0.01
Scotland	2	493	211	38 (0–100)	100	0.2	*P* < 0.01
Turkey	2	200	8	4 (0–25)	0	0.0003	0.47
Greece	1	264	18	7 (4–10)	NR[a]	NR	NR
Russia	1	1261	15	1 (1–2)	NR	NR	NR
Slovakia	1	73	3	4 (1–10)	NR	NR	NR
Poland	1	64	2	3 (0–9)	NR	NR	NR
Netherlands	1	22	1	5 (0–17)	NR	NR	NR
Norway	1	52	1	2 (0–7)	NR	NR	NR
Austria	1	298	5	2 (1–3)	NR	NR	NR
America	**31**	**9782**	**314**	**4 (3–7)**	**94**	**0.01**	***P* < 0.01**
USA	15	6962	226	4 (2–8)	96	0.01	*P* < 0.01
Brazil	11	1230	64	5 (2–11)	88	0.02	*P* < 0.01
Canada	3	1537	17	1 (0–4)	64	0.001	0.06
Colombia	1	46	6	13 (5–24)	NR	NR	NR
Costa Rica	1	7	1	14 (0–47)	NR	NR	NR
Asia	**21**	**4635**	**190**	**6 (3–9)**	**84**	**0.01**	***P* < 0.01**
Iraq	5	363	40	13 (2–31)	83	0.02	*P* < 0.01
Iran	5	590	21	4 (0–17)	90	0.02	*P* < 0.01
Japan	4	2028	64	4 (0–12)	77	0.008	*P* < 0.01
China	4	976	42	4 (2–7)	60	0.001	0.06
Thailand	2	146	10	6 (0–100)	82	0.01	0.02
Indonesia	1	532	13	2 (1–4)	NR	NR	NR
Africa	**3**	**214**	**54**	**14 (0–91)**	**97**	**0.11**	***P* < 0.01**
Egypt	1	59	12	20 (11–31)	NR	NR	NR
Kenya	1	103	42	41 (32–50)	NR	NR	NR
Nigeria	1	52	0	0 (0–2)	NR	NR	NR
Oceania	**8**	**2082**	**72**	**5 (1–14)**	**93**	**0.03**	***P* < 0.01**
Australia	8	2082	72	5 (1–14)	93	0.03	*P* < 0.01

[a] R: Not reported.

between *Cryptosporidium* spp. and age of ≤12 months (OR = 2.54; 95% CI, 1.47–4.38%). Incidence of diarrhea and gender were not correlated with infection rates. Detailed characteristics of the associated risk factors are displayed in Table 3.

3.4. Prevalence according to detection methods

In relation to detection methods, the pooled prevalence was estimated to be 26% (95% CI: 1–67%; 335/1352) using serological detection methods, 6% (95% CI: 3–10%; 157/2431) using coproantigen detection methods, 5% (95% CI: 3–7%; 143/2767) using molecular detection methods, and 4% (95% CI: 3–7%; 491/17,038) using microscopic detection methods (Fig. 2 and Table 2). Considering the molecular methods, species identification using various genes represented that *C. felis* was the most prevalent species/genotype, followed by *C. parvum* and *Cryptosporidium* rat genotype III (Supplementary Table 2).

3.5. Prevalence rates according to geographical and climatic parameters

We also conducted subgroup analyses for geographical and climate parameters, to identify possible sources of heterogeneity on the prevalence of *Cryptosporidium* spp. in cats (Table 2). About the geographical parameters, the highest prevalence rates of *Cryptosporidium* spp. were found at latitude of 11–20° (9%; 95% CI: 1–22%; 18/204) and longitude of ≥141° (22%; 95% CI: 0–100%; 5/26) (Table 2). As shown in Table 2, the highest prevalence was observed at ≤50% (10%; 95% CI: 5–17%; 103/1249) relative humidity and 8–14 °C (8%; 95% CI: 4–12%; 587/8291) mean temperature; while, the precipitation rates were almost the same (~6%) in all ranges. Also, the lowest prevalence was determined at latitude of 21–30° (5%; 95% CI: 2–8%; 135/3197), longitude of 121–140° (3%; 95% CI: 2–6%; 98/3303), at 51–75% relative humidity (5%; 95% CI: 3–7%; 678/18,080), ≤7 mean temperature (1%; 95% CI: 0–3%; 27/2323), and ≥ 1001 mean annual precipitation (4%; 95% CI: 1–10%; 90/2505).

