Wang et al. BMC Veterinary Research (2025) 21:136
https://doi.org/10.1186/s12917-025-04571-9

BMC Veterinary Research

SYSTEMATIC REVIEW

Open Access

Prevalence of hepatitis E virus in domestic animals in the Chinese mainland: a systematic review and meta-analysis

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Abstract

Background China, especially the Chinese mainland, is a highly endemic area of hepatitis E, and its incidence rate has been increasing in recent years. Hepatitis E virus (HEV) is the causative agent of hepatitis E, with a variety of domestic animals as potential hosts. The shift in the main epidemic strain and the increasing trend of zoonotic HEV infection in the Chinese mainland need urgent attention. This systematic review aimed to provide a summary of HEV detection and its characteristics in domestic animals in the Chinese mainland.

Methods A total of 1,019 literatures published in Chinese and English before 2024.1.15 were retrieved from four databases including Pubmed, ScienceDirect, Wan Fang and CNKI. Eventually, 73 eligible studies were included in this review, involving HEV detection data of 64,813 samples collecting from 13 kinds of common domestic animals, locating in 28 provinces and municipalities.

Results HEV antibodies and RNA were detected among 12 and 7 kinds of domestic animals respectively, with the pooled prevalence of 37.94% (95% CI:32.28–43.77) and 7.62% (95% CI: 5.56–9.96) respectively. The prevelance of HEV for swine samples was higher than other species. In addition, the prevalence of HEV among Tibetan swine, cattle and goats were also at a relatively high level. Further subgroup analysis focusing on comprehensive data from swine was conducted. The results showed, the seroprevalence of HEV antibodies gradually decreased over the time of sampling. HEV RNA was detected in various samples, including bile, feces, liver, and serum. The detection rate for fecal samples was the highest, which was 16.60% (95% CI: 12.17–21.55). Further genotyping of HEV RNA was classified. The results warn us about the circulation of genotype 3 HEV in the eastern region of the Chinese mainland.

Conclusion The results collected from the included studies provided valuable data on HEV prevalence across various species, and the characteristics, trends, and potential influencing factors were fully discussed. This review provides public health professionals, policymakers, and researchers with comprehensive and up-to-date research data on zoonotic HEV.

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Keywords Hepatitis E virus, Zoonotic diseases, Systematic review, Meta-analysis

Introduction

Hepatitis E virus (HEV), species *Paslahepevirus balayani*, genus *Paslahepevirus*, is the causative agent of hepatitis E. According to World Health Organization estimates, the epidemic of HEV affects 20 million people globally every year, among whom pregnant women infected with HEV are prone to develop severe hepatitis and have a high fatality rate [1]. Prevention and control of HEV infection have become a public health challenge.

Currently, eight genotypes of HEV have been identified. Genotypes 1 and 2 only infect humans, while genotypes 3 and 4 can cause zoonotic infections, with a variety of mammals as potential hosts [2]. Food contaminated with feces or sewage or animal products that have not been subjected to strict sterilization treatment are the potential zoonotic transmission pathways. Genotypes 5 and 6 were found in wild boars in Japan [3], and genotypes 7 and 8 were detected in camels in Dubai and Xinjiang, China, respectively [4, 5]. One study reported human infection of genotype 7 HEV [6]; however, no further evidence of human infection has been confirmed.

China, especially the Chinese mainland, is a highly endemic area of hepatitis E, and its incidence rate has been increasing in recent years [7]. From 1986 to 1988, there was an outbreak of hepatitis E in Xinjiang Uygur Autonomous Region, infecting more than 200,000 people. Studies have confirmed that the circulating strain was genotype 1 HEV. With the continuous improvement of sanitary conditions in the Chinese mainland, the transmission pathway of HEV has changed from contaminated water sources to foodborne infection, the number of outbreaks has considerably reduced, and the main epidemic strain of HEV has shifted from genotype 1 to genotype 4 [8]. Meanwhile, since 2007, genotype 3 HEV has been detected in patients and pigs in the eastern region of the Chinese mainland. Because genotypes 3 and 4 HEV are largely zoonotic, the shift in the main epidemic strain and the increasing trend of zoonotic HEV infection in the Chinese mainland need urgent attention.

The livestock industry in the Chinese mainland is the pillar industry of agriculture and is also closely related to people's daily lives. However, many domestic animals, such as pigs, cows, and the results showed, are the potential sources of zoonotic HEV transmission. Relevant studies focusing on the prevalence of HEV among these species, the role of animal hosts in the transmission chain of HEV, and the potential transmission pathway across species have been increasing over the past years. However, reviews and meta-analyses focusing on the findings and progress of research are still deficient. Hence, this systematic review aimed to provide a summary of HEV detection and its characteristics in domestic animals in the Chinese mainland. Furthermore, this review provides public health professionals, policymakers, and researchers with comprehensive and up-to-date research data on zoonotic HEV.

Materials and methods

Guidelines and search strategy

The Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines [9] was followed throughout the whole study. PRISMA checklist was submitted and items involved were stated in line. Two researchers were investigated independently in this study.

Articles published in English or Chinese were all considered in this review. Four databases, including Pubmed, ScienceDirect, the Wan Fang Database and the China National Knowledge Infrastructure (CNKI), the latter two of which are databases of literatures published in Chinese, were searched comprehensively for published articles containing terms in the title, abstract or keywords according to the following query: (Hepatitis E Virus) and (China) and (domestic animals or livestock or pig or swine or cattle or cow or yak or goat or sheep or horse or camel or rabbit or cat or dog). The references of studies published before 2024.1.15 were imported into NoteExpress.

Selection process and data collection

Several rounds of screening were performed. The primary screening was conducted through titles and abstracts, followed by intensive reading of the full text. A final assessment was conducted during the process of data collection.

The following conditions should be satisfied as an included study for this review: (1) The article was published in a peer reviewed journal with full text available. (2) The article was an original cross sectional or descriptive study. (3) The subjects were farmed and collected in the Chinese mainland, the location of which was accurate to the province or municipality. (4) The sample size in the same subgroup was greater than 30, and the raw data was provided with both positive and total numbers. (5) If both RNA and antibodies were tested in serum samples in one study, the samples tested by each method should be consistent, otherwise only the results of the test with a larger sample size will be included. (6) Duplicated studies were excluded.

A standardized table was designed in Microsoft Excel to extract data from articles, including: the first author and the publication year, the sampling period, the species of animals, the type of samples, the sampling location, the method of detection, the number of positive and total animals.

The risk of study bias was assessed simultaneously using tool developed by Hoy et al. [10]. Ten items were included: the study's target population representation, the sampling representation, the form of random selection, the likelihood of nonresponse bias, the approach of data collection, the acceptable definition, the validity and reliability of detection method, the mode of data collection, the length of the study period, the numerator(s) and denominator(s). One point was awarded for each item. The papers with 7–10 points were considered as low risk of study bias and proceeded to further analysis.

Data synthesis and statistical analysis

The pooled prevalence was defined as the number of positives divided by the total, synthesized using meta-analysis package in Stata 16, data conversion by metaprop command and visualized using the Forest plots. The 95% confidence intervals (CI) were estimated, as well as p values. The I^2 statistic was used representing heterogeneity between studies. $I^2 > 50\%$ was considered as high heterogeneity, and $I^2 \leq 50\%$ as low heterogeneity, random or fixed effects model was applied respectively. The possible causes of heterogeneity were explored through subgroup analysis. Publication bias were evaluated by Egger's test. Influence analysis was conducted, using random pooling model.

