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Review

Animals as amplification hosts in the spread of severe fever with thrombocytopenia syndrome virus: A systematic review and meta-analysis

Can Chen[a,b,c,1], Peng Li[b,c,1], Ke-Feng Li[b,c,1], Hong-Ling Wang[b,c], Ya-Xin Dai[b,c], Xi Cheng[a,b,c], Jian-Bo Yan[a,b,c,*]

[a] Jiangxi Provincial Key Laboratory of Preventive Medicine, Department of Public Health, Nanchang University, Nanchang, Jiangxi, China
[b] Zhoushan Center for Disease Control and Prevention, Zhoushan, Zhejiang, China
[c] Zhejiang Provincial Key Laboratory of Health Risk Factors for Seafood, Zhoushan Center for Disease Control and Prevention, Zhoushan, Zhejiang, China

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A B S T R A C T

Objectives: Severe fever with thrombocytopenia syndrome (SFTS) is an emerging tick-borne infectious disease caused by severe fever with thrombocytopenia syndrome virus (SFTSV). The seroprevalence of anti-SFTSV antibodies specific to SFTSV (IgG or IgM) has been investigated in different animal hosts in many epidemiological studies, but no systematic estimation of seroprevalence has yet been performed. Hence, this meta-analysis was conducted in order to obtain a more comprehensive result to clarify the prevalence of SFTSV in animals.
Methods: A search for all relevant articles was conducted in the major national and international electronic databases up to August 2018. Data on seroprevalence of SFTSV antibodies (IgM and IgG) were extracted as the primary outcome. The pooled seroprevalence rates and 95% confidence intervals (95% CI) were determined.
Results: Overall, anti-SFTSV antibodies (IgG or IgM) were detected in 15 animal species. The pooled seroprevalence of anti-SFTSV antibodies was 45.70% in goats and sheep, 36.70% in cattle, 29.50% in dogs, 9.60% in chickens, 3.20% in rodents, and 3.20% in pigs. The seroprevalence of SFTSV in animals that had a confined range was significantly lower than that in free-range animals. SFTSV RNA was detected in 11 animal species, with a carriage rate varying from 0.23% to 26.31%.
Conclusions: SFTSV has a wide spectrum of animal hosts, including domestic and wild animals. The prevalence of SFTSV is high among specific animal species.

Contents

* Corresponding author at: Jiangxi Provincial Key Laboratory of Preventive Medicine, Department of Public Health, Nanchang University, Nanchang, Jiangxi, China.
E-mail address: yanjianbo02@163.com (J.-B. Yan).
[1] Can Chen, Peng Li, and Ke-Feng Li contributed equally to this article.

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Introduction

Severe fever with thrombocytopenia syndrome (SFTS) is an emerging tick-borne zoonosis. The common manifestations of the disease include high fever, gastrointestinal symptoms, thrombocytopenia, leukocytopenia, and lymphadenopathy (Li, 2013). The causative agent of this disease is the severe fever with thrombocytopenia syndrome virus (SFTSV), which belongs to the genus *Phlebovirus*, family *Bunyaviridae*. It was first reported in China in 2009 (Yu et al., 2011). From 2011 to 2016, a total of 5360 laboratory-confirmed SFTS cases were reported, and the annual number of reported cases has shown an increasing trend by year (Sun et al., 2017a). SFTS cases outside China have been identified in Japan and Korea. Heartland virus, which is another *Phlebovirus* and is genetically closely related to SFTSV, was isolated from two patients in the USA (Denic et al., 2011; McMullan et al., 2012; Shin et al., 2015; Takahashi et al., 2014). Due to the high fatality rates, heavy disease burden, and lack of a licensed SFTSV vaccine, this disease has become an important public health issue in China, as well as in other parts of the world.

A previous study suggested that *Haemaphysalis longicornis* is the major vector of SFTSV (Luo et al., 2015). However, the prevalence of SFTSV in these ticks was low. Both domestic and wild animals are regular hosts of ticks, and the prevalence of SFTSV in animals has been surveyed in many research studies through the identification of viral RNA or antibody positivity, with high infection rates found in several animal species (Yun et al., 2015). Transmission feeding experiments have shown that ticks feeding on SFTSV-infected mice can acquire the virus and that SFTSV-infected ticks can also transmit the virus to mice during feeding (Niu et al., 2013). Phylogenetic studies on SFTSV sequences have revealed that the migration of birds could be a potential source for the spread and geographic expansion of SFTSV (Fu et al., 2016; Shi et al., 2017; Yoshikawa et al., 2015). The results of these studies suggest that the circulation of SFTSV between ticks and animals may be necessary for the maintenance of SFTSV in nature.