4. Discussion

Over the years, zoonotic transmission of various species of *Cryptosporidium* spp. and the role of animals as reservoir for human infection are important issues in medical and veterinary practices (Hunter and Thompson, 2005; Ryan et al., 2014). Cats are considered as one of the potential reservoirs for human-infecting *Cryptosporidium* spp. According to our results, the prevalence of *Cryptosporidium* spp. with the serological, coproantigen, molecular and microscopic detection methods were estimated at 26%, 6%, 5% and 4%, respectively (Table 2). One of the most important reasons for the difference in prevalence is that each of the studied methods has its own sensitivity and specificity (Elsafi et al., 2013). Traditionally, light microscopy using specific staining techniques is one of the methods to diagnose *Cryptosporidium* spp. infection (Robinson and Chalmers, 2020; Taghipour et al., 2019). Since cats shed only low numbers of oocysts (around 10^3 and 10^4 oocyst/g of feces), this technique may not be very sensitive in cats (Mekaru et al., 2007; Weber et al., 1991; Webster et al., 1996). In addition to its low sensitivity, this method needs an experienced scientist due to oocysts similarity to bacteria or yeasts in stool samples (Ukwah and Ezeonu, 2013). Although serological techniques are more sensitive than the mi-

Table 2
Sub-group analysis of the prevalence of *Cryptosporidium* based on geographical location, climate variables, diagnostic methods and type of cat.

Variable/sub-groups	Number of datasets	Total samples (n)	Infected samples (n)	Pooled prevalence (95% CI)	Heterogeneity		
					I^2(%)	t^2	*P*-value
Latitude							
0–10°	5	761	62	8 (0–33)	96	0.06	$P < 0.01$
11–20°	4	204	18	9 (1–22)	65	0.07	0.04
21–30°	15	3197	135	5 (2–8)	88	0.01	$P < 0.01$
31–40°	36	10,819	412	6 (4–8)	94	0.01	$P < 0.01$
41–50°	17	2518	161	5 (2–10)	95	0.02	$P < 0.01$
≥51°	15	6089	338	6 (1–15)	99	0.06	$P < 0.01$
Latitude (N&S)							
North	72	19,732	949	6 (4–8)	96	0.02	0
South	20	3856	177	6 (2–10)	93	0.03	$P < 0.01$
Longitude							
0–20°	26	5202	455	6 (3–12)	98	0.05	$P < 0.01$
21–40°	4	1687	87	14 (0–50)	98	0.06	$P < 0.01$
41–60°	21	2285	118	6 (3–9)	87	0.02	$P < 0.01$
61–80°	7	2425	83	4 (1–9)	91	0.01	$P < 0.01$
81–100°	6	3678	109	7 (2–17)	98	0.01	$P < 0.01$
101–120°	19	4982	171	4 (2–6)	91	0.01	$P < 0.01$
121–140°	7	3303	98	3 (2–6)	58	0.003	0.003
≥141°	2	26	5	22 (0–100)	67	0.04	0.08
Longitude (W&E)							
West	38	11,931	569	6 (3–9)	97	0.03	$P < 0.01$
East	54	11,657	557	6 (4–8)	93	0.02	$P < 0.01$
Humidity (%)							
≤50	12	1249	103	10 (5–17)	89	0.02	$P < 0.01$
51–75	58	18,080	678	5 (3–7)	95	0.02	$P < 0.01$
≥76	22	4259	345	6 (2–12)	98	0.04	$P < 0.01$
Mean temperature (°C)							
26≤	8	1266	86	7 (1–20)	95	0.04	$P < 0.01$
21–25	7	1148	59	5 (1–10)	91	0.01	$P < 0.01$
15–20	40	10,560	367	5 (3–7)	93	0.01	$P < 0.01$
8–14	31	8291	587	8 (4–12)	98	0.04	$P < 0.01$
≤7	6	2323	27	1 (0–3)	51	0.002	0.07
Precipitation (mm)							
0–250	20	4378	202	6 (3–10)	93	0.02	$P < 0.01$
251–500	36	9458	393	6 (3–9)	96	0.03	$P < 0.01$
501–750	23	6801	414	6 (3–11)	98	0.03	$P < 0.01$
751–1000	2	446	27	6 (0–21)	0	0.0003	0.53
≥1001	11	2505	90	4 (1–10)	84	0.02	$P < 0.01$
Diagnostic methods							
Microscopic methods	49	17,038	491	4 (3–7)	94	0.02	$P < 0.01$
Molecular methods	21	2767	143	5 (3–7)	76	0.005	$P < 0.01$
Coproantigen methods	17	2431	157	6 (3–10)	90	0.01	$P < 0.01$
[a]Immunofluorescence assay (IFA)	13	1682	113	6.8 (4.5–10.3)	74.56	0.41	0
[a]Enzyme linked immunosorbent assay (ELISA)	3	617	42	6 (0–35.9)	96.82	3.55	0
[a]Rapid immunochromatographic assay	1	132	2	1.5 (0–5.9)	0	0	1
Serological methods	5	1352	335	26 (1–67)	99	0.11	$P < 0.01$
[b]Immunofluorescence assay (IFA)	2	393	250	59.8 (28.3–84.8)	97.2	0.8	0
[b]Enzyme linked immunosorbent assay (ELISA)	3	959	85	8.9 (5–15.4)	83.5	0.2	0.002
Type of cat							
Stray cats	15	2293	152	10 (5–17)	89	0.03	$P < 0.01$
Pet (Domestic) cats	58	15,871	683	4 (3–7)	96	0.03	$P < 0.01$
Unknown (mixed)	26	5424	351	10 (5–17)	96	0.06	$P < 0.01$