Results

Search and selection process

A total of 1019 literatures, 190 ones published in English and 829 ones published in Chinese were searched from four databases. After that, 687 distinct records were screening preliminarily through title and abstract, and further, 190 reports with full-text available were sought for thorough screening. Eventually, a total of 73 studies, published between 2004 and 2022, were considered eligible with low risk of study bias, and were included in this review (Fig. 1). There were 30 studies published in English and 43 ones in Chinese. Each included study with the data in detail was listed in the Table 1. Overall, studies of 13 kinds of common domestic animals, locating in 28 provinces and municipalities in the Chinese mainland were involved in this review (Fig. 2). The total samples tested for HEV antibodies or RNA or both was 64,813.

Pooled prevalence of HEV antibody detection

Eighty-six sets of data extracted from 42 studies were included to calculate the pooled prevalence of HEV antibody detection. Among the total of 39,846 samples tested, 13,727 were positive for HEV antibodies, with a total positive rate of 37.94% (95% CI: 32.28–43.77) (Fig. 3).

Pooled prevalence of HEV RNA detection

Sixty-four sets of data extracted from 42 studies were included to calculate the pooled prevalence of HEV RNA detection. Among the total of 28,471 animals tested, 2116 were positive for HEV RNA, with a total positive rate of 7.62% (95% CI: 5.57–9.96) (Fig. 4).

HEV prevalence categorized by species

The samples collected from 12 kinds of domestic animals were tested for HEV antibodies (Table 2). The pooled prevalence of HEV antibodies in swine samples was 61.03% (95% CI: 51.39–70.26), which was far higher than that of other species. The positive rate in Tibetan swine was 38.70% (95% CI: 28.68–49.23), which was also higher than the overall pooled prevalence rate. In addition, the positive rates among cattle and goats were at a relatively high level, which were 31.21% (95% CI: 13.68–52.09) and 29.30% (95% CI: 14,88–46.19), respectively. The pooled prevalence rates for cats and yaks were relatively low, which were 6.28% (95% CI: 3.29–10.72) and 9.51% (95% CI: 1.83–21.95), respectively.

HEV RNA was detected in the samples collected from eight kinds of domestic animals. The results showed that for the pooled prevalence rates of HEV RNA for the samples collected from swine, Tibetan swine, and goat were 9.82% (95% CI: 7.12–12.88), 9.30% (95% CI: 6.84–12.08), and 8.26% (95% CI: 5.19–11.92), respectively, which were higher than the overall pooled prevalence rate. HEV RNA was not detected in the samples collected from cows.

Subgroup analysis of HEV detection in swine

Since swine were extensively studied, we focused on comprehensive data from swine to conduct further subgroup analysis (Table 3). The seroprevalence of HEV antibodies gradually decreased over the time of sampling, from the highest peak of 70.65% (95% CI: 50.29–87.46, before 2010) down to 21.52% (95% CI: 20.01–23.07, after 2020). The positive rate was the highest for the samples collected from the eastern region of the Chinese mainland, which was 75.18% (95% CI: 67.61–82.06), and was the lowest for the samples collected from the northeastern region, which was 48.52% (95% CI: 16.96–80.76). The HEV RNA prevalence rate for samples collected from 2015 to 2020 was 5.29% (95% CI: 2.45–9.10), which was lower than that for samples collected earlier. HEV RNA was detected in various samples, including bile, feces, liver, and serum. The detection rate for fecal samples was the highest, which was 16.60% (95% CI: 12.17–21.55). The prevalence rate in descending order was as follows: serum, liver, and bile samples. HEV RNA was not detected in the lymphonodi mesenterici and spleen samples of swine. The real-time PCR and RT-nested PCR methods were used to test HEV RNA, with positive rates of 4.75% (95% CI: 2.22–8.11) and 11.20% (95%

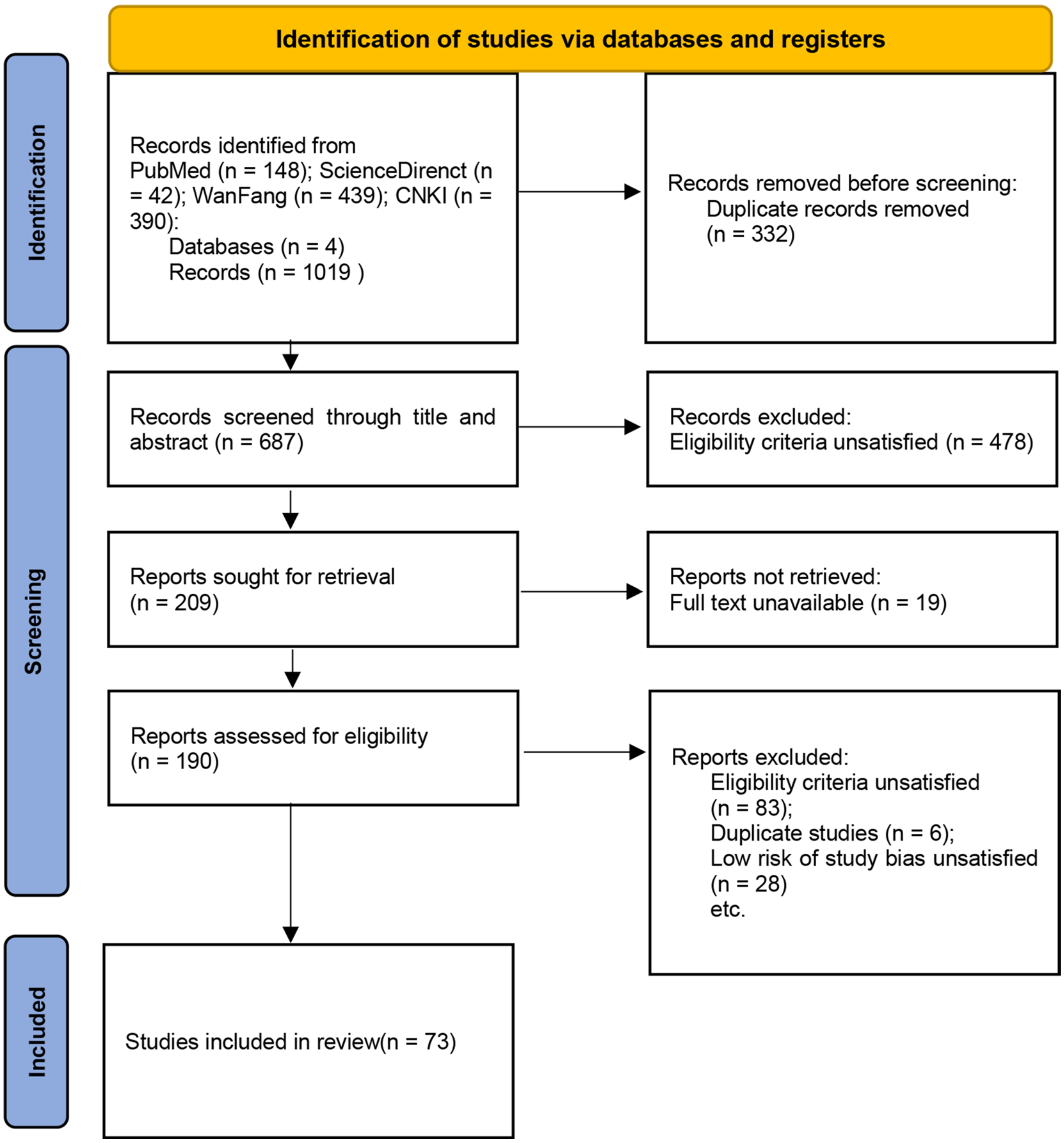

Fig. 1 PRISMA flow diagram of record selection procedure

CI: 7.87–15.02), respectively. That is, the positive rate of the real-time PCR method was lower than that of the RT-nested PCR method.

