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The global prevalence of *Cryptosporidium* in sheep: a systematic review and meta-analysis

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Research Article

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Abstract

Cryptosporidium spp. are important pathogens with some species causing diarrhoea in humans and animals. Sheep are one of the most common potential hosts for various *Cryptosporidium* spp. The prevalence of *Cryptosporidium* in sheep globally was evaluated from published information including molecular data via meta-analysis. In total, 126 datasets from 41 countries were included for final quantitative analysis. Sheep aged <3 months had a significantly higher prevalence (27.8%; 3284/11 938) than those at the age of 3–12 and >12 months. The prevalence of *Cryptosporidium* in sheep with diarrhoea of 35.4% (844/1915) was higher than in sheep that did not show diarrhoea (11.3%; 176/1691). Fourteen *Cryptosporidium* species/genotypes were detected in sheep globally. The proportion of subgenotype family XIIa of *Cryptosporidium ubiquitum* was 90.0% (216/240); the proportions of subgenotypes IIdA20G1 and IIaA15G2R1 of *Cryptosporidium parvum* were 15.4% (62/402) and 19.7% (79/402). The results indicate that *C. parvum* is the dominant species in Europe while *Cryptosporidium xiaoi* is the dominant species in Oceania, Asia and Africa and *C. ubiquitum* is the dominant species in North America and South America. Subgenotype family IIa of *C. parvum* is particularly widespread among sheep worldwide. The results highlight the role of sheep as a reservoir host for zoonotic cryptosporidia and the need for further study of prevalence, transmission and control of this pathogen in sheep.

Introduction

Cryptosporidium is an opportunistic zoonotic parasite that can infect many animals more than 150 species of animals, including humans (Kotloff, 2017; Khan *et al.*, 2018). *Cryptosporidium* is common in ruminants and can cause watery diarrhoea in juvenile ruminants in particular (Santin, 2013). It is well known that small ruminants, such as sheep and goats, play a significant role in some zoonotic infections (Casemore, 1989). Cryptosporidiosis causes huge economic losses to farmers, and the lack of effective prevention and/or treatment in livestock is an unresolved issue (Ryan *et al.*, 2014). Cryptosporidiosis is also a major cause of foodborne and waterborne disease outbreaks in high-income countries and is also the main cause of diarrhoea in young children in low- and middle-income countries (Zahedi and Ryan, 2020; Yang *et al.*, 2021). In South Asia and sub-Saharan Africa, *Cryptosporidium* infection causes diarrhoea in close to 2.9–4.7 million children under 2 years of age each year (Kotloff *et al.*, 2013; Sow *et al.*, 2016). Currently, no effective vaccine has been developed for the treatment of cryptosporidiosis (Ryan *et al.*, 2016).

A few years ago, *Cryptosporidium* was designated as one of the 24 most destructive foodborne parasites by the expert committees of the Food and Agriculture Organization of the United Nations (FAO) and World Health Organization (WHO) (Bouwknegt *et al.*, 2018). The clinical diagnosis of cryptosporidiosis is done using detection methods such as microscopy of acid-fast-stained preparations, immunofluorescent antibody staining, nested polymerase chain reaction, enzyme-linked immunosorbent assay and immunochromatography (Chalmers and Katzer, 2013; Checkley *et al.*, 2015; Xiao and Feng, 2017; Adeyemo *et al.*, 2018). Currently, 44 *Cryptosporidium* species and more than 120 genotypes have been recognized (Feng *et al.*, 2018; Ryan *et al.*, 2021). So far, many *Cryptosporidium* species and genotypes have been discovered in sheep using molecular tools. *Cryptosporidium xiaoi*, *Cryptosporidium parvum* and *Cryptosporidium ubiquitum* are the 3 dominant *Cryptosporidium* species in sheep (Guo *et al.*, 2021). The 2 major *Cryptosporidium* species in sheep responsible for zoonotic infections in humans are *C. parvum* and *C. ubiquitum* (Xiao and Feng, 2008).

Cryptosporidiosis causes losses in the sheep breeding industry, and threatens human health by spreading through water sources. A systematic review and meta-analysis were conducted to evaluate cryptosporidiosis infection in sheep worldwide. The potential risk factors including region, age, the presence or absence of diarrhoea and *Cryptosporidium* species/genotypes were also analysed. The results describe the regional distribution characteristics of *Cryptosporidium* species and subtypes and may contribute to the prevention and control of *Cryptosporidium* infection.

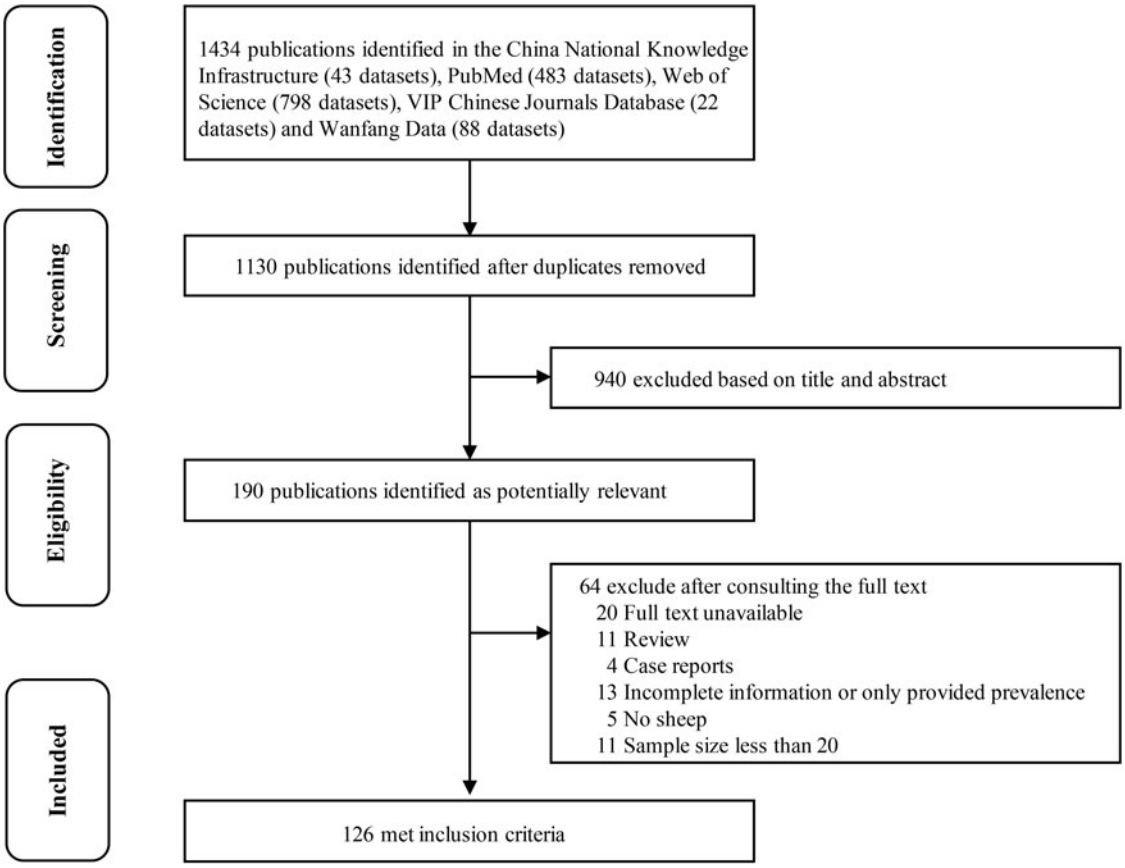

Fig. 1. Flow diagram of the selection of eligible studies.