NR: Not reported.
[a] Subgroup of different diagnostic methods for coproantigen methods.
[b] Subgroup of different diagnostic methods for serological methods.

croscopic methods, high costs, false-positive reactions and no differentiation of active infection from past infection are considered as disadvantages (Doing et al., 1999; Frost et al., 2004). They have limited use to identify parasites in a clinical environment and are mainly used to study overall exposure of a population or understanding dynamics of infections. The results of the serological prevalence are higher than the other three methods, which may be due to false-positive reactions with other pathogens. The use of coproantigen detection tests has helped to

Table 3
Risk factors of *Cryptosporidium* infection among cats.

Risk factors	Number of datasets	Variables	Total samples (n)	Infected samples (n)	Pooled prevalence (95% CI)	OR (95%CI)	OR Heterogeneity		
							I^2%	τ^2	*P*-value
Diarrhea	14	With diarrhea	896	64	7 (3–12)	1.38 (0.78–2.45)	33	0.50	0.11
		Without diarrhea	2734	174	5 (2–10)				
Gender	14	Male	1657	128	7 (4–11)	0.99 (0.66–1.46)	14	0.20	0.30
		Female	1766	122	8 (4–13)				
Age	18	≤ 12 months	2304	93	7 (4–12)	2.54 (1.47–4.38)	6	0.49	0.38
		> 12 months	3660	111	3 (1–6)				

identify *Cryptosporidium* spp., especially in farm animals (Cirak and Bauer, 2004). This immunodiagnostic method is an alternative, complementary and/or confirmatory test to coprological oocyst detection under the microscope. It is based on the detection of anti-*Cryptosporidium* spp. antibodies and/or coproantigens released by the parasite (Papini and Verin, 2019). Coproantigenic tests can be helpful, when it is difficult to detect *Cryptosporidium* spp. microscopically. Hence, one of the most important advantages of coproantigen assays is the ability to detect cryptic, asymptomatic and chronic/intermediary infections (Van den Bossche et al., 2015). Immunofluorescent assay (IFA) is consider for many veterinarian researchers as a gold standard for detection of *Cryptosporidium* spp. oocysts in cats and dogs (Ballweber et al., 2009; Scorza et al., 2011); whereas enzyme linked immunosorbent assay (ELISA) are not routinely used for veterinary clinicians for detection of feline cryptosporidiosis (Bowman and Lucio-Forster, 2010; Cirak and Bauer, 2004). The use of ELISA results in false positives but IFA for detection of feline cryptosporidiosis is highly sensitive in comparison with other diagnostic techniques (Ayinmode and Fagbemi, 2011). In addition, false positives using IFA are not common as with the use of commercial ELISA since they rely on the morphological detection of the oocysts and the fluorescent staining (Ayinmode and Fagbemi, 2011; Ballweber et al., 2009). Molecular techniques are considered superior for the detection and differentiation of *Cryptosporidium* spp. at the species/genotype levels (Robinson et al., 2020). The main advantage of molecular methods is higher sensitivity and specificity, along with easier interpretation (Robinson et al., 2020). In this regard, the pooled prevalence obtained by molecular methods (5%) can be considered as "true" prevalence.