Discussion

The Chinese mainland is a highly endemic area of hepatitis E, with the average annual incidence of HEV infection gradually increasing. Based on the data obtained from hepatitis E cases reported online through the China Disease Control and Prevention Information System, the incidence rates of hepatitis E in 2004, 2014, and 2023 were 1.26, 1.99, and 2.11 per 100,000 population, respectively. Meanwhile, the shift of HEV genotypes and potential trends are gradually becoming prominent. In the past, HEV transmission often occurred through fecal contamination of the drinking water supply, and other contributing factors included limited access to clean water, poor sanitary hygiene, and an immature health care delivery system. Due to continuous improvement in hygiene standards in the Chinese mainland, the predominant circulating strain of HEV has shifted from waterborne genotype 1 HEV to foodborne genotype 4 HEV. One major concern is the continued detection of genotype 3 HEV in humans and pigs in the Chinese mainland. In this study, among the included research, further genotyping of HEV RNA was classified. In total, 898 cases were reported as genotype 4 HEV, involving animals such as pigs, sheep, cattle, goats, and Tibetan pigs. One Study identified genotype 8 HEV in the samples collected from camels [5]. Furthermore, genotype 3 HEV was only detected in the samples collected from 200 pigs; except for two cases reported in Guangxi, the remaining 198

Table 1 Included studies of HEV detection in domestic animals in the Chinese mainland, sorted by the year of publication

Study ID	Sampling Period	Species	Sample Type	Sampling Location	HEV Detection Method	Number of Positive	Number of Total	Prevalence (%)	Risk of Study Bias	Reference
Ma X, 2004	2001	Swine	Feces	Xinjiang	RNA (RT-nested PCR)	13	70	18.57	7	[11]
Fu LP, 2005	NA	Swine	Serum	Heilongjiang	Antibody (ELISA)	62	151	41.06	8	[12]
				Liaoning		118	208	56.73		
				Jilin		13	110	11.82		
				Guangxi		57	127	44.88		
				Shanghai		57	65	87.69		
				Nei Mongol		11	42	26.19		
				Chongqing		154	242	63.64		
				Qinghai		95	99	95.96		
				Yunnan		79	91	86.81		
Wang LL, 2006	NA	Dog	Serum	Fujian	Antibody (ELISA)	19	49	38.78	8	[13]
		Cow				28	120	23.33		
		Swine				425	596	71.31		
		Goat				50	58	86.21		
Zhou JP, 2006	NA	Swine	Serum	Shanghai	Antibody (ELISA)	301	417	72.18	8	[14]
		Cow				6	100	6.00		
		Goat				12	50	24.00		
		Horse				8	49	16.33		
		Dog				18	101	17.82		
Zheng YJ, 2006	2004	Swine	Bile	Zhejiang	RNA (RT-nested PCR)	5	160	3.13	7	[15]
Qu LC, 2007	NA	Sheep	Serum	Xinjiang	Antibody (ELISA)	158	826	19.13	7	[16]
Liang JR, 2007	NA	Swine	Feces	Xinjiang	RNA (RT-nested PCR)	2	55	3.64	7	[17]
				Guangxi		3	79	3.80		
Ning HQ, 2007	2006	Swine	Feces	Shanghai	RNA (RT-nested PCR)	15	65	23.08	7	[18]
Xie BD, 2008	NA	Swine	Serum	Jiangxi	Antibody (ELISA)	359	410	87.56	8	[19]
Gong G, 2008	2007	Swine	Bile	Shanghai	RNA (RT-nested PCR)	2	60	3.33	8	[20]
			Liver			0	60	0.00		
			Spleen			0	60	0.00		
			Lymphonodi mesenterici			0	60	0.00		
			Feces			1	160	0.63		
			Serum			2	61	3.28		
Ning HQ, 2008	NA	Swine	Feces	Shanghai	RNA (RT-nested PCR)	111	426	26.06	8	[21]
Yan YJ, 2008	2007	Swine	Feces	Shanghai	RNA (RT-nested PCR)	24	480	5.00	9	[22]
Ji YL, 2008	2006–2007	Swine	Feces	Guangxi	RNA (RT-nested PCR)	29	120	24.17	8	[23]
Xie BD, 2009	2005	Swine	Feces	Jiangxi	RNA (RT-nested PCR)	17	120	14.17	7	[24]

Table 1 (continued)

Study ID	Sampling Period	Species	Sample Type	Sampling Location	HEV Detection Method	Number of Positive	Number of Total	Prevalence (%)	Risk of Study Bias	Reference
Ma YH, 2009	2007	Swine	Bile	Xinjiang	RNA (RT-nested PCR)	3	212	1.42	7	[25]
		Cattle				0	48	0.00		
		Goat				0	196	0.00		
Zhou JP, 2009	2007–2008	Swine	Bile	Shanghai	RNA (RT-nested PCR)	9	127	7.09	8	[26]
			Feces			201	1699	11.83		
Cao WB, 2009	NA	Cattle	Serum	Xinjiang	Antibody (ELISA)	39	675	5.78	7	[27]
		Goat				52	673	7.73		
Wu JY, 2009	NA	Sheep	Serum	Xinjiang	Antibody (ELISA)	140	434	32.26	7	[28]
Zhao CY, 2009	NA	Rabbit	Serum	Gansu	Antibody (ELISA)	191	335	57.01	7	[29]
					RNA (RT-nested PCR)	25	335	7.46		
Li Z, 2009	NA	Swine	Feces	Shanghai	RNA (RT-nested PCR)	110	493	22.31	8	[30]
Chang YB, 2009	NA	Swine	Serum	Beijing	Antibody (ELISA)	321	390	82.31	7	[31]
		Cow				54	184	29.35		
		Sheep				20	207	9.66		
		Swine	Feces		RNA (RT-nested PCR)	19	83	22.89		
Xia YG, 2010	2009	Swine	Bile	Anhui	RNA (RT-nested PCR)	22	400	5.50	7	[32]
Zhao W, 2010	2008–2010	Swine	Feces	Guangxi	RNA (RT-nested PCR)	194	508	38.19	8	[33]
	2008–2010		Liver			33	182	18.13		
Wang DR, 2010	2008–2009	Dog	Serum	Yunnan	Antibody (ELISA)	130	268	48.51	7	[34]
Wu JY, 2010	2008	Sheep	Serum	Xinjiang	Antibody (ELISA)	142	490	28.98	9	[35]
Fu HW, 2010	2007–2008	Swine	Feces	Xinjiang	RNA (RT-nested PCR)	70	125	56.00	7	[36]
		Swine	Serum		Antibody (ELISA)	66	78	84.62		
		Donkey				38	276	13.77		
		Horse				11	100	11.00		
		Goat				15	200	7.50		
		Cow				13	200	6.50		
Jinshan, 2010	2009	Swine	Serum	Nei Mongol	Antibody (ELISA)	186	356	52.25	8	[37]
					RNA (RT-nested PCR)	30	356	8.43		
Ren RQ, 2011	2009	Swine	Feces	Guizhou	RNA (RT-nested PCR)	49	216	22.69	7	[38]
Bi L, 2011	2007	Swine	Serum	Heilongjiang	Antibody (ELISA)	591	696	84.91	8	[39]
		Cattle				97	242	40.08		
Song TF, 2011	2008	Swine	Bile	Shandong	RNA (RT-nested PCR)	32	106	30.19	7	[40]
Li WG, 2011	NA	Swine	Liver	Yunnan	RNA (RT-nested PCR)	6	95	6.32	8	[41]
			Feces			5	60	8.33		