More detailed information about the susceptible animal species and estimates of the prevalence of SFTSV infection in animals has yet to be obtained systematically. With this background, a meta-analysis was performed to reach a more comprehensive result in order to clarify the role of different animal species in the process of SFTSV transmission; the meta-analysis is an effective method of pooling data from individual studies (Khan et al., 2015).

Materials and methods

This meta-analysis was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA-P) guidelines (Hutton et al., 2015).

Search strategy

The literature on the seroprevalence of SFTSV in different animal species was searched via multiple English and Chinese electronic databases: PubMed, Embase, Web of Science, Chinese WanFang Database, and Chinese National Knowledge Infrastructure (CNKI). The search was conducted up to August 2018. In addition, the reference lists of the included original articles and reviews were manually searched to identify further studies. Keywords and terms in English and Chinese that were used in the search were ("seroprevalence" or "seroepidemiology" or "serum" or "antibodies" or "serum") and ("severe fever with thrombocytopenia syndrome virus" or "SFTSV" or "severe fever with thrombocytopenia syndrome" or "SFTS").

Eligibility criteria

The following inclusion criteria were established in order to obtain the valid articles needed: (1) the seroprevalence of SFTSV in animals was reported, or sufficient source data (samples and positive samples) were presented to calculate the seroprevalence; (2) the host species, location of the study, and origin were recorded in the research; (3) the methods for detecting specific antibody (IgG and IgM) to SFTSV were recorded in the research. Exclusion criteria included duplicate publications, as well as other articles such as abstracts, case reports, letters, and conferences papers.

Data collection

Data were extracted independently and carefully by two reviewers after assessment of the article title and abstract, based on the eligibility criteria. If some studies shared the same sample sources, only the study showing the greatest epidemiological quality was selected. The following items were extracted from each eligible article: first author, publication year, country in which the research was conducted, sampling time, sampling location, sample size, host species, SFTSV RNA carriage rate for each species, feeding model, number of research spots, and antibody testing method.

Meta-analysis

Pooled seroprevalence values with 95% confidence intervals (CI) of SFTSV antibodies were calculated for each animal species. Cochran Q and I^2 statistics were used to assess heterogeneity (Ades et al., 2005). A Cochran Q test with a p-value of <0.05 was considered to be statistically significant. An I^2 value of more than 75% indicated high heterogeneity; in such cases the random-effects model with DerSimonian and Laird method was applied. Otherwise, the Mantel–Haenszel method in a fixed-effects model was used. Potential publication bias was appraised using the funnel plot and Egger weighted regression. All statistical analyses were performed using Stata software version 11.0 (StataCorp, College Station, TS, USA). A p-value of <0.05 was considered statistically significant.

Results

Search results

As presented in Figure 1, the database searches retrieved 770 relevant articles, of which 158 were removed due to duplication. Based on the eligibility criteria and title and abstract review, a further 542 studies were excluded for one of the following reasons: irrelevant to topic, unable to access full-length article, or article type being letter, review, abstract, comment, or case report. After