In the sequencing results of this meta-analysis research, *C. parvum* and *Cryptosporidium* rat genotype III are the second most common species infecting cats after *C. felis*. *C. parvum* is the most common species in various hosts and it can be transmitted from different sources to cats (Berahmat et al., 2017). In the analysis of the subgroup based on the type of cats, the prevalence of *Cryptosporidium* spp. in stray cats were higher than that in pet (domestic) cats. Stray cats are freely scattered in the environment and easily access to other animals (e.g. ungulates) or contact with environmental sources (e.g. consumption of oocyst contaminated water and food). They can be considered as an important reservoir of *Cryptosporidium* spp. (Hatam-Nahavandi et al., 2019; Javanmard et al., 2020).

By considering the prevalences of infection in different continents, the highest rate was reported from Africa but only three studies have been conducted in Africa and therefore cannot be decisive. Infection rates in Oceania, America, Asia and Europe were relatively low. The variation in infection rates of different geographical areas may be due to a variety of reasons, including climatic variation, animal husbandry methods, parasite control measures, Human Development Index (HDI), and the use of different diagnostic methods in different areas (Jagai et al., 2009; Taghipour et al., 2020c; Yoder and Beach, 2010). The need for further studies and more attention to *Cryptosporidium* spp. infection in cats in these countries is evident (Table 1). On the other hand, most studies based on molecular analysis have been conducted in developed countries, where laboratory tools are more accessible compared to those in developing countries (Gil et al., 2017). Therefore, access to modern molecular tools with high sensitivities and specificities can be one of the reasons for the low infection rate in developed countries.

In the present meta-analysis, we observed a higher *Cryptosporidium* spp. prevalence in cats aged ≤12 months, female gender and cats suffering from diarrhea; however, these differences were only significant in cats aged ≤12 months. One of the reasons for the higher prevalence of infection in younger animals may be related to the underdeveloped immune system for acquisition of *Cryptosporidium* spp. infection (Paul et al., 2010; Tzannes et al., 2008). The clinical signs caused by this parasite are generally associated with malnutrition and diarrhea in cats, which can lead to animal death, if left untreated (Goodwin and Barsanti, 1990; Tzannes et al., 2008). In this regard, clinical signs such as weight loss, fever, loss of appetite and watery diarrhea in kitten should be noted, which can prevent the transmission of infection to high-risk groups by timely diagnosis and treatment of sick cats.

The study shows a heterogeneity in prevalence of *Cryptosporidium* spp. with geographic and climate parameters. Climatic conditions and geographical locations have major effect on survival of oocysts (Jagai et al., 2009; Sterk et al., 2013). It is well known that the survival rate of *Cryptosporidium* spp. oocysts is higher in areas with higher humidity and warmer climate in soil, while the survival rate is lower in colder climates (Jagai et al., 2009). Nevertheless, comparisons of prevalence rates between regions based on climatic conditions should be made with caution, since there are several confounding factors, notably different management practices.

The strengths of the present meta-analysis include a comprehensive literature search, rigorous methodology, large sample size, defined clear inclusion and exclusion criteria, studies from different countries and continents, different subgroup analysis and quality assessment. However, the present systematic review and meta-analysis has certain limitations, including (1) although a comprehensive search of the available peer-reviewed literature has been undertaken and included a large number of studies that had assessed the prevalence of *Cryptosporidium* spp. in cats; (2) the lack of published information on the prevalence of *Cryptosporidium* spp. in cats from many low and middle-income countries; (3) lack of risk factors (i.e. age and gender) and clinical signs (i.e. gastrointestinal disorders) in most studies; (4) finally, the fact that most included studies applied only a single fecal/serum sample for detection and diagnosis of the parasite. The meta-analysis results may not reflect the true prevalence, and the reported numbers are apparent prevalence. Nevertheless, the report is close to the true *Cryptosporidium* spp. prevalence in cats from a global perspective.