Table 1 (continued)

Study ID	Sampling Period	Species	Sample Type	Sampling Location	HEV Detection Method	Number of Positive	Number of Total	Prevalence (%)	Risk of Study Bias	Reference
Geng YS, 2011	2009–2010	Rabbit	Serum	Jilin	Antibody (ELISA)	17	180	9.44	9	[42]
				Beijing		45	107	42.06		
				Hebei		34	463	7.34		
				Shanxi		14	180	7.78		
				Hubei		55	103	53.40		
				Guangxi		1	33	3.03		
				Jilin	RNA (RT-nested PCR)	0	180	0.00		
				Beijing		2	107	1.87		
				Hebei		6	463	1.30		
				Shanxi		2	180	1.11		
				Hubei		12	103	11.65		
				Guangxi		0	33	0.00		
Liu YL, 2012	NA	Swine	Serum	Guangxi	Antibody (ELISA)	659	850	77.53	7	[43]
		Cattle				109	392	27.81		
		Sheep				90	428	21.03		
Si FS, 2012	2009–2010	Swine	Feces	Shanghai	RNA (RT-nested PCR)	297	1487	19.97	9	[44]
Xiao P, 2012	2008	Swine	Serum	Hebei	Antibody (ELISA)	157	276	56.88	7	[45]
			Feces		RNA (RT-nested PCR)	8	56	14.29		
Shi XC, 2013	2010	Tibetan Swine	Serum	Xizang	Antibody (ELISA)	204	421	48.46	7	[46]
Geng YS, 2013	2012	Swine	Serum	Hebei	Antibody (ELISA)	58	94	61.70	7	[47]
					RNA (RT-nested PCR)	22	94	23.40		
			Feces		RNA (RT-nested PCR)	37	125	29.60		
		Rabbit	Serum		Antibody (ELISA)	67	289	23.18		
					RNA (RT-nested PCR)	29	289	10.03		
Wang S, 2013	2009–2010	Rabbit	Bile	Jiangsu	RNA (RT-nested PCR)	42	661	6.35	7	[48]
Lu YH, 2013	2008–2011	Swine	Bile	Anhui	RNA (RT-nested PCR)	92	2400	3.83	8	[49]
				Guangxi		47	1800	2.61		
Wang XZ, 2014	NA	Yak	Serum	Qinghai	Antibody (ELISA)	19	658	2.89	8	[50]
		Sheep				28	629	4.45		
Shu XH, 2014	2011–2012	Swine	Feces	Yunnan	RNA (RT-nested PCR)	20	256	7.81	7	[51]
Liang HB, 2014	2012–2013	Dog	Serum	Guangdong	Antibody (ELISA)	31	233	13.30	7	[52]
				Shanghai		28	120	23.33		
				Beijing		71	242	29.34		
		Cat		Guangdong		12	191	6.28		
Liang HB, 2014	2011–2013	Swine	Serum	Guangdong	Antibody (ELISA)	363	561	64.71	9	[53]
Tang JH, 2015	NA	Tibetan swine	Serum	Xizang	Antibody (ELISA)	595	1440	41.32	7	[54]

Table 1 (continued)

Study ID	Sampling Period	Species	Sample Type	Sampling Location	HEV Detection Method	Number of Positive	Number of Total	Prevalence (%)	Risk of Study Bias	Ref-er-ence
Wu JY, 2015	2014	Sheep	Serum	Xinjiang	Antibody (ELISA)	176	500	35.20	8	[55]
			Liver		RNA (RT-nested PCR)	4	75	5.33		
Peng DP, 2016	2015	Swine	Serum	Guangdong	Antibody (ELISA)	138	225	59.11	7	[56]
Wu JY, 2016	2015	Cow	Serum	Xinjiang	Antibody (ELISA)	78	1110	7.03	8	[57]
					RNA (RT-nested PCR)	0	1110	0.00		
Wu JY, 2016	2015	Swine	Serum	Xinjiang	Antibody (ELISA)	884	1660	53.25	7	[58]
Yan BY, 2016	2011	Cattle	Serum	Shandong	Antibody (ELISA)	120	254	47.24	7	[59]
					RNA (RT-nested PCR)	8	254	3.15		
Woo PCY, 2016	2012–2013	Camel	Feces	Xinjiang	RNA (RT-nested PCR)	3	251	1.20	7	[5]
Wang LF, 2016	NA	Dog	Serum	Guangdong	Antibody (ELISA)	84	442	19.00	7	[60]
Tong TT, 2017	2014–2016	Swine	Serum	Guangdong	Antibody (ELISA)	780	1127	69.21	7	[61]
Zhang SD, 2017	2015–2016	Swine	Serum	Hubei	Antibody (ELISA)	66	174	37.93	8	[62]
Li S, 2017	2017	Goat	Serum	Shandong	Antibody (ELISA)	50	120	41.67	8	[63]
Long FY, 2017	2015–2016	Goat	Feces	Yunnan	RNA (RT-nested PCR)	52	74	70.27	7	[64]
Su Q, 2018	2015–2016	Swine	Bile	Jiangsu	RNA (Real-Time PCR)	13	510	2.55	7	[65]
Qin L, 2018	2017	Swine	Serum	Henan	Antibody (ELISA)	104	328	31.71	9	[66]
Gong G, 2018	2016–2017	Tibetan Swine	Serum	Xizang	Antibody (ELISA)	81	305	26.56	8	[67]
Zhang LH, 2018	2017–2018	Tibetan Swine	Bile	Xizang	RNA (RT-nested PCR)	11	253	4.35	7	[68]
Guo J, 2019	2015–2017	Goat	Serum	Yunnan	Antibody (ELISA)	370	1500	24.67	7	[69]
		Cattle				220	500	44.00		
Geng YS, 2019	2017–2018	Cow	Feces	Hebei	RNA (RT-nested PCR)	0	467	0.00	7	[70]
			Milk			0	276	0.00		
Zhou JH, 2019	NA	Swine	Serum	Sichuan	Antibody (ELISA)	374	596	62.75	7	[71]
				Fujian		61	91	67.03		
				Hubei		75	120	62.50		
				Anhui		76	121	62.81		
				Jiangxi		73	99	73.74		
				Ningxia		106	145	73.10		
				Gansu		422	596	70.81		
Li HX, 2019	NA	Swine	Serum	Shaanxi	Antibody (ELISA)	1111	7187	15.46	7	[72]
Zhang Y, 2020	2019–2020	Swine	Feces	Sichuan	RNA (Real-Time PCR)	82	800	10.25	9	[73]
			Serum		Antibody (ELISA)	657	1600	41.06		
Yin WJ, 2020	2018–2019	Swine	Bile	Beijing	RNA (Real-Time PCR)	12	100	12.00	7	[74]
				Hebei		16	212	7.55		
				Shandong		18	220	8.18		
Tian H, 2022	2015–2020	Swine	Bile	Jiangsu	RNA (Real-Time PCR)	198	5588	3.54	7	[75]
Wang W, 2022	2017–2020	Swine	Bile	Shanghai	RNA (Real-Time PCR)	11	2400	0.46	8	[76]