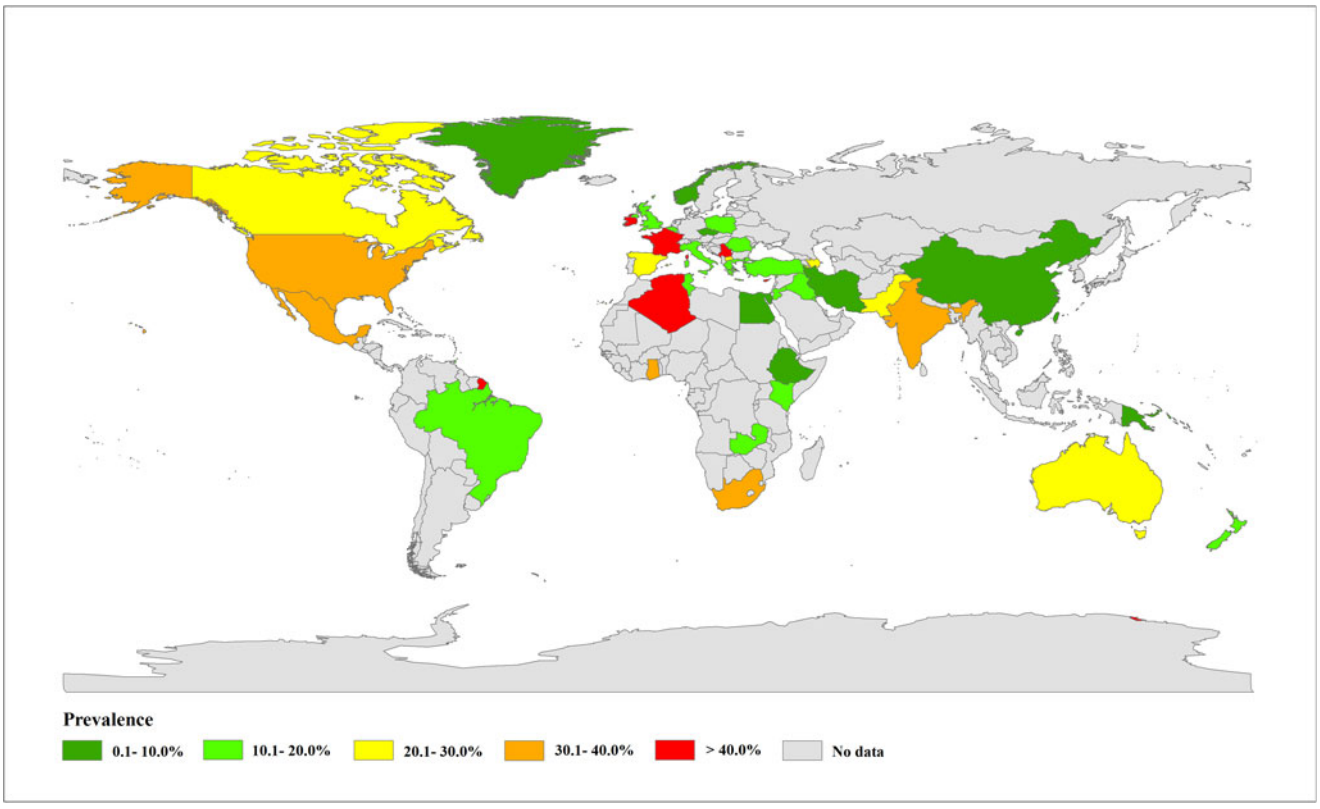

Fig. 2. Map of *Cryptosporidium* infection in sheep across the world. Prevalence ranges are shown in different colours. [The figure was designed by Arcgis 10.2, and the original vector diagram imported in Arcgis was adapted from Natural Earth (http://www.naturalearthdata.com).]

Table 1. Prevalence calculated from pooled published data of *Cryptosporidium* infection in sheep

Country	No. studies	Region	No. tested	No. positive	% Prevalence	% (95% CI)
Azerbaijan	1	Asia	280	75	26.8	21.6–32.0
China	28	Asia	14 483	1398	9.7	9.2–10.1
Cyprus	1	Asia	39	30	76.9	63.1–90.8
India	3	Asia	212	76	35.8	29.3–42.4
Iran	6	Asia	3171	300	9.5	8.4–10.5
Iraq	1	Asia	45	8	17.8	6.2–29.4
Jordan	1	Asia	63	10	15.9	6.6–25.2
Kuwait	2	Asia	462	54	11.7	8.7–14.6
Pakistan	3	Asia	1590	324	20.4	18.4–22.4
Turkey	7	Asia	1420	279	19.6	17.6–21.7
Belgium	1	Europe	137	18	13.1	7.4–18.9
Czech Republic	1	Europe	43	1	2.3	0.0–7.0
France	2	Europe	174	76	43.7	36.2–51.1
Greece	3	Europe	687	74	10.8	8.4–13.1
Ireland	1	Europe	104	51	49.0	39.3–58.8
Italy	2	Europe	1064	118	11.1	9.2–13.0
Macedonia	1	Europe	523	152	29.1	25.2–33.0
Norway	1	Europe	1095	42	3.8	2.7–5.0
Poland	2	Europe	393	61	15.5	11.9–19.1
Romania	1	Europe	175	24	13.7	8.6–18.9
Serbia	1	Europe	126	53	42.1	33.3–50.8
Spain	9	Europe	3192	680	21.3	19.9–22.7
United Kingdom	8	Europe	3161	469	14.8	13.6–16.1
Algeria	4	Africa	958	395	41.2	38.1–44.4
Egypt	1	Africa	120	3	2.5	0.0–5.3
Ethiopia	2	Africa	651	8	1.2	0.4–2.1
Ghana	1	Africa	217	74	34.1	27.7–40.5
Kenya	1	Africa	388	76	19.6	15.6–23.6
South Africa	1	Africa	85	26	30.6	20.6–40.6
Tunisia	1	Africa	89	10	11.2	4.5–17.9
Zambia	1	Africa	152	19	12.5	7.2–17.8
Canada	1	North America	89	21	23.6	14.6–32.6
Greenland	1	North America	43	1	2.3	0.0–7.0
Grenada	1	North America	100	14	14.0	7.1–20.9
Mexico	4	North America	2650	987	37.2	35.4–39.1
Trinidad and Tobago	1	North America	90	18	20.0	11.6–28.4
United States	3	North America	316	105	33.2	28.0–38.4
Brazil	6	South America	1123	190	16.9	14.7–19.1
Australia	9	Oceania	7274	1472	20.2	19.3–21.2
New Zealand	1	Oceania	325	38	11.7	8.2–15.2
Papua New Guinea	1	Oceania	276	6	2.2	0.4–3.9

Materials and methods

Search strategy and selection criteria

Five literature databases were used to search for studies on the global prevalence of *Cryptosporidium* in sheep, namely, PubMed, Web of Science, the China National Knowledge Infrastructure (CNKI), VIP Chinese Journals Database and Wanfang Data. All published studies so far on *Cryptosporidium* in sheep from 15 September 2021 onwards were retrieved. In PubMed, the search formula used was '[((((sheep) OR (ovine)) OR (ram)) OR (ewe)) OR

Table 2. Pooled prevalence of *Cryptosporidium* infection in sheep across the world

					Heterogeneity			Univariate meta-regression		Correlation analysis
	Number of datasets	Total samples	Positive samples	Prevalence % (95% CI)	χ^2	*P* value	I^2 (%)	*P* value	Coefficient (95% CI)	Adj R^2 (%)
Region								0.069	−0.359 (−0.746 to 0.028)	1.90
Asia	53	21 765	2554	14.8 (12.9–16.7)	2549.08	<0.001	98.0			
Europe	33	10 874	1819	20.2 (16.6–23.9)	1941.58	<0.001	98.4			
Africa	12	2660	611	21.7 (11.0–32.5)	761.65	<0.001	98.7			
North America	11	3288	1146	29.8 (20.5–39.2)	331.95	<0.001	97.0			
South America	6	1123	190	20.3 (9.4–31.2)	217.99	<0.001	97.7			
Oceania	11	7875	1516	19.1 (12.7–25.5)	651.70	<0.001	98.5			
Age								<0.001	0.902 (0.555–1.249)	21.85
<3 months	52	11 938	3284	27.8 (23.3–32.4)	2238.90	<0.001	97.8			
3–12 months	12	4054	614	17.2 (11.7–22.7)	308.37	<0.001	96.4			
>12 months	31	8392	895	10.2 (7.8–12.6)	593.60	<0.001	95.1			
Diarrhoea								0.001	1.133 (0.497–1.769)	38.03
Yes	17	1915	844	35.4 (26.8–44.0)	213.10	<0.001	93.4			
No	8	1691	176	11.3 (7.1–15.5)	38.35	<0.001	84.4			
Species/genotypes								0.128	0.363 (−0.105 to 0.831)	1.01
C. parvum	44	16 354	722	4.8 (4.0–5.6)	540.40	<0.001	92.2			
C. ubiquitum	41	19 655	720	3.2 (2.6–3.9)	477.62	<0.001	91.6			
C. xiaoi	33	15 667	1301	6.6 (5.3–8.0)	1362.49	<0.001	97.7			
Other[a]	17	9595	175	1.7 (1.1–2.3)	181.63	<0.001	91.2			
Total	126	47 585	7836	18.9 (17.2–20.6)	8436.00	<0.001	98.5			

Note: [a]Other including *C. bovis*, *C. scrofarum*, *C. andersoni*, *C. hominis*, *C. canis*, *C. ryanae*, *C. suis*, *C. fayeri*, *C. meleagridis*, *C. muris*, *Cryptosporidium* spp., sheep genotype I.