In conclusion, despite some of the above limitations, the systematic review and meta-analysis study provides a comprehensive and useful overview of the *Cryptosporidium* spp. prevalence in cats worldwide. It becomes evident that there is a considerably burden of *Cryptosporidium* spp. in cats (6%). The results also show that *C. felis* followed by *C. parvum* were the main species found in cats. This information can be taken into consideration by the health policymakers, physicians, veterinarians, and cats' owners to implement measures to reduce the incidence of this parasite. Veterinarians can inform their clients of this parasite and advise them for the clinical significance of *Cryptosporidium* spp., the infection risks from cats to humans, particularly if their clients or other members of the household are immunosuppressed. People

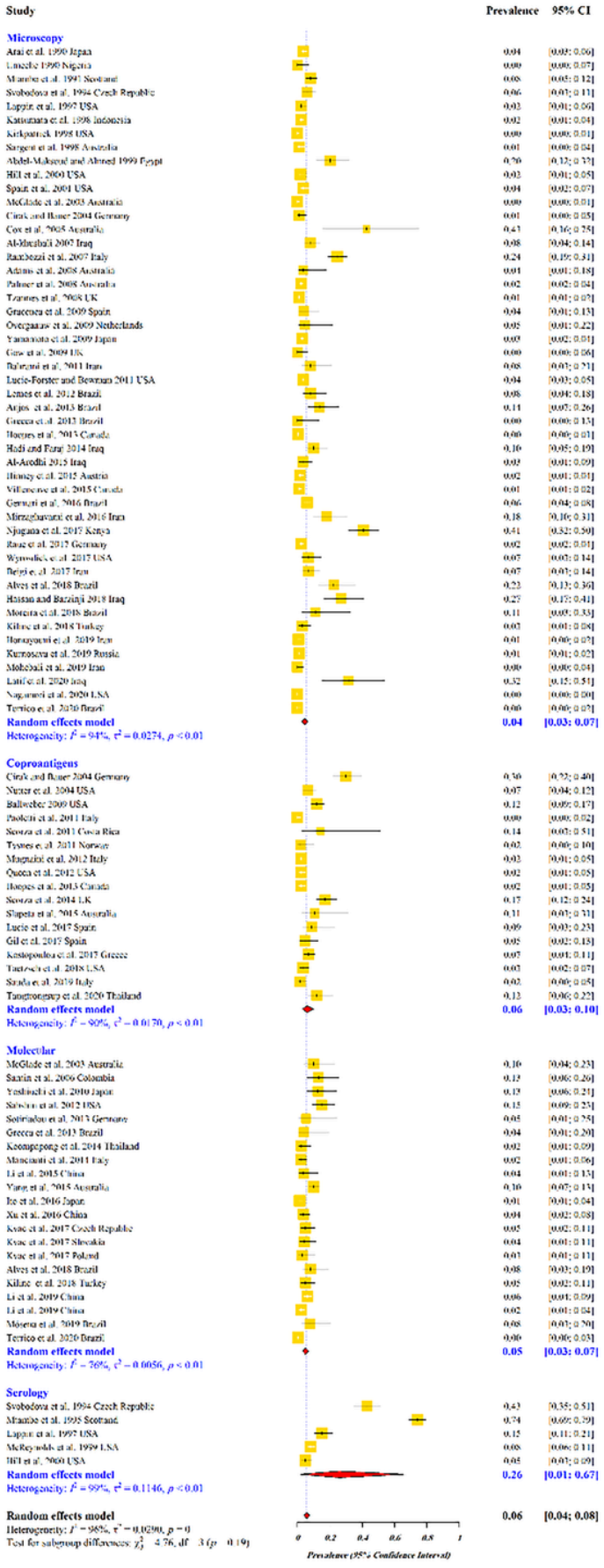
Study
Prevalence
95% CI
Microscopy
Arai et al. 1990 Japan 0.04 [0.03; 0.06]
Lincoln 1990 Nigeria 0.00 [0.00; 0.07]
Mannie et al. 1993 Scotland 0.08 [0.05; 0.12]
Svobodova et al. 1994 Czech Republic 0.06 [0.03; 0.11]
Lappin et al. 1997 USA 0.03 [0.01; 0.06]
Katsumata et al. 1998 Indonesia 0.02 [0.01; 0.04]
Kirkpatrick 1998 USA 0.00 [0.00; 0.01]
Sargent et al. 1998 Australia 0.01 [0.00; 0.04]
Abdel-Maksoud and Ahmed 1999 Egypt 0.20 [0.13; 0.27]
Hill et al. 2000 USA 0.03 [0.01; 0.05]
Spain et al. 2001 USA 0.04 [0.02; 0.07]
McGlade et al. 2003 Australia 0.00 [0.00; 0.01]
Cirak and Bauer 2004 Germany 0.01 [0.00; 0.05]
Cox et al. 2005 Australia 0.43 [0.16; 0.75]
Al-Ibrahali 2007 Iraq 0.08 [0.04; 0.14]
Rambozzi et al. 2007 Italy 0.24 [0.19; 0.31]
Adams et al. 2008 Australia 0.01 [0.01; 0.18]
Palmer et al. 2008 Australia 0.02 [0.02; 0.04]
Travnicek et al. 2008 UK 0.01 [0.01; 0.07]
Graceneo et al. 2009 Spain 0.04 [0.01; 0.13]
Overgaauw et al. 2009 Netherlands 0.05 [0.01; 0.22]
Yamamoto et al. 2009 Japan 0.03 [0.02; 0.04]
Gow et al. 2009 UK 0.00 [0.00; 0.06]
Bahrami et al. 2011 Iran 0.08 [0.03; 0.21]
Lucie-Forster and Bowman 2011 USA 0.04 [0.03; 0.05]
Lemes et al. 2012 Brazil 0.08 [0.04; 0.18]
Arjos et al. 2013 Brazil 0.11 [0.07; 0.26]
Greeca et al. 2013 Brazil 0.00 [0.00; 0.13]
Hoepes et al. 2013 Canada 0.00 [0.00; 0.01]