Table 1 (continued)

Study ID	Sampling Period	Species	Sample Type	Sampling Location	HEV Detection Method	Number of Positive	Number of Total	Prevalence (%)	Risk of Study Bias	Ref-er-ence
Lei MY, 2022	2019–2021	Swine	Bile	Guizhou	RNA (Real-Time PCR)	2	140	1.43	8	[77]
Qu K, 2022	2021	Swine	Serum	Henan	Antibody (ELISA)	144	226	63.72	7	[78]
Yang DJ, 2022	2018–2019	Tibetan swine	Feces	Sichuan	RNA (RT-nested PCR)	38	229	16.59	8	[79]
Duan TC, 2022	2015–2016	Swine	Serum	Sichuan	Antibody (ELISA)	173	307	56.35	8	[80]
Zuo YG, 2022	2021	Swine	Serum	Yunnan	Antibody (ELISA)	470	2548	18.45	9	[81]
Lou YZ, 2022	2018–2021	Yak	Serum	Qinghai	Antibody (ELISA)	16	120	13.33	7	[82]
				Xizang		19	120	15.83		
		Sheep		Xizang		6	120	5.00		

Note: ELISA: Enzyme linked immunosorbent assay, RT-nested PCR: Reverse transcription-nested polymerase chain reaction

cases were all detected in Shanghai. In 2007, for the first time, Ning et al. [18] detected seven genotype 3 HEV isolates in pig feces collected from Shanghai pig farms. Subsequently, genotype 3 HEV was also detected in humans and pigs in the eastern region of the Chinese mainland [76, 83–85]. The high detection rate of genotype 3 HEV in the samples collected in Shanghai may be due to the large number of research projects conducted in this region. Furthermore, because this region is along the East China Sea and is the most economically developed region, the geographical location, the frequent international trade, and the large flow of inbound and outbound travel may also be the risk factors for genotype 3 HEV emergence. These results warn us about the circulation of genotype 3 HEV in the eastern region of the Chinese mainland. One potential transmission pathway of genotype 3 HEV was imported cases from abroad because genotype 3 HEV is widely distributed around the world. The consumption of undercooked animal meat, offal, and shellfish also increases the transmission of genotype 3 HEV. Because genotype 3 HEV is predominantly zoonotic, the detection of genotype 3 HEV in humans in the Chinese mainland in recent years suggests the possibility of cross-species transmission of zoonotic HEV, although no direct evidence has been obtained. The susceptibility and pathogenicity of different genotypes and subtypes to the population and the shift in genotypes deserve long-term monitoring and in-depth studies.

The Chinese mainland has a total of 31 provincial-level administrative regions, comprising 22 provinces, five autonomous regions, and four municipalities. In this study, data collected from 28 of 31 provinces and municipalities were included in the meta-analysis. Data were not available for Hubei, Hainan, and Tianjin. Through the literature review process, we found that several studies conducted sampling in Hubei and Hainan, however, these data were excluded because they did not meet the inclusion criteria. The widespread detection of HEV suggests that health administrative departments and agricultural departments need to urgently refine prevention and control strategies. According to the geographical location, the Chinese mainland is divided into seven regions. In the subgroup analysis of HEV seroprevalence in swine, the positive rate was the highest in the eastern region of the Chinese mainland and was the lowest in the northeastern region. This is corroborated by the results of a spatial-temporal scanning analysis, which identified one clustering area of high incidence of hepatitis E in the eastern coastal provinces of China [86]. However, the HEV RNA prevalence rate in the eastern region was lower than those in other regions, which was inconsistent with the trend of antibodies. This may be related to the diversity and sensitivity of different sampling methods used in HEV RNA testing, which are further explored in