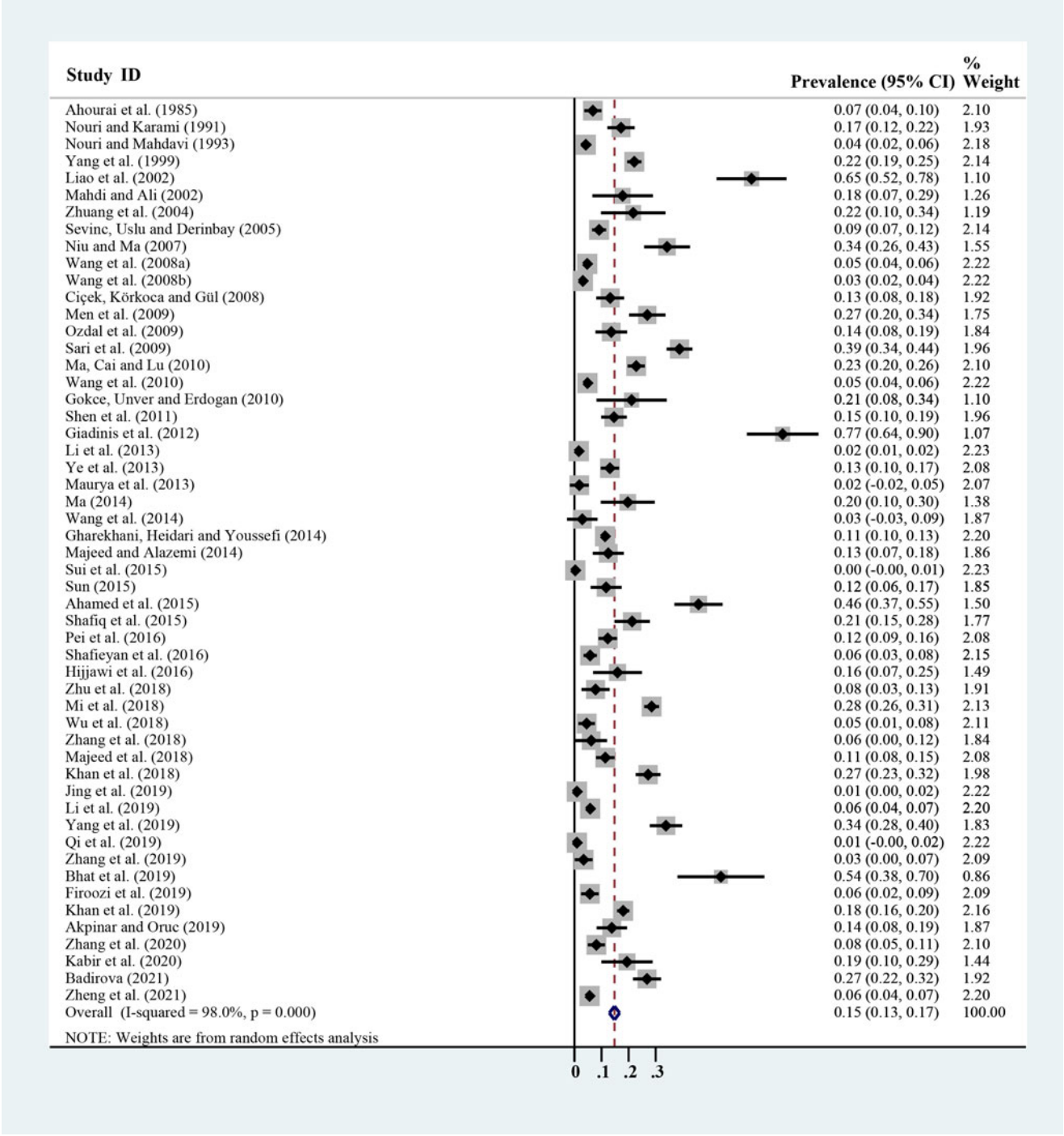

Fig. 3. Forest plot of the prevalence estimates of *Cryptosporidium* infection in sheep in Asia.

(small ruminant)) AND ((*Cryptosporidium*) OR (cryptosporidiosis)]'. In Web of Science, the search formula used was '[((((TS = (sheep)) OR TS = (ovine)) OR TS = (ram)) OR TS = (ewe)) OR TS = (small ruminant)) AND ((TS = (*Cryptosporidium*)) OR TS = (cryptosporidiosis)]'. In the 3 Chinese databases, 'sheep' (Chinese) and '*Cryptosporidium*' (Chinese) were used as keywords. Selected eligible studies were designed and analysed according to the preferred reporting items of the systematic reviews and meta-analysis (PRISMA) statement (Table S1).

The following clauses were used as the criteria for article exclusion: (1) the purpose of the study was not the prevalence of *Cryptosporidium* in sheep; (2) the total number of sheep tested and the number of sheep that tested positive were not provided; (3) there was no clear testing method; (4) the sample was a mixture of specimens from multiple sheep; (5) the study sample size was less than 20; (6) the study was a review or case report. For articles whose full text was not available, the first author was not contacted for more research information and/or statistics.

Quality assessment

Established methods were used to evaluate the quality of studies (Guyatt *et al.*, 2008). Studies were awarded points for aspects that were suitable to assess the quality studies. A study received 1 point for each of the following items: a clear research goal, a clear detection method, a clear research period, analysis involving 3 or more influencing factors and a sample size of more than 200. Studies with scores of 4 or 5 points were considered to be of high

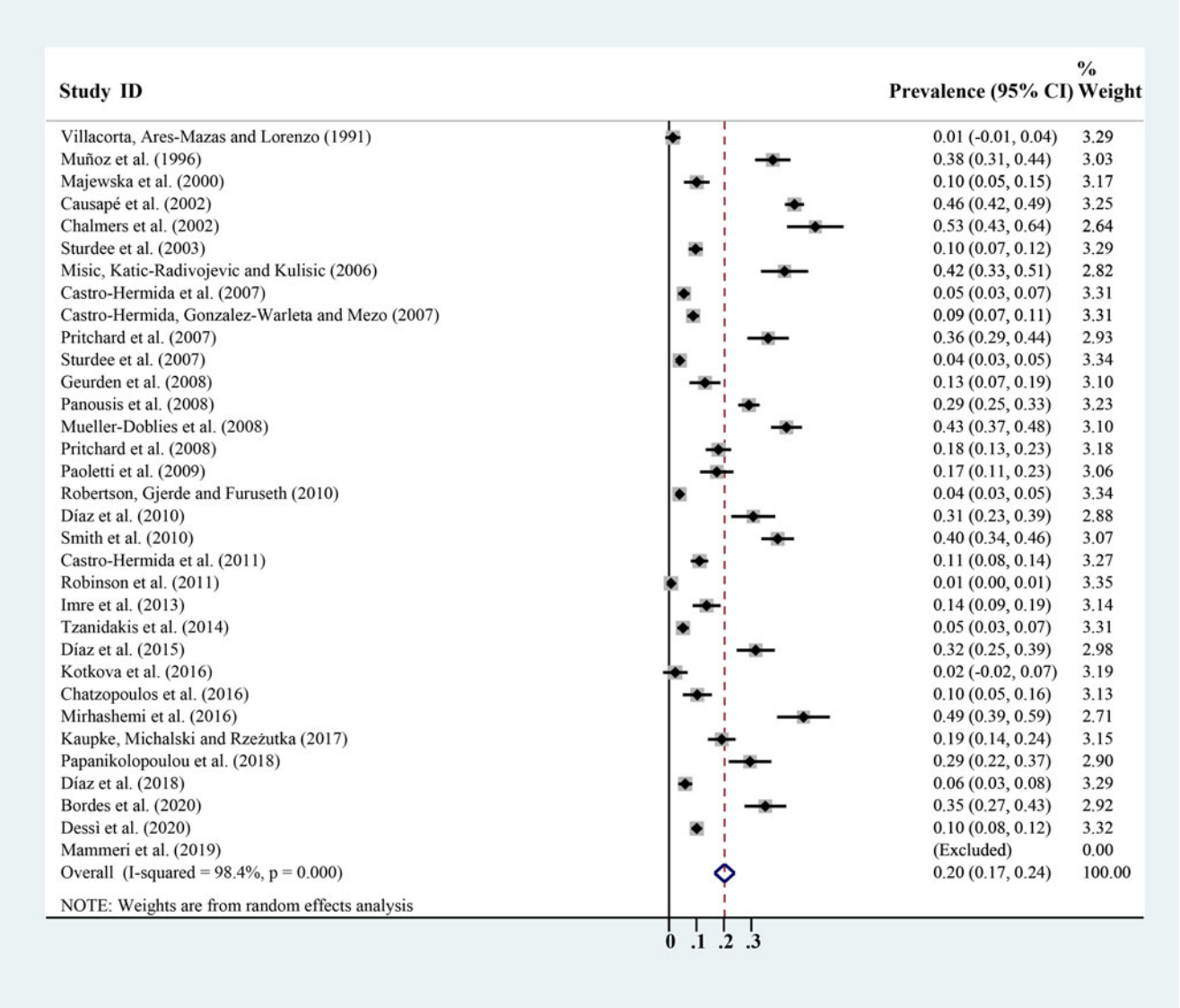

Fig. 4. Forest plot of the prevalence estimates of *Cryptosporidium* infection in sheep in Europe.

quality; studies with scores of 2 or 3 points were considered to be of medium quality; studies with scores of 0 or 1 point were classified as low quality.