Hadi and Faraj 2014 Iraq 0.10 [0.05; 0.19]
Al-Aredhi 2015 Iraq 0.03 [0.01; 0.09]
Hinney et al. 2015 Austria 0.02 [0.01; 0.04]
Villeneuve et al. 2015 Canada 0.01 [0.01; 0.02]
Gennari et al. 2016 Brazil 0.06 [0.04; 0.08]
Mirzaghavami et al. 2016 Iran 0.18 [0.10; 0.31]
Njoguna et al. 2017 Kenya 0.41 [0.32; 0.50]
Raue et al. 2017 Germany 0.02 [0.02; 0.04]
Wysmolek et al. 2017 USA 0.07 [0.03; 0.14]
Bejzi et al. 2017 Iran 0.07 [0.03; 0.14]
Alves et al. 2018 Brazil 0.23 [0.13; 0.36]
Hassan and Barzinji 2018 Iraq 0.27 [0.17; 0.41]
Moreira et al. 2018 Brazil 0.11 [0.05; 0.35]
Kilinc et al. 2018 Turkey 0.03 [0.01; 0.08]
Hosseyoni et al. 2019 Iran 0.01 [0.00; 0.07]
Kumoseva et al. 2019 Russia 0.01 [0.01; 0.02]
Mohebali et al. 2019 Iran 0.00 [0.00; 0.04]
Latif et al. 2020 Iraq 0.32 [0.15; 0.54]
Nagamori et al. 2020 USA 0.00 [0.00; 0.00]
Terrico et al. 2020 Brazil 0.00 [0.00; 0.07]
Random effects model 0.04 [0.03; 0.07]
Heterogeneity: $I^2 = 94\%$, $\tau^2 = 0.0274$, $p < 0.01$
Coproantigens
Cirak and Bauer 2004 Germany 0.36 [0.22; 0.40]
Nutter et al. 2004 USA 0.07 [0.04; 0.12]
Ballweber 2009 USA 0.12 [0.09; 0.17]
Paoletti et al. 2011 Italy 0.00 [0.00; 0.02]
Souza et al. 2011 Costa Rica 0.14 [0.03; 0.51]
Tysnes et al. 2011 Norway 0.02 [0.00; 0.10]
Magnaldi et al. 2012 Italy 0.03 [0.01; 0.05]
Queca et al. 2012 USA 0.02 [0.01; 0.05]
Hoepes et al. 2013 Canada 0.02 [0.01; 0.05]
Souza et al. 2014 UK 0.17 [0.12; 0.24]
Slapeta et al. 2015 Australia 0.11 [0.03; 0.31]
Lucie et al. 2017 Spain 0.09 [0.03; 0.23]
Gil et al. 2017 Spain 0.05 [0.02; 0.13]
Kostopoulou et al. 2017 Greece 0.07 [0.03; 0.11]
Taetzsch et al. 2018 USA 0.03 [0.02; 0.07]
Sauda et al. 2019 Italy 0.02 [0.00; 0.05]
Taogtongsup et al. 2020 Thailand 0.13 [0.06; 0.22]
Random effects model 0.06 [0.03; 0.10]
Heterogeneity: $I^2 = 90\%$, $\tau^2 = 0.0170$, $p < 0.01$
Molecular
McGlade et al. 2003 Australia 0.16 [0.04; 0.23]
Saarin et al. 2006 Colombia 0.13 [0.06; 0.26]
Yoshiuchi et al. 2010 Japan 0.13 [0.06; 0.21]
Saleem et al. 2012 USA 0.15 [0.09; 0.23]
Sotiriadou et al. 2013 Germany 0.05 [0.01; 0.25]
Greeca et al. 2013 Brazil 0.04 [0.01; 0.20]
Koompapong et al. 2014 Thailand 0.02 [0.01; 0.09]
Mancianti et al. 2011 Italy 0.02 [0.01; 0.06]
Li et al. 2015 China 0.04 [0.01; 0.13]