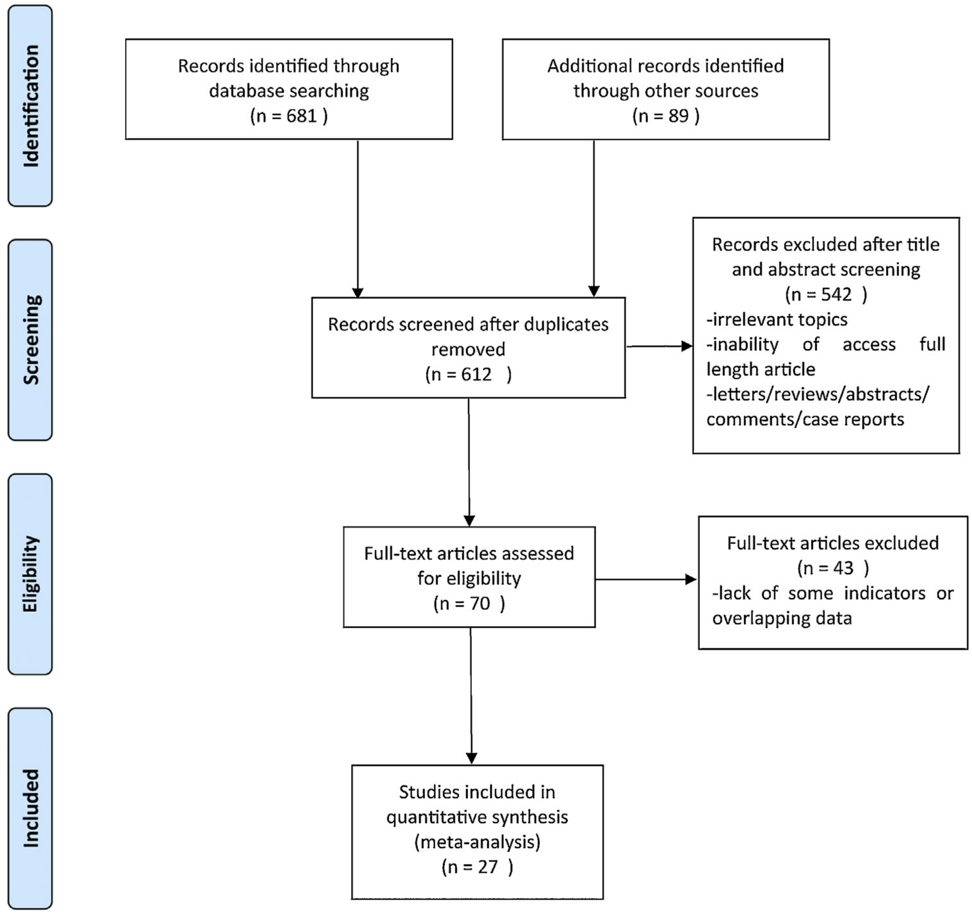

Figure 1. Flowchart of the study selection process for this meta-analysis.

carefully scanning the full texts and extracting data from the remaining 70 articles, 43 papers were excluded due to the lack of certain indicators or overlapping data. Finally, 27 studies were included for final analysis, which reported 12 903 blood samples from 15 animal species. The basic information from these included studies is shown in Table 1.

Characteristics of included studies

The sample sizes in the 27 studies ranged from 14 to 3039. Seventeen of the studies were published in English and 10 in Chinese. Most studies were conducted in China (provinces of Shangdong, Jiangsu, Hubei, Henan, Liaoning, and Anhui, and the city of Shanghai), followed by Korea, Japan, and the USA. Overall, antibodies (IgG/IgM) against SFTSV were detected in 15 animal species (Table 2).

Overall seroprevalence of SFTSV

The seroprevalence of SFTSV antibody in the different animal species varied from 0.33% to 100%. The pooled rate was obtained for the six main animal species; only studies with a sample size greater than 10 were included in the analysis. The pooled seroprevalence of SFTSV antibody was 45.70% (95% CI 28.40–63.00%) in goats and sheep, 36.70% (95% CI 13.00–63.00%) in cattle, 29.50% (95% CI 18.00–40.90%) in dogs, 9.60% (95% CI 3.50–15.60%) in chickens, 3.20% (95% CI 1.10–5.20%) in rodents, and 3.20% (95% CI 2.30–4.10%) in pigs.

A subgroup analysis by feeding model was also conducted for these species. In the confined-range subgroup, the pooled seroprevalence of SFTSV antibody was 8.30% (95% CI 6.60–10.10%) in goats and sheep, 8.70% (95% CI −4.30–21.80%) in cattle, 6.40% (95% CI 4.30–8.60%) in dogs, and 0.60% (95% CI 0.20–1.10%) in chickens. In the free-range subgroup, the pooled seroprevalence of SFTSV antibody was 58.60% (95% CI 42.00–75.20%) in goats and sheep, 49.00% (95% CI 28.50–69.50%) in cattle, and 55.20% (95% CI 31.90–78.50%) in dogs (Table 3).

Forest plots for the meta-analysis of the different animal species are shown in Figure 2. The shape of the funnel plot was evidently symmetrical, showing a lack of publication bias (goats and sheep) (Figure 3).

SFTSV carriage rates in the different animal species

The SFTSV carriage rates were also investigated in the different animal species in the articles included. Twelve articles reported the results of testing for SFTSV RNA in 6637 blood samples from 11 animal species. The carriage rates of SFTSV RNA ranged from 0.23% to 26.31%. The highest carriage rate of SFTSV RNA was detected in cattle (up to 26.31%), followed by cats (17.46%), goats (9.10%), and rodents (8.44%) (Table 4).