Data extraction

All titles, abstracts and full texts were separately screened by 2 authors (YCC and HKQ) and the data were independently extracted. Disagreements were resolved by discussion with JYH. The following information was extracted by YCC and HKQ: study ID (the first author and publication date), country, sampling time, detection method, total samples, positive sample, prevalence, study quality and *Cryptosporidium* species/genotypes (Table S2).

Statistical analysis

All data were analysed using Stata version 14.0. Because of high heterogeneity ($I^2 > 50\%$, $P < 0.1$), a random-effects model was used for meta-analysis. Sensitivity, subgroup and meta-regression analyses were conducted to investigate potential sources of heterogeneity [code: gen ser = sqrt (rate × (1 − rate)/n); metan rate ser, random label (namevar = study); metaninf rate ser, label (namevar = study) random; metan rate ser, label (namevar = study) by (region) random *x*label (0, 0.1, 0.2, 0.3); metareg logr region, wsse (selogr) bsest (reml)]. To test the stability of the data, a sensitivity analysis of the data was done. The effect of selected studies on the pooled prevalence by excluding single studies sequentially was evaluated (Wang *et al.*, 2018). The overall study was evaluated using forest plots, and the publication bias of the study was evaluated using a funnel plot and Egger's tests (Egger *et al.*, 1997). The following potential sources of heterogeneity were examined: region (Asia compared with other regions), age (<3 months compared with the other age group), the presence or absence of diarrhoea (diarrhoea compared with no diarrhoea) and *Cryptosporidium* species/genotypes (*C. parvum* compared with the other species/genotypes). If multiple detection methods were involved in the research, microscopy results were the first choice (Robinson and Chalmers, 2020). Microscopic detection is a simple, fast and cheap method for the detection of *Cryptosporidium* oocysts (Robinson and Chalmers, 2020). Immunofluorescence microscopy is generally considered the gold standard in laboratories in Europe and the United States.

Results

Characteristics of studies

A total of 1434 records were initially identified, and 190 potentially relevant studies were selected for full-text search after

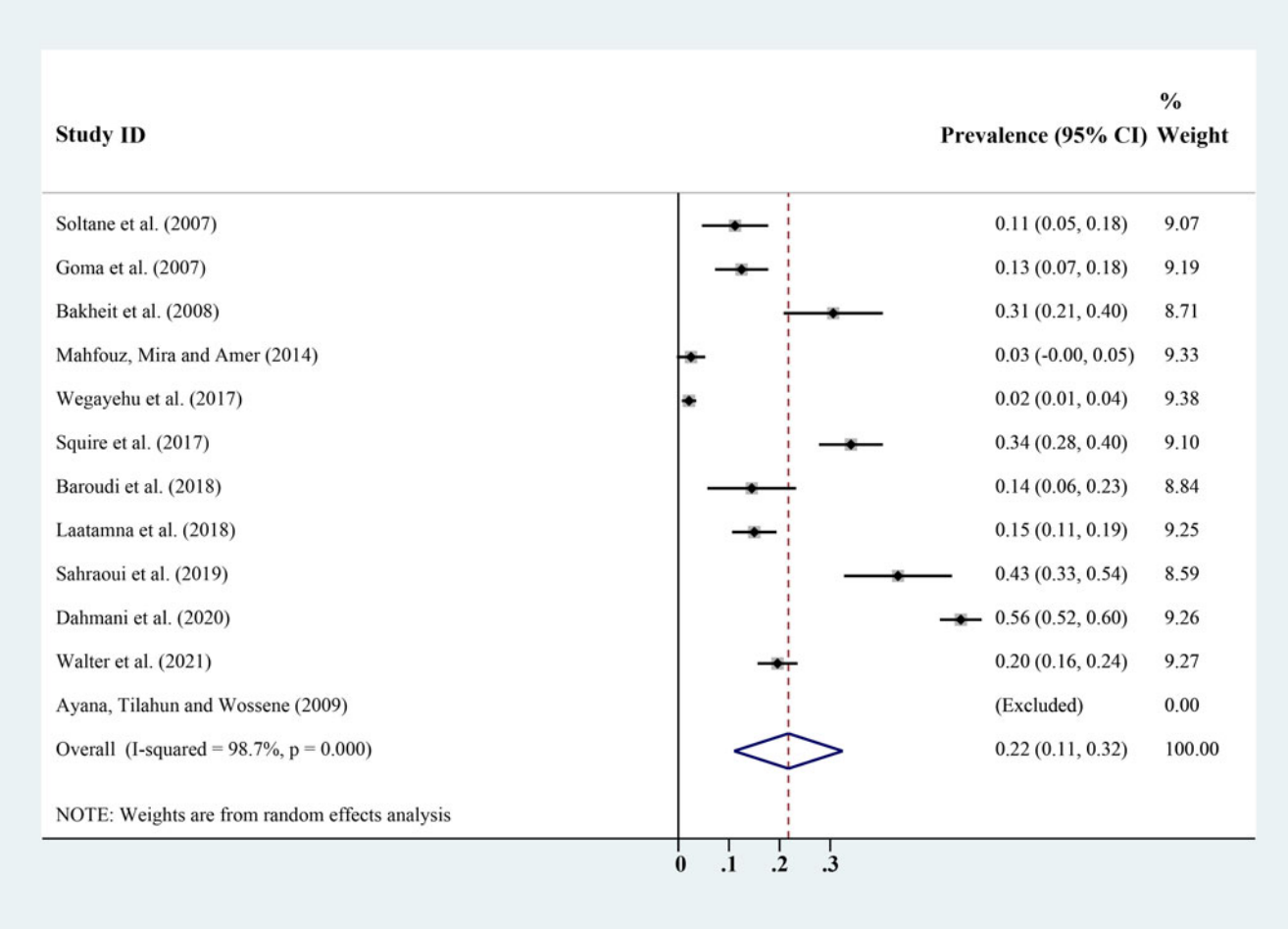

Fig. 5. Forest plot of the prevalence estimates of *Cryptosporidium* infection in sheep in Africa.

screening of the title and abstract. Of these, 11 were review studies, 4 were case reports, 13 had incomplete information or only provided prevalence, 5 did not examine sheep, 11 had sample sizes less than 20 and 20 did not have full text available. In total, 126 articles of sufficient quality were considered for meta-analysis (Fig. 1).

The selected studies came from 41 countries (Fig. 2, Table 1). Fifty-three datasets originated from Asia [Azerbaijan ($n = 1$), China ($n = 28$), Cyprus ($n = 1$), India ($n = 3$), Iran ($n = 6$), Iraq ($n = 1$), Jordan ($n = 1$), Kuwait ($n = 2$), Pakistan ($n = 3$), Turkey ($n = 7$)]. Thirty-three datasets were from countries in Europe [Belgium ($n = 1$), Czech Republic ($n = 1$), France ($n = 2$), Greece ($n = 3$), Ireland ($n = 1$), Italy ($n = 2$), Macedonia ($n = 1$), Norway ($n = 1$), Poland ($n = 2$), Romania ($n = 1$), Serbia ($n = 1$), Spain ($n = 9$) and the United Kingdom ($n = 8$)]. Twelve datasets were from countries in Africa [Algeria ($n = 4$), Egypt ($n = 1$), Ethiopia ($n = 1$), Ghana ($n = 1$), Kenya ($n = 1$), South Africa ($n = 1$), Tunisia ($n = 1$), Zambia ($n = 1$)]. Eleven datasets were from countries in North America [Canada ($n = 1$), Greenland ($n = 1$), Grenada ($n = 1$), Mexico ($n = 4$), Trinidad and Tobago ($n = 1$), United States ($n = 3$)]. Six datasets were from South America [all 6 datasets were from Brazil ($n = 6$)]. Eleven datasets were from countries in Oceania [Australia ($n = 9$), New Zealand ($n = 1$), Papua New Guinea ($n = 1$)] (Tables 1 and 2). The age of sheep was <3 months in 52 datasets, 3–12 months in 12 datasets and >12 months in 31 datasets. Most datasets did not contain any information on health status. Diarrhoea in sheep was reported in 17 datasets, and no diarrhoea was reported in sheep in 8 datasets (Table 2).