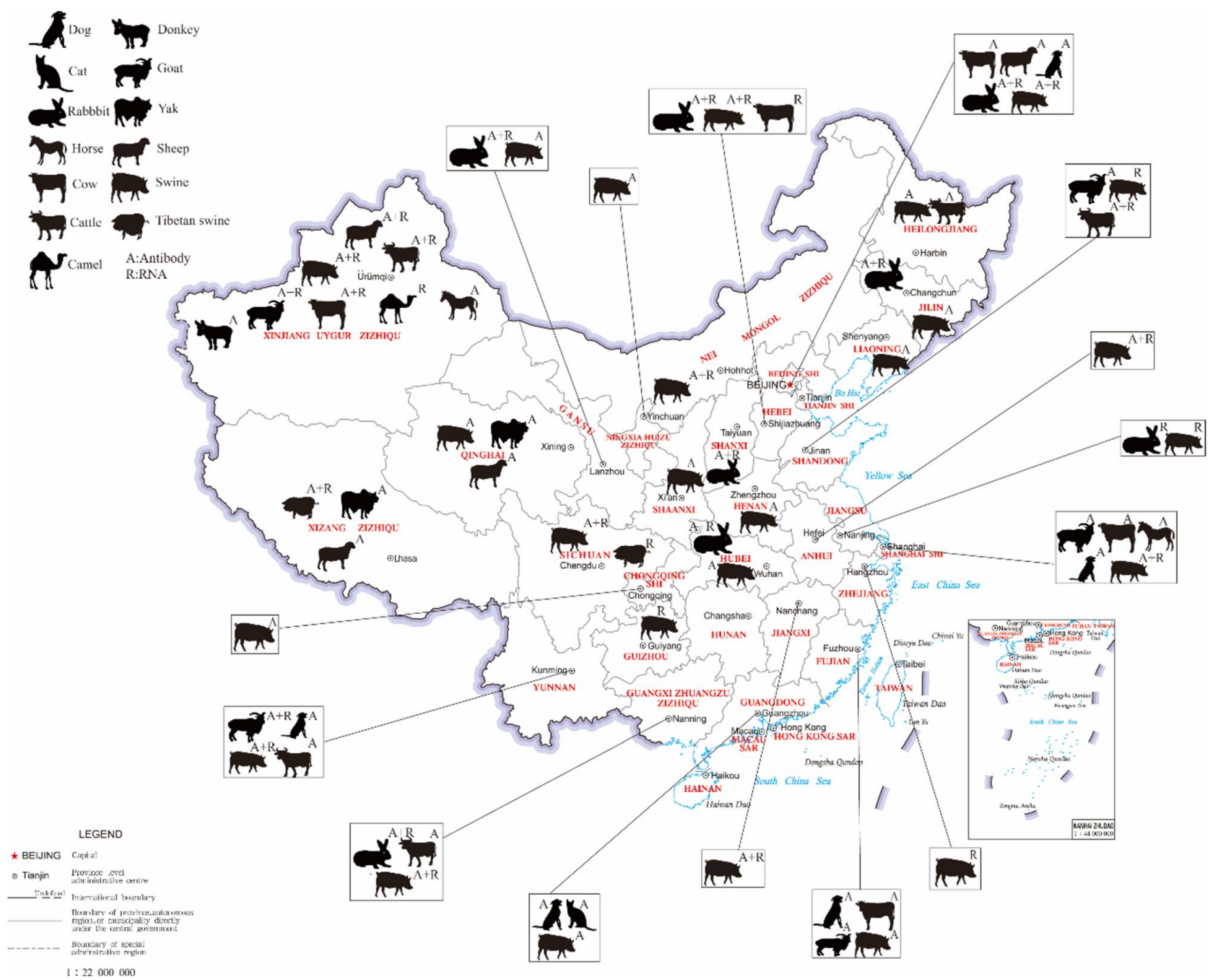

Fig. 2 Distribution of the animals tested for HEV antibodies or RNA

the following text. Furthermore, the geographical location does not fully explain the results of this study. Due to the wide geographical area, large population, and multiple ethnic groups in the Chinese mainland, there are differences in people's lifestyles, dietary habits, livestock species and feeding, relevant natural environment, and socioeconomic situations between different regions, which pose challenges to the subgroup analysis classified by region. The disease control department and researchers must include the above risk factors in epidemic surveillance and regional epidemiological studies to provide a more scientific interpretation of the results, as well as a theoretical basis for formulating prevention and control strategies adapted to local conditions.

Pigs are recognized as the major animal reservoirs for HEV. Pig farming plays an important role in the Chinese mainland's traditional agricultural economy. Data from the National Bureau of Statistics of China showed that in 2022, the Chinese mainland's pork production accounted for approximately 44.47% of global pork production. At the same time, pork is also the most consumed meat product in China. In addition, pork liver, pork stomach, and other pig offal are consumed as food. In this study, the prevalence rates of both antibodies and RNA of HEV for the samples collected from swine were the highest. HEV RNA was detected in various samples, including feces, serum, liver, and bile. Therefore, the risk of HEV infection through the consumption of contaminated pork products is rather high. Government departments should strengthen the management of pig farms and devise quality standards of HEV detection for pork and other related products. Our findings showed that the seroprevalence of HEV antibodies gradually decreased over the time of sampling, and the HEV RNA prevalence rate for recently collected samples was the lowest. This may be attributed to the improvement of sanitation on farms and increased government regulation. However, the continuing increase in the incidence rate indicates that existing prevention

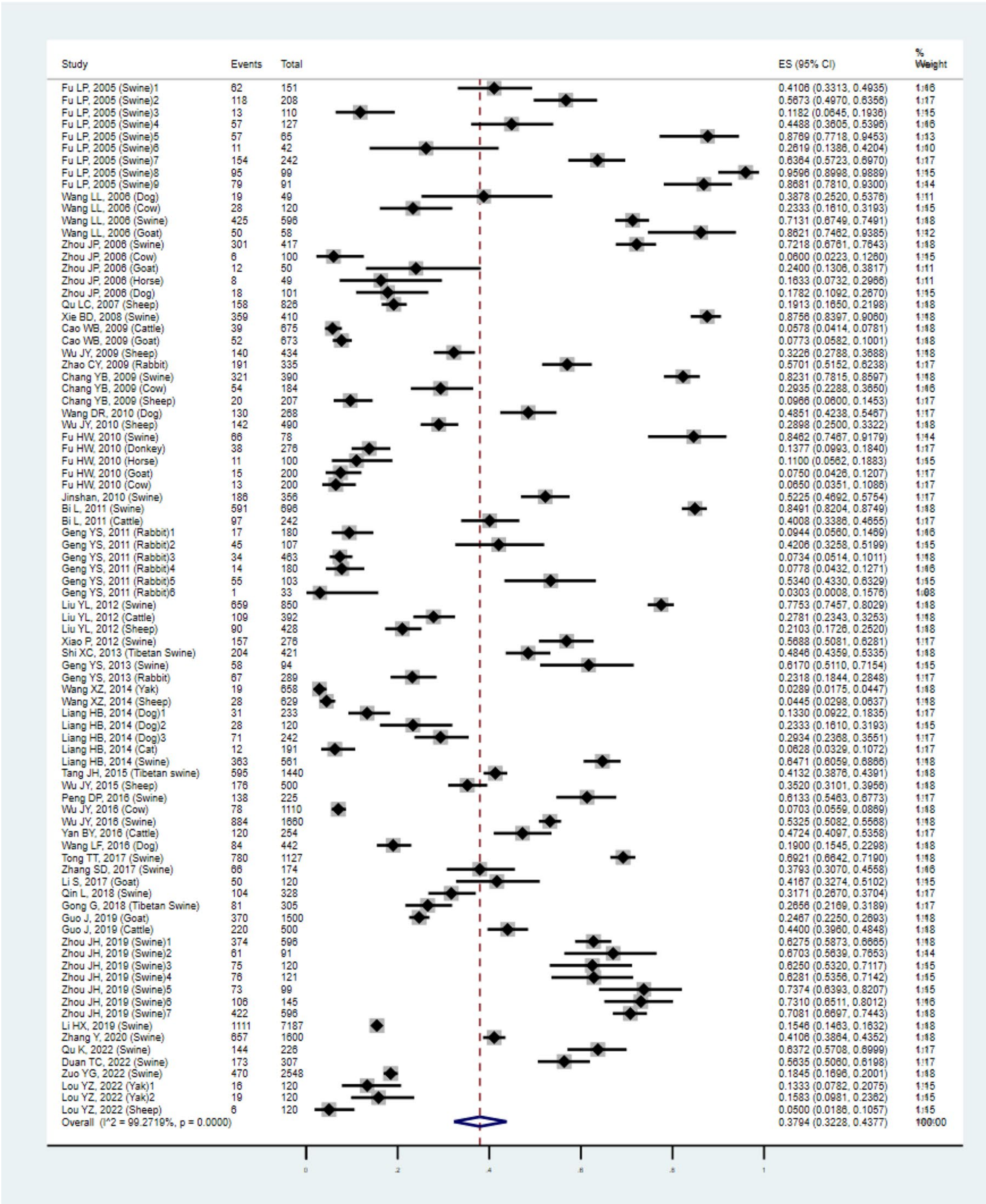

Fig. 3 Pooled prevalence of HEV antibody detection

and control measures are still inadequate. The government should raise awareness of the risk of HEV infection and potential transmission pathways, and individuals should practice good hygiene to ensure that drinking water and food are clean and safe. Meanwhile, researchers should be encouraged to develop more effective vaccines and drugs against HEV. Studies have also shown that the levels of HEV antibodies are higher in swineherds and pig slaughterers than in the general population, suggesting that prolonged occupational exposure to pigs may also increase the risk of HEV infection [31]. Biosecurity protection and vaccination should be strengthened for people engaged in the whole process from breeding, slaughtering, processing, and distributing and selling.