Discussion

Up to now, the natural transmission mode of SFTSV among vectors, hosts, and humans has remained unclear. SFTS was believed to be first caused by animals being fed or bitten by infected ticks (Ding et al., 2014). Several case–control studies have highlighted that raising domestic animals is a risk factor for human

Table 1
Basic characteristics of the studies included in the meta-analysis.

First author	Publication year	Country	Sampling time	Region	Sample size	Prevalence (%)	No. of research spots	Endemic	Language	Test method
Kang (Kang et al., 2018a)	2018	Korea	2014–2015	Urban & rural	737	6.89	9 provinces	Mix	English	D-ELISA
Yu (Yu et al., 2018)	2018	Korea	2017.3–2017.8	Urban & rural	207	14.49	1 province	NA	English	ELISA
Zhao (Zhao et al., 2012)	2012	China	2011.6	Rural	134	82.84	8 villages	Yes	English	D-ELISA
Niu (Niu et al., 2013)	2013	China	2011.4–12	Rural	3039	41.10	2 cities	Yes	English	D-ELISA
Xing (Xing et al., 2013)	2013	USA	2012.9–2012.10	Rural	889	13.72	24 counties	Yes	English	ELISA
Liu (Liu et al., 2014a)	2014	China	2013.1–2013.8	Rural	755	1.19	1 city	NA	English	D-ELISA
Tabara (Tabara et al., 2016)	2016	Japan	2014.6–2015.3	Urban & rural	510	2.16	3 counties	Yes	English	ELISA
Hayasaka (Hayasaka et al., 2016)	2016	Japan	2006–2012	Rural	190	18.42	6 counties	Yes	English	ELISA
Li (Li et al., 2014)	2014	China	2012.3–2013.2	Rural	2741	12.22	6 counties	Yes	English	D-ELISA
Xing (Xing et al., 2016)	2016	China	2012.8–2013.5	Rural	50	54.00	7 villages	Yes	English	ELISA
Oh (Oh et al., 2016)	2016	Korea	2013.5–2013.8	Rural	91	6.59	3 provinces	No	English	IFA
Li (Li et al., 2016)	2016	China	2013–2014	Rural	823	5.71	9 counties	Yes	English	D-ELISA
Lee (Lee et al., 2018)	2018	Korea	2016.3–2016.11	Urban & rural	426	13.85	1 country	No	English	IFA
Sun (Sun et al., 2017b)	2017	China	2014, 2016	Rural	14	64.29	2 district	NA	English	ELISA
Cui (Cui et al., 2013)	2013	China	2011.6–2012.12	Rural	78	25.64	2 villages	Yes	English	ELISA
Wang (Wang et al., 2017)	2017	China	2015–2016	Rural	178	8.43	7 mink farms	NA	English	D-ELISA
Jiang (Jiang, 2018)	2012	China	2010.9	Rural	106	32.08	2 counties	Yes	Chinese	D-ELISA
Zhu (Zhu et al., 2017)	2017	China	2012–2104	Urban	354	0	6 district	No	Chinese	ELISA
Du (Du et al., 2014a)	2014	China	2012.7–2012.10	Rural	315	44.76	2 counties	Yes	Chinese	ELISA
Zhang (Zheng et al., 2011)	2011	China	2010.7–11	Rural	931	11.06	6 counties	Mix	Chinese	D-ELISA
Liu (Liu et al., 2013)	2013	China	2009–2011	Rural	103	19.42	8 city	Yes	Chinese	IFA
Xu (Xu et al., 2015)	2015	China	2013.9–10	Rural	205	47.32	8villages	Mix	Chinese	ELISA
He (He et al., 2014)	2014	China	2010.5–2012.12	Rural	31	38.71	2 villages	Yes	Chinese	D-ELISA
Xu (Xu et al., 2014)	2014	China	2010–201	Rural	444	2.03	1 city	Yes	Chinese	D-ELISA
Tan (Tan et al., 2015)	2015	China	2010–201	Rural	215	2.79	5 district	Yes	Chinese	D-ELISA
Liu (Liu et al., 2012)	2012	China	2010	Rural	19	63.16	11 city	Yes	Chinese	D-ELISA
Kimura (Kimura et al., 2018)	2018	Japan	2013.12–2014.2	Rural	107	18.69	1 country	Yes	English	ELISA

D-ELISA,; ELISA, enzyme-linked immunosorbent assay; IFA, immunofluorescence assay; NA, not available.
[a]Prevalence (%): positive rate for SFTSV-specific IgG or IgM.