Cryptosporidium *infection in sheep by region*

Overall, the estimated *Cryptosporidium* prevalence in sheep ranged from 14.8% [95% confidence interval (CI) 12.9–16.7%] to 29.8% (95% CI 20.5–39.2%) with substantial heterogeneity ($I^2 = 98.5\%$, $P < 0.001$). On the global scale, pooled estimated prevalence of *Cryptosporidium* infection in sheep was 18.9% (95% CI 17.2–20.6%, 7836/47 585) (Table 2). On 6 continents (Table 2, Figs 3–8), the infection rates of *Cryptosporidium* in sheep were 14.8% (Asia), 20.2% (Europe), 21.7% (Africa), 29.8% (North America), 20.3% (South America) and 19.1% (Oceania). The highest number of studies on *Cryptosporidium* infections in sheep originated from Asia ($n = 53$), while the infection rate in Asia was the lowest among the 6 continents, with values below 10.0% in China and Iran. Europe had the second most positive samples, with a total of 13 countries reporting *Cryptosporidium* infection in sheep. The highest prevalence rate was reported for Cyprus [76.9% (95% CI 63.1–90.8%)], and the lowest prevalence rate was in Ethiopia [1.2% (95% CI 0.4–2.1%)] (Table 1).

Prevalence according to age, presence or absence of diarrhoea and Cryptosporidium *species/genotypes*

Subgroup analysis according to age showed that the *Cryptosporidium* infection rate in sheep <3 months was 27.8% (95% CI 23.3–32.4%, 3284/11 938). This was significantly higher than in sheep 3–12 months [17.2%; 95% CI 11.7–22.7%, 614/4054, odds ratio (OR) 2.13, $P < 0.05$] and in sheep >12 months of

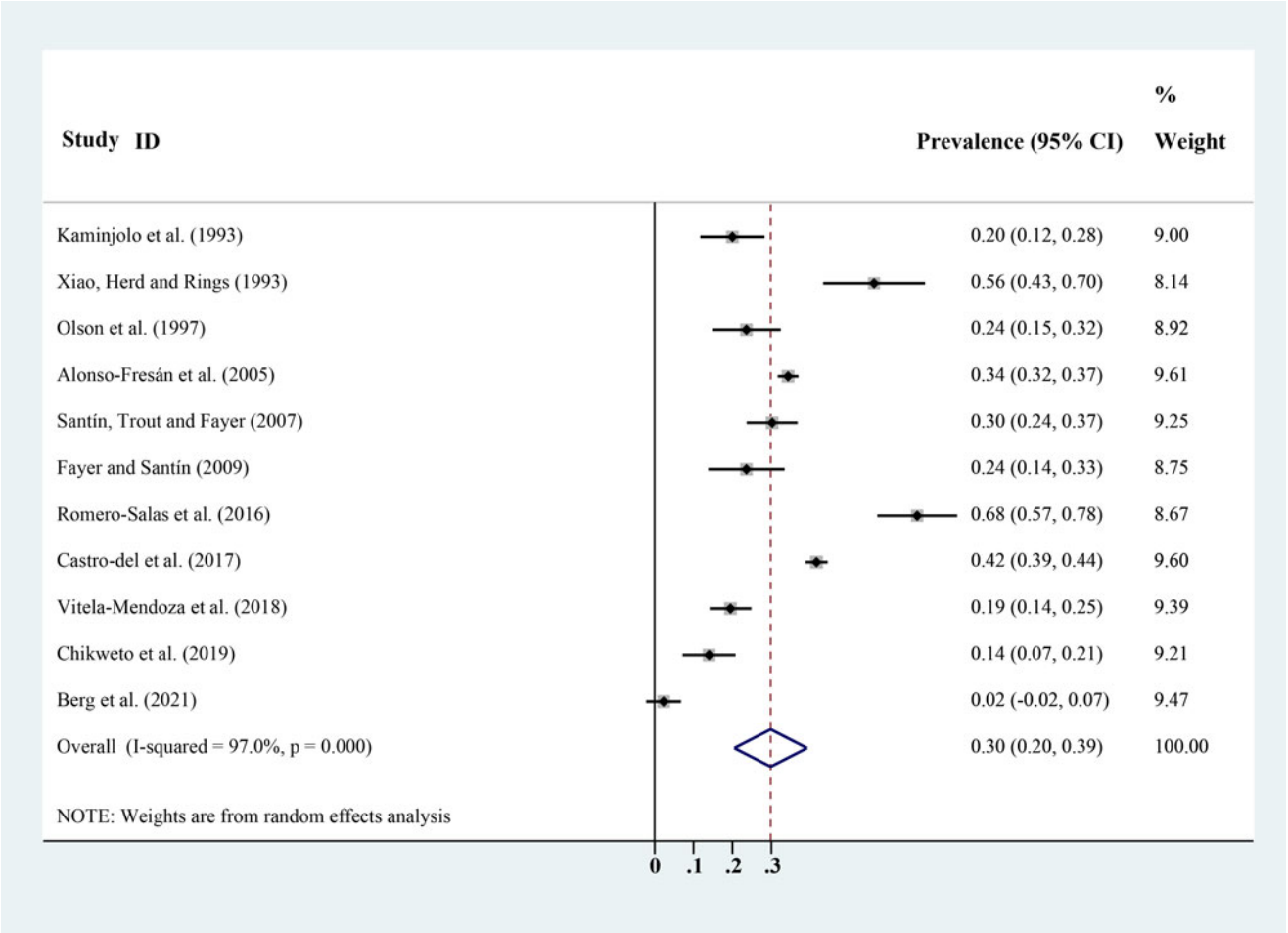

Fig. 6. Forest plot of the prevalence estimates of *Cryptosporidium* infection in sheep in North America.

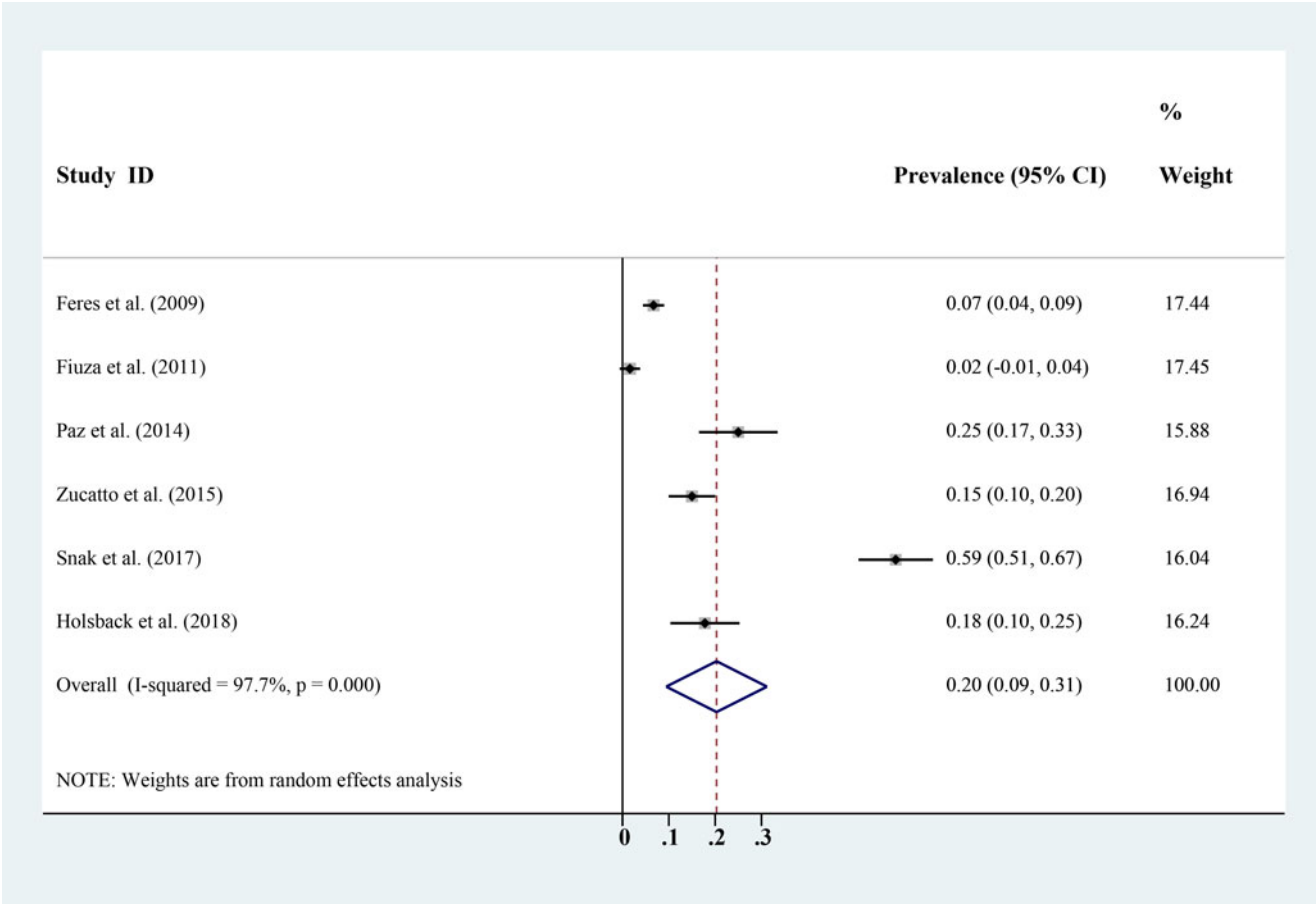

Fig. 7. Forest plot of the prevalence estimates of *Cryptosporidium* infection in sheep in South America.