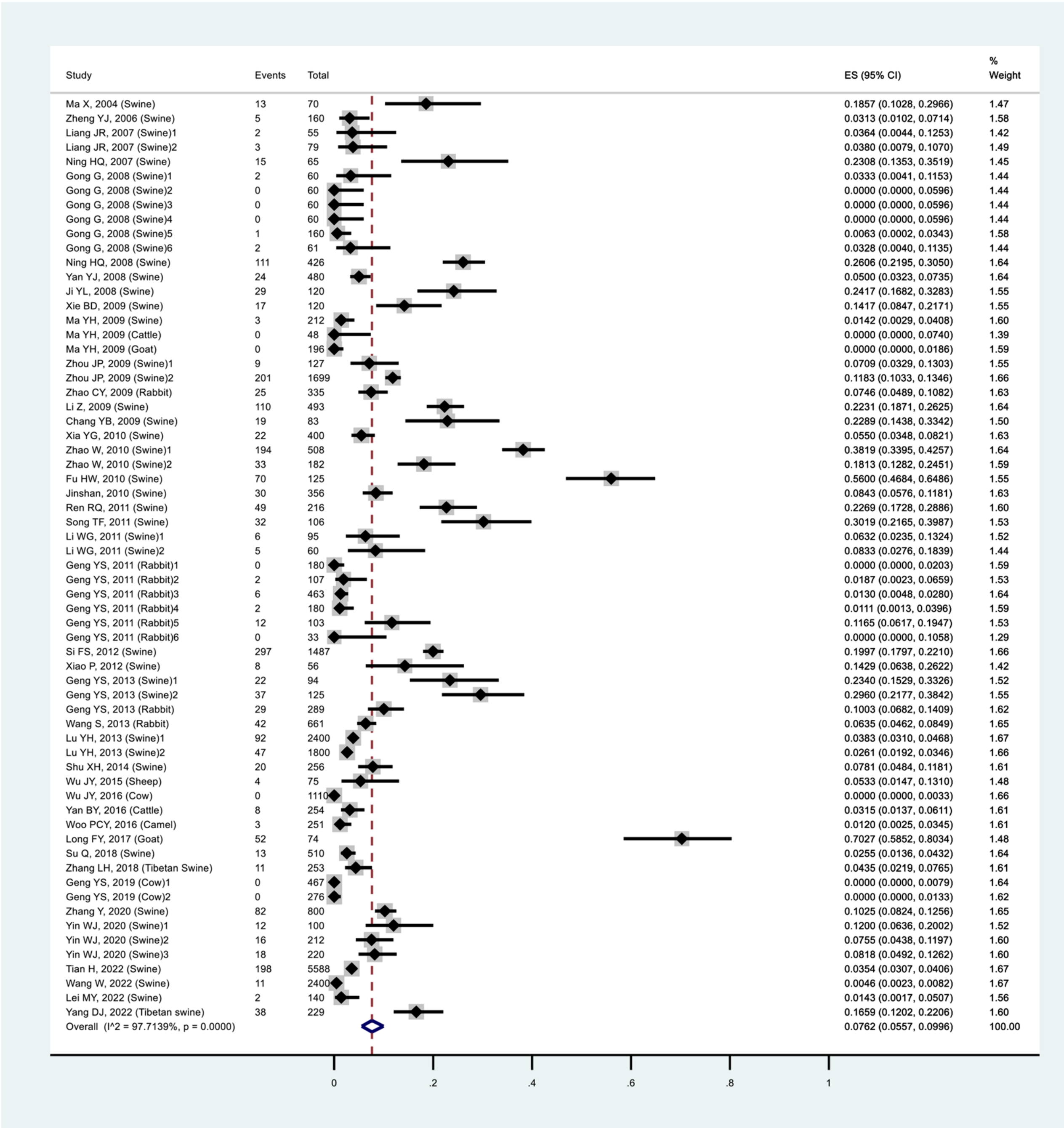

Fig. 4 Pooled prevalence of HEV RNA detection

In rural areas in the Chinese mainland, there are small-scale farms that breed pigs, rabbits, and other domestic animals together; therefore, various species of animals use common utilities and are fed by the same workers. This form of feeding has raised concerns about the cross-species transmission of HEV. One study included in this review compared the HEV genotypes of rabbits and pigs living in the adjoining area and the results showed that there was no evidence of cross-species transmission of HEV between pigs and rabbits [47]. It is worth mentioning that the seroprevalence of HEV antibodies in rabbit in the study was 23.18%. There was no significant difference compared to the pooled seropevalence in rabbit in this review, which was 22.63%. However, the current study found that the prevalence of HEV among many other common domestic animals, such as Tibetan swine, goats, and cows, was at a high level. These animals make up a significant part of the livestock industry. In addition,

Table 2 HEV prevalence categorized by species

	Species	Number of Sets	Number of Positive	Number of Total	Prevalence %	95% CI	I^2%
Antibody	Cat	1	12	191	6.28	3.29–10.72	-
	Cattle	5	585	2,063	31.21	13.68–52.09	98.93
	Cow	5	179	1,714	13.04	5.56–22.97	95.01
	Dog	7	381	1,455	26.24	16.99–36.67	94.27
	Donkey	1	38	276	13.77	9.93–18.40	-
	Goat	6	549	2,601	29.30	14,88–46.19	98.23
	Horse	2	19	149	12.58	7.60–18.51	-
	Rabbit	8	424	1,690	22.63	9.21–39.74	98.21
	Sheep	8	760	3,634	18.05	10.32–27.35	97.78
	Swine	37	9,846	23,009	61.03	51.39–70.26	99.50
	Tibetan Swine	3	880	2,166	38.70	28.68–49.23	-
	Yak	3	54	898	9.51	1.83–21.95	-
	Overall	86	13,727	39,846	37.94	32.28–43.77	99.27
RNA	Camel	1	3	251	1.20	0.25–3.45	-
	Cattle	2	8	302	2.17	0.66–4.30	-
	Cow	3	0	1,853	0.00	0.00–0.08	-
	Goat	2	52	270	8.26	5.19–11.92	-
	Rabbit	9	118	2,351	3.45	1.25–6.54	90.32
	Sheep	1	4	75	5.33	1.47–13.10	-
	Swine	44	1,882	22,887	9.82	7.12–12.88	97.87
	Tibetan Swine	2	49	482	9.30	6.84–12.08	-
	Overall	64	2,116	28,471	7.62	5.56–9.96	97.71

HEV was widely detected in cats, dogs, donkeys, horses, rabbits, sheep, yaks, and camels. Interestingly, research found that the pooled prevalence rate of HEV antibodies for yaks was relatively low and that the prevalence rate for sheep in the same studies was also lower than the pooled prevalence rate. Because yaks and sheep were all fed through grazing in these studies, the low prevalence might have been related to the mode of feeding [40, 73]. In recent years, an increasing number of HEV animal hosts have been discovered [3–4]. Although the roles of these animals in the transmission of zoonotic HEV are still unclear, the increasing number of host animals and the ongoing animal-to-animal and potential animal-to-human transmission may lead to mutations of HEV, which may in turn lead to cross-species transmission. Therefore, HEV testing should be performed to monitor pathogens among a wider range of domestic animals. Scientific management of animal husbandry can help reduce the risk of zoonotic disease transmission from infectious sources.