Yang et al. 2015 Australia 0.10 [0.07; 0.13]
Ito et al. 2016 Japan 0.01 [0.01; 0.04]
Xu et al. 2016 China 0.04 [0.02; 0.08]
Kvac et al. 2017 Czech Republic 0.05 [0.02; 0.11]
Kvac et al. 2017 Slovakia 0.04 [0.01; 0.11]
Kvac et al. 2017 Poland 0.01 [0.01; 0.11]
Alves et al. 2018 Brazil 0.08 [0.03; 0.19]
Kilinc et al. 2018 Turkey 0.05 [0.02; 0.11]
Li et al. 2019 China 0.06 [0.01; 0.09]
Li et al. 2019 China 0.02 [0.01; 0.04]
Moreira et al. 2019 Brazil 0.08 [0.03; 0.20]
Terrico et al. 2020 Brazil 0.00 [0.00; 0.03]
Random effects model 0.05 [0.03; 0.07]
Heterogeneity: $I^2 = 76\%$, $\tau^2 = 0.0056$, $p < 0.01$
Serology
Svobodova et al. 1994 Czech Republic 0.43 [0.35; 0.51]
Mannie et al. 1995 Scotland 0.74 [0.69; 0.79]
Lappin et al. 1997 USA 0.15 [0.11; 0.21]
McReynolds et al. 1999 USA 0.08 [0.06; 0.11]
Hill et al. 2000 USA 0.05 [0.03; 0.09]
Random effects model 0.26 [0.01; 0.67]
Heterogeneity: $I^2 = 99\%$, $\tau^2 = 0.1146$, $p < 0.01$
Random effects model 0.06 [0.04; 0.08]
Heterogeneity: $I^2 = 98\%$, $\tau^2 = 0.0290$, $p = 0$
Test for subgroup differences: χ^2_3 4.76, df 3 (p 0.19)
0 0.2 0.4 0.6 0.8 1
Prevalence (95% Confidence Interval)

Fig. 2. Forest plot of the prevalence of *Cryptosporidium* infection in cats worldwide, based on detection methods.

should practice good sanitation and hygiene to reduce environmental contamination with infectious oocysts that may be shed by their pets. We recommend further investigations to enhance knowledge on the prevalence and genetic diversity of *Cryptosporidium* spp. in cats worldwide to guide the development of appropriate public health interventions.

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Authors' contributions

All authors contributed to study design. ATa contributed to all parts of the study. ATa and SK contributed to study implementation. MO, MF, AVE and MB collaborated in the analysis and interpretation of data. ATa, PK, SG, MS and AT collaborated in the manuscript writing and revision. All the authors commented on the drafts of the manuscript and approved the final version of the article.

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Competing interests

None declared.

Ethical approval

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