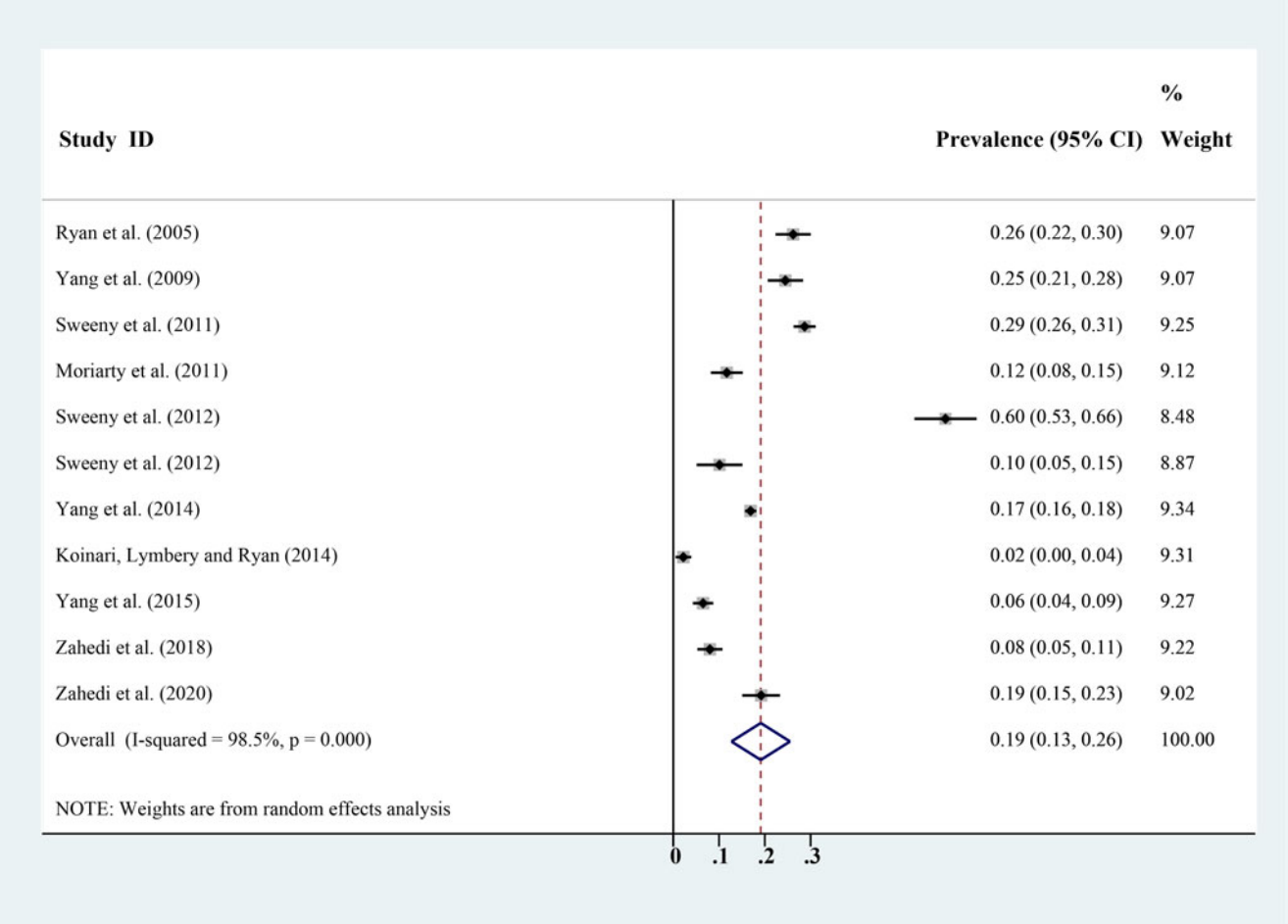

Fig. 8. Forest plot of the prevalence estimates of *Cryptosporidium* infection in sheep in Oceania.

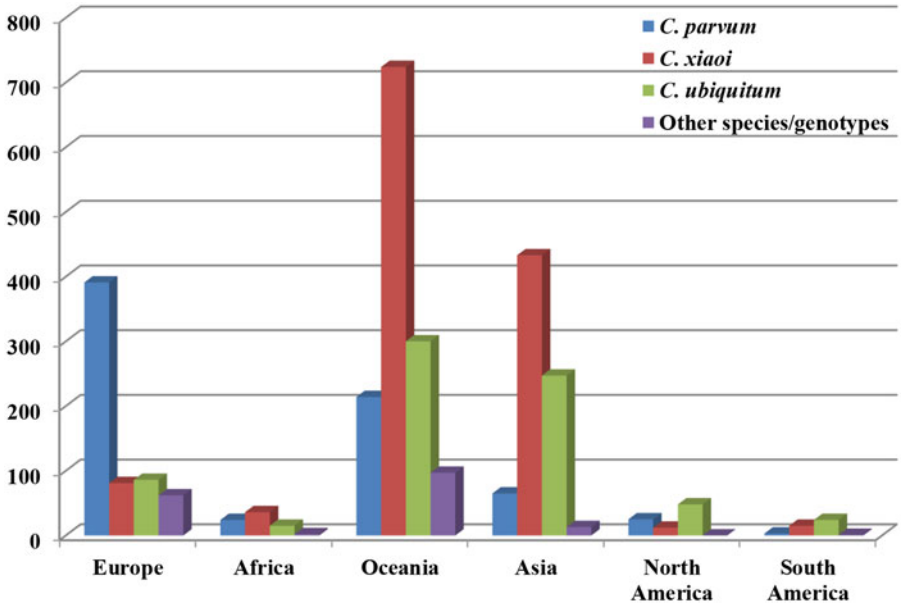

Fig. 9. Diversity of *Cryptosporidium* species/genotypes in sheep across the world. The horizontal axis shows the 6 continents, and the vertical axis shows the number of species/genotypes.

age (10.2%; 95% CI 7.8–12.6%, 895/8392, OR 3.18, $P < 0.05$) (Table 2). The infection rate for sheep with diarrhoea was 35.4% (95% CI 26.8–44.0%, 844/1915), while the infection rate for sheep without diarrhoea was 11.3% (95% CI 7.1–15.5%, 176/1691) (Table 2). Fourteen *Cryptosporidium* species/genotypes (*C. parvum*, *C. ubiquitum*, *C. xiaoi*, *Cryptosporidium bovis*, *Cryptosporidium scrofarum*, *Cryptosporidium andersoni*, *Cryptosporidium hominis*, *Cryptosporidium canis*, *Cryptosporidium ryanae*, *Cryptosporidium*