The detection results of HEV antibodies and HEV RNA were synthesized separately considering that there were significant differences between these two markers in terms of the representation, detection methods, and prevalence. The seroprevalence of HEV antibodies was tested using ELISA. The included studies were all aimed at measuring HEV-specific IgG antibodies or total antibodies with a detailed description of the principle and application of the commercial kits or self-developed methods used in these studies. This criterion ensured the poolability of the results of the included studies. In terms of HEV RNA detection, prevalence rates varied between different sampling types. Among the various samples collected from pigs, the detection rate in feces was the highest, which was 16.60% (95% CI: 12.17–21.55). However, the pooled prevalence rate of HEV RNA in various samples of swine was almost half of the value in feces, which was 9.82% (95% CI: 7.12–12.88). This was because the number of fecal samples only accounts for less than 1/3 of the total number of pig samples. The number of bile samples was the largest in the studies of swine; meanwhile, the positive rate for bile samples was the lowest. When the results for fecal samples of all animals were screened, there were data from other animals such as camels, cows, goats, and Tibetan swine; however, each had only one study, which made the results not suitable for poolability. It is necessary to unify the types of sampling among studies of different species. However, in the studies conducted before 2020, only RT-nested PCR was used to detect HEV RNA, which was generally self-developed and complex in operation. After 2020, commercial real-time PCR kits were widely applied, which facilitated high-throughput screening; however, the sensitivity of these commercial kits is less than that of the RT-nested PCR method. In terms of the experiment principle, RT-nested PCR has one more round of amplification than real-time PCR, which is beneficial for the detection of small amounts of viral load. Sequences obtained using

Table 3 Subgroup prevalence of HEV detection in Swine

	Subgroup		Sets	Positive	Total	Prevalence %	95% CI	I^2%
Antibody	Sampling Period	< 2010	4	1,000	1,406	70.65	50.29–87.46	98.18
		≥ 2010, < 2015	2	421	655	64.32	60.60–67.97	-
		≥ 2015, ≤ 2020	6	2,022	4,294	46.87	38.93–54.89	95.70
		>2020	2	614	2,774	21.52	20.01–23.07	-
	Sampling Region	East	7	1,352	1,799	75.18	67.61–82.06	91.02
		Middle	4	389	848	48.76	31.89–65.78	95.99
		North	5	733	1,158	57.14	40.40–73.08	96.65
		Northeast	4	784	1,165	48.52	16.96–80.76	99.11
		Northwest	6	2,684	9,765	67.06	38.99–89.78	99.76
		South	5	1,997	2,890	64.54	56.36–72.32	94.51
		Southwest	6	1,907	5,384	54.82	35.69–73.25	99.40
	Total		37	9,846	23,009	61.03	51.39–70.26	99.50
RNA	Sampling Period	≤ 2010	24	1,056	6,950	10.93	6.96–15.64	96.62
		> 2010, < 2015	3	79	476	18.99	6.36–36.16	-
		≥ 2015, ≤ 2020	7	350	9,830	5.29	2.45–9.10	97.99
	Sampling Region	East	22	1,180	17,142	6.75	3.94–10.20	98.17
		North	7	144	1,027	15.84	9.65–23.18	87.69
		Northwest	4	88	462	15.47	0.00–48.43	98.24
		South	5	306	2,689	14.97	1.92–36.70	99.10
		Southwest	6	164	1,567	8.68	4.27–14.38	89.94
	Sample Type	Bile	15	482	14,435	4.63	3.06–6.49	94.17
		Feces	21	1,307	7,483	16.60	12.17–21.55	96.22
		Liver	3	39	337	6.22	0.00–20.38	-
		Lymphonodi mesenterici	1	0	60	0.00	0.00–0.596	-
		Serum	3	54	512	10.50	2.87–21.80	-
		Spleen	1	0	60	0.00	0.00–0.596	-
	Detection Method	Real-Time PCR	8	352	9,970	4.75	2.22–8.11	96.86
		RT-nested PCR	36	1,530	12,917	11.20	7.87–15.02	97.31
	Total		44	1,882	22,887	9.82	7.12–12.88	97.87

RT-nested PCR can be further studied for genotyping and homology analysis. Meanwhile, it is difficult to design primers in Real-Time PCR for conserved sequences of HEV covering a wide range of genotypes due to the high difference between different genotypes. From our previous results [76], the sensitivity of commercial Real-Time PCR kits was lower than that of RT-nested PCR, resulting in false negatives for RNA detection. These two methods have their advantages and drawbacks; therefore, we recommend combining these methods to study the prevalence of HEV RNA. Currently, there are no recognized fragments for HEV genotyping due to the lack of an in vitro model of HEV culture and difficulties in obtaining HEV genome sequences. The RdRp region, ORF2/3 overlap region, ORF2 5' end, and ORF2 3' end are usually selected for HEV genotyping [87]. Only short fragments of less than 1 kb were obtained. This limits the uniform analysis of genotyping and even subtyping results across different studies, as well as systematic cross-species homology analysis. With the development of the next-generation sequencing method, further research should be conducted to overcome this limitation.

One limitation of this review is that the included studies reported the prevalence of HEV with high heterogeneity. The influence analysis showed that the meta-analysis model was highly stable. The potential causes of heterogeneity were explored through subgroup analysis. The results showed that the heterogeneity decreased slightly. This suggests that the determinants of heterogeneity remain to be explored. Furthermore, a P value of < 0.05 was considered to indicate the presence of publication bias. To ensure the quality of this review, the included studies were limited to published articles in peer-reviewed journals; therefore, negative results reported in unpublished studies or other forms of reports, such as conference reports or dissertations, might have been neglected.

In general, this review systematically searched and assessed studies on the detection of HEV in domestic animals in the Chinese mainland published in both Chinese and English. The results collected from the included studies provided valuable data on HEV prevalence across various species, and the characteristics, trends, and potential influencing factors were fully discussed. This review provides public health professionals, policymakers, and researchers with comprehensive and up-to-date research data on zoonotic HEV.

Abbreviations

HEV	Hepatitis E virus
CI	Confidence intervals
ELISA	Enzyme linked immunosorbent assay
RT-nested PCR	Reverse transcription-nested polymerase chain reaction

Acknowledgements

We thank Prof. Lu Yihan and Wang Fengge for the recommendations in data analysis.

Author contributions

Wei Wang: research design, data collection and analysis, article writing. Wencheng Wu: research design, data collection, article writing. Min Chen: article revision. Zheng Teng: research design, article revision and other support.

Funding

This study is sponsored by Shanghai Sailing Program (23YF1436900) and Shanghai three-year action plan for strengthening the construction of the public health system (2023–2025) (GWVI-3, GWVI-11.1-09).

Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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Received: 19 August 2024 / Accepted: 5 February 2025
Published online: 03 March 2025

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