Table 3. *Cryptosporidium parvum* subtypes in sheep

Country	Author (year of publication)	*C. parvum* positive	*C. parvum* subtypes (No.)	Unidentified subtypes/*C. parvum* positive
Algeria	Baroudi *et al.* (2018)	3	IIaA13G2R1 (3)	0/3
	Sahraoui *et al.* (2019)	16	IIaA21G2R1 (3), IIaA13G2R1 (1), IIdA16G1 (11)	1/16
China	Ye *et al.* (2013)	1	IIaA15G2R1 (1)	0/1
	Mi *et al.* (2018)	15	IIaA15G2R1 (5), IIaA17G2R1 (1), IIdA19G1 (2), IIdA18G1 (1)	6/15
	Qi *et al.* (2019)	1	IIdA15G1 (1)	0/1
Jordan	Hijjawi *et al.* (2016)	3	IIaA19G2R1 (2), IIaA16G1R1 (1)	0/3
Kuwait	Majeed *et al.* (2018)	16	IIdA20G1 (13), IIaA15G2R1 (2)	1/16
Turkey	Kabir *et al.* (2020)	13	IIaA15G2R1 (3), IIaA13G2R1 (3), IIaA11G2R1 (1), IIaA12G3R1 (1), IIaA14G3R1 (1), IIaA13G4R1 (1)	3/13
Belgium	Geurden *et al.* (2008)	1	IIaA15G2R1 (1)	0/1
France	Bordes *et al.* (2020)	10	IIaA16G3R1 (2), IIaA13G2R1 (1), IIdA21G2 (1), IIdA15G1 (1)	5/10
	Mammeri *et al.* (2019)	23	IIaA15G2R1 (22), IIaA16G3R1 (1)	0/23
Greece	Papanikolopoulou *et al.* (2018)	16	IIaA15G2R1 (4), IIaA20G1R1 (5), IIdA15G1 (1), IIdA16G1 (3)	3/16
	Tzanidakis *et al.* (2014)	7	IIdA4G2T14, IIdA4G3T13	0/7
Italy	Dessì G *et al.* (2020)	11	IIaA15G2R1 (5), IIdA20G1 (1)	5/11
Poland	Kaupke *et al.* (2017)	2	IIaA17G1R1 (2)	0/2
Romania	Imre *et al.* (2013)	20	IIaA17G1R1 (2), IIaA16G1R1 (1), IIdA20G1 (2), IIdA24G1 (1), IIdA22G2R1 (1)	13/20
Spain	Díaz *et al.* (2015)	32	IIaA15G2R1 (16), IIaA16G3R1 (8), IIaA13G1R1 (1), IIaA14G2R1 (1)	6/32
	Díaz *et al.* (2018)	13	IIaA15G2R1 (6), IIaA14G2R1 (2)	5/13
	Díaz *et al.* (2010)	14	IIaA16G3R1 (7), IIaA15G2R1 (3)	4/14
United Kingdom	Smith *et al.* (2010)	31	IIaA17G1R1 (9), IIaA15G2R1 (1), IIaA17G2R1 (1)	20/31
Australia	Yang *et al.* (2014)	61	IIaA15G2R1 (5), IIdA18G1 (23), IIdA19G1 (10)	23/61
	Yang *et al.* (2015)	4	IIdA18G1 (4)	0/4
	Sweeny *et al.* (2011)	54	IIdA20G1 (18)	36/54
	Sweeny *et al.* (2012)	28	IIdA20G1 (28)	0/28
Papua New Guinea	Koinari *et al.* (2014)	4	IIaA15G2R1 (2), IIaA19G4R1 (1)	1/4
Brazil	Paz *et al.* (2014)	3	IIaA15G2R1 (3)	0/3
Total		**402**	**IIa (141), IId (129)**	**132/402**

suis, *Cryptosporidium fayeri*, *Cryptosporidium meleagridis*, *Cryptosporidium muris* and sheep genotype I) were detected in sheep globally. The prevalence rate of *C. parvum* was 4.8% (95% CI 4.0–5.6%, 722/16 354), of *C. xiaoi* 6.6% (95% CI 5.3–8.0%, 1301/15 667) and of *C. ubiquitum* 3.2% (95% CI 2.6–3.9%, 720/19 655) (Table 2). The distribution of the *Cryptosporidium* species/genotypes found in sheep across the 6 continents was as follows: *C. parvum* was most common in Europe while *C. xiaoi* was most common in Oceania, Asia and Africa and *C. ubiquitum* was most common in North America and South America (Fig. 9). Proportions of subgenotype families IIa and IId of *C. parvum* were 35.1% (141/402) and 32.1% (129/402). The most common subgenotypes IIdA20G1 and IIaA15G2R1 of *C. parvum* were reported in 15.4% (62/402) and 19.7% (79/402) of positive samples. Subgenotype family IId was most common in Oceania, Asia and Europe, whereas IIa was obviously distributed evenly in all evaluated regions (Table 3). Proportions of subgenotype families XIIa and XIId of *C. ubiquitum* were 90.0% (216/240) and 3.8% (9/240). XIIa was most common in Oceania, Europe, Asia and Africa, whereas XIId was found in Oceania (Table 4).

Sensitivity analysis and publication bias

Sensitivity analysis showed that the analysis was reliable (Figs S1–S6). A funnel plot was used to measure the publication bias of the selected studies. An asymmetrical funnel plot, with some points falling outside the funnel, indicates publication bias. The funnel plot showed obvious asymmetry (Fig. 10), and $P < 0.001$ was obtained using Egger's test (Table S3), indicating that obvious publication bias was detected.

Sources of heterogeneity by meta-regression analysis

The result indicated substantial heterogeneity ($I^2 = 98.5\%$, $P < 0.001$). Univariate meta-regression analysis was conducted to further identify the source of heterogeneity. The results showed that

Table 4. *Cryptosporidium ubiquitum* subtypes in sheep

Country	Author (year of publication)	*C. ubiquitum* positive	*C. ubiquitum* subtypes (No.)	Unidentified subtypes/*C. ubiquitum* positive
Ghana	Squire *et al.* (2017)	2	XIIa (1)	1/2
China	Mi *et al.* (2018)	64	XIIa (55)	9/64
	Qi *et al.* (2019)	1	XIIa (1)	0/1
	Li *et al.* (2019)	21	XIIa (21)	0/21
	Li *et al.* (2016)	4	XIIa (4)	0/4
	Wu *et al.* (2018)	8	XIIa (8)	0/8
Iran	Firoozi *et al.* (2019)	5	XIIa (2)	3/5
Kuwait	Majeed *et al.* (2018)	3	XIIa (3)	0/3
Italy	Dessi *et al.* (2020)	4	XIIa (4)	0/4
Spain	Díaz *et al.* (2018)	1	XIIa (1)	0/1
Australia	Yang *et al.* (2014)	88	XIIa (88)	0/88
	Yang *et al.* (2015)	9	XIId (9)	0/9
	Zahedi *et al.* (2018)	30	XIIa (28)	2/30
Total		**240**	**XIIa (216), XIId (9)**	**15/240**

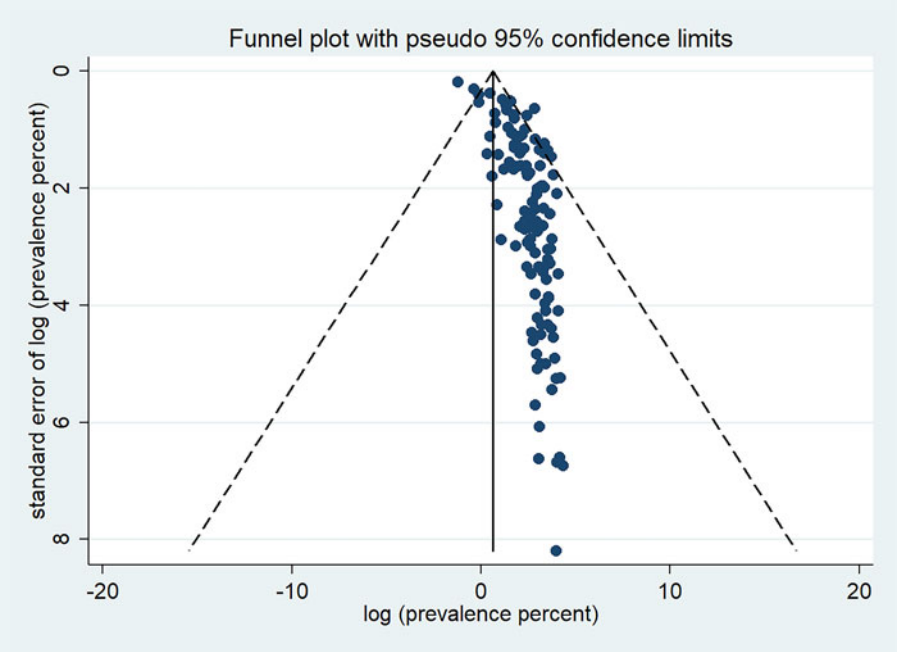

Fig. 10. Funnel plot for examination of publication bias of the prevalence estimates of *Cryptosporidium* in sheep across the world.

age ($P < 0.001$) and presence or absence of diarrhoea ($P = 0.001$) were factors that fostered heterogeneity. Region ($P = 0.069$) and species/genotypes ($P = 0.128$) were not related to heterogeneity (Table 2).

Discussion

A reliable estimate of the prevalence of *Cryptosporidium* in sheep was produced through a meta-analysis based on datasets comprising a large population of sheep ($n = 47\,585$) across 41 countries on 6 continents. In Europe, the highest infection rate was 49.0% (95% CI 39.3–58.8%) in Ireland (Mirhashemi *et al.*, 2016), while the lowest rate was 2.3% (95% CI 0.0–7.0%) in the Czech Republic (Kotkova *et al.*, 2016). *Cryptosporidium* infection in sheep differs not only between countries but also in different regions of the same country. In China an infection rate of only 0.9% (3/318) was reported for sheep in Xinjiang (Qi *et al.*, 2019), while a much higher infection rate of 13.1% (49/375) was found in sheep in Inner Mongolia (Ye *et al.*, 2013).

In the age subgroup analysis, the *Cryptosporidium* infection rate in sheep under 3 months of age was significantly higher than in sheep 3–12 months of age and in sheep older than 12 months. This is supported by studies in China (Wang *et al.*, 2010; Zhang *et al.*, 2020), though other studies documented slightly divergent findings. Ye *et al.* (2013) reported that the *Cryptosporidium* infection rate in sheep aged 3–12 months was higher (26.7%; 20/70) than in sheep less than 3 months of age (18.4%; 16/87) or in sheep older than 12 months (6.1%; 13/213). Mi *et al.* (2018) investigated *Cryptosporidium* infection in sheep in 10 provinces in China and confirmed that the highest infection rate occurred between 3 and 12 months of age (34.6%; 116/335), followed by sheep less than 3 months of age (28.2%; 108/383) and older than 12 months of age (22.4%; 71/317). In general, *Cryptosporidium* infection in sheep under 3 months

of age is paid more attention. However, high rates of *Cryptosporidium* infection in other age groups suggest that different management measures in different geographical areas may play a role. The global prevalence of *Cryptosporidium* infection in sheep suffering diarrhoea was approximately 3 times higher than in sheep without diarrhoea ($P < 0.05$). However, most of the publications considered in our analysis did not mention whether feces samples represented sheep with diarrhoea and inadequate data collection may also affect the stability of the results. Due to the limited amount of suitable data, the relationship between infection and diarrhoea should be interpreted with caution. The results showed that feces of healthy sheep may also contain *Cryptosporidium* oocysts. Therefore, prevention of *Cryptosporidium* transmission in healthy sheep should not be neglected. In a 2020 study from Algeria, a *Cryptosporidium* infection rate of 100% (280/280) in neonatal lambs with diarrhoea was reported (Dahmani *et al.*, 2020). Therefore, timely control of sheep diarrhoea may also be an effective way to prevent the spread of *Cryptosporidium*.

As mentioned in a previous review, *C. parvum* was the dominant species in sheep in Europe, while *C. xiaoi* was the dominant species in Australia and *C. ubiquitum* appeared to dominate in the Americas and Asia (Ryan *et al.*, 2014). Compared with previous study the prevalence of *C. xiaoi* in Asian sheep appeared to increase in recent years. Altogether *C. parvum*, *C. xiaoi* and *C. ubiquitum* are still the dominant species in sheep. Other species/genotypes that occasionally infected sheep such as *C. hominis* (Ryan *et al.*, 2005; Pritchard *et al.*, 2008; Kaupke *et al.*, 2017), *C. canis* (Zhang *et al.*, 2018), *C. fayeri* (Ryan *et al.*, 2005), *C. meleagridis* (Zucatto *et al.*, 2015), *C. muris* (Mahdi and Ali, 2002; Kotkova *et al.*, 2016; Zhang *et al.*, 2020), *C. suis* (Ryan *et al.*, 2005; Goma *et al.*, 2007), *C. andersoni* (Ryan *et al.*, 2005; Wang *et al.*, 2010; Sweeny *et al.*, 2011; Koinari *et al.*, 2014; Yang *et al.*, 2014; Hijjawi *et al.*, 2016) and *C. bovis* (Ryan *et al.*, 2005; Pritchard *et al.*, 2008; Yang *et al.*, 2009; Smith *et al.*, 2010; Mirhashemi *et al.*, 2016; Kaupke *et al.*, 2017; Squire *et al.*, 2017) may play a role in zoonotic transmission. *Cryptosporidium ryanae* (Mirhashemi *et al.*, 2016), *C. scrofarum* (Ryan *et al.*, 2005; Koinari *et al.*, 2014; Yang *et al.*, 2014) and sheep genotype I (Sweeny *et al.*, 2011; Yang *et al.*, 2014) were also detected in sheep, but there was currently no evidence of human infection by these species/genotypes. The XIIa subgenotype family of *C. ubiquitum* was found in sheep in Iran (Firoozi *et al.*, 2019), Italy (Dessi *et al.*, 2020), Spain (Díaz *et al.*, 2018), Ghana (Squire *et al.*, 2017), Kuwait (Majeed *et al.*, 2018), China (Li *et al.*, 2016; Mi *et al.*, 2018) and Australia (Yang *et al.*, 2014), while XIId was only detected in Australian sheep (Yang *et al.*, 2015). It was reported from Canada, Turkey, the United States and the United Kingdom that *C. ubiquitum* XIIa subgenotypes were found to infect humans, and XIId subgenotypes were also found to infect humans in the United States (Li *et al.*, 2014). IIaA15G2R1 was the most widely distributed subtype found in sheep across the world (Geurden *et al.*, 2008; Díaz *et al.*, 2010, 2015, 2018; Smith *et al.*, 2010; Ye *et al.*, 2013; Koinari *et al.*, 2014; Paz e Silva *et al.*, 2014; Yang *et al.*, 2014; Majeed *et al.*, 2018; Mammeri *et al.*, 2019) and was the dominant *C. parvum* subgenotype infecting sheep. In recent years, there was an increasing occurrence of *C. parvum* IIa in humans, especially in Colombia and Mexico (Urrea-Quezada *et al.*, 2018; Higuera *et al.*, 2020). Feng *et al.* (2018) reported IId subtypes mainly in lambs and goat kids in some European and Middle Eastern countries. In our analysis, other IId subtypes, including IIdA15G1 (Papanikolopoulou *et al.*, 2018; Qi *et al.*, 2019; Bordes *et al.*, 2020), IIdA16G1 (Papanikolopoulou *et al.*, 2018; Sahraoui *et al.*, 2019), IIdA18G1 (Yang *et al.*, 2014, 2015; Mi *et al.*, 2018), IIdA19G1 (Yang *et al.*, 2014; Mi *et al.*, 2018), IIdA24G1 (Imre *et al.*, 2013), and other subgenotypes were also detected in sheep. *Cryptosporidium xiaoi* generally did not infect humans (Guo *et al.*, 2021). Although *C. xiaoi* was detected in HIV/AIDS patients (Adamu *et al.*, 2014), the authors did not describe *C. xiaoi* as zoonotic. In earlier studies, Robertson (2009) found little evidence that human cryptosporidiosis was contracted from sheep and the transmission of cryptosporidiosis between sheep and animal breeders was only occasionally suspected (Mahdi and Ali, 2002). In spite of this, many *Cryptosporidium* species/genotypes infecting sheep were found to be zoonotic. Overall, the *Cryptosporidium* infection rate in sheep slightly increased from 13.5% (1837/13 631) during 2011–2015 to 19.0% (2746/14 458) during 2016–2021 (Table S2). Therefore, measures should be considered to reduce and/or mitigate risks associated with contact between breeders and sheep to prevent the transmission of *Cryptosporidium* from sheep to humans.

Five databases were selected for comprehensive literature retrieval, which covers a large time span and a large total sample size. However, there are also some limitations associated. First, there were only few reports on *Cryptosporidium* infection in sheep from some countries, with some countries only having 1 report published within the last 30 years. As a result, *Cryptosporidium* infections in sheep in these countries are not yet fully understood. Second, all available data were not fully included; there were some data associated with unpublished literature, conference abstracts and other data sources that were not considered suitable for this analysis. Moreover, some articles could not be downloaded in full, and these publications were thus excluded. Third, when it came to explaining the source of heterogeneity, only certain factors were analysed. Other aspects such as sheep breed and feeding may also have contributed to data heterogeneity. However, even with these constraints, the results of the current study are close to the true global prevalence of *Cryptosporidium* in sheep.

Conclusions

This analysis shows that *Cryptosporidium* infections in sheep are widespread (18.9%) globally and can lead to disease and, consequently, huge economic losses in the sheep breeding industry. Risk factors related to cryptosporidiosis in sheep, such as age, should be accounted for so that farmers can apply effective management plans according to local conditions that may differ between geographical regions and environments, and prevent zoonotic transmission. In conclusion, the result provides a theoretical basis for the prevention and control of *Cryptosporidium* infection.

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Data availability. All data generated or used during the study appear in the submitted article.

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