SFTS and moreover that living and working with domesticated animals, especially those showing high levels of SFTSV antibodies, increases SFTS incidence rates (Liu et al., 2014b; Du et al., 2014b; Sun et al., 2015). The hypothesis was that intimate contact with animals increases the probability of a tick bite and this then increases the chances of SFTSV infection, and in addition, contact with the secretions of infected animals may also be a route of transmission leading to SFTSV infection (Sun et al., 2016; Liu et al., 2014c).

Currently, data from research studies on SFTSV infection in animals are diverse. This systematic review and meta-analysis was performed to evaluate both SFTSV infection rates and susceptible species of animals. This study included research on the seroprevalence of SFTSV in animals reported in China (19/27), Korea (4/27), Japan (3/27), and the USA (1/27). Antibodies (IgG/IgM) against SFTSV were detected in animals including goats and sheep, cattle, dogs, pigs, chickens, geese, elk, deer, shrews, rodents, boar, mink, hedgehogs, *Anser cygnoides*, and *Streptopelia chinensis*. Goats and sheep (45.70%), cattle (36.70%), dogs (27.00%), chickens (9.60%), pigs (3.20%), and rodents (3.20%) were the predominant species infected with SFTSV, and these species are closely related to human life. Stratified by feeding model in the meta-analysis, it was found that the seroprevalence of SFTSV in animals that had a confined range was significantly lower than that in free-range animals. Free-range livestock were always grazed on pastures or hills during the day and kept in household backyards at night. This situation made free-range domestic animals more susceptible to SFTSV, due to the greater opportunity of exposure to tick bites (Xu et al., 2011).

SFTSV RNA was detected in 11 animal species, including goats and sheep, cattle, dogs, pigs, chickens, cats, rodents, deer, boar, and hedgehogs, with carriage rates ranging from 0.23% to 26.31%. The SFTSV RNA sequences isolated from animals were always found to be highly homologous (>95%) to the corresponding sequences of SFTSV from human cases (Li et al., 2014). However, neither animal to animal transmission, nor animal to human transmission has been proven. Further studies to understand SFTSV transmission in nature are necessary.

In China, most cases have been distributed in low elevation hills, mountains with abundant forests, and grasslands, which are suitable for tick activity and the breeding of domestic animals (Kilpatrick and Randolph, 2012). Compared to other animals, free-range domestic animals were found to contribute significantly more to the spread of SFTSV, because of the higher viral infection rates, tick-carrying rates, and chance of human exposure. This directly increases the SFTSV exposure and transmission via tick survival, free-range livestock, and human activities (Agustin and Fuente, 2014; Pfaffle et al., 2013; Liu et al., 2015). Some studies revealed that cattle density, raising cattle, and contact with cattle ticks, rather than goats and sheep, are associated with human SFTS (Xing et al., 2017). This may be due to the important role that cattle play in agriculture activities in hilly and mountainous areas compared to goats, sheep, and others animals. Frequent close contact with cattle could increase exposure to ticks. Surveillance of the prevalence of SFTSV in wild animals found that many animals such as elk and deer, boar, feral cats, shrews, rodents, *Sores araneus*, and *Streptopelia chinensis* had been infected with SFTSV. Thus, hunters, farmers, and persons with an outdoor lifestyle may be exposed to SFTSV.

In summary, data from 27 published studies suggest that SFTSV has a wide spectrum of animal hosts, including domestic and wild animals. The susceptible animal species and the prevalence of SFTSV infection in animals were assessed systematically in this study. However, whether SFTSV undergoes animal to human transmission or animal to animal transmission requires further

Table 2
Seroprevalence of antibodies (IgG/IgM) against SFTSV in the different animal species in the included studies.

Species	Prevalence (%)	Feeding model	Reference
Goats and sheep	43/624 (6.89%)	Confined-range	17
	30/207 (14.49%)	Confined-range	18
	111/134 (82.84%)	Free-range	19
	10/92 (10.87%)	Confined-range	20
	185/277 (66.79%)	Free-range	24
	13/22 (59.10%)	Free-range	25
	19/20 (95.00%)	Free-range	30
	30/52 (60.00%)	Free-range	32
	45/59 (76.27%)	Free-range	34
	58/90 (64.44%)	Free-range	35
	92/185 (49.73%)	Free-range	37
	2/3 (66.67%)	Free-range	38
	5/74 (6.76%)	Free-range	39
	4/29 (13.79%)	Free-range	40
	2/3 (66.67%)	Free-range	41
	328/472 (69.5%)	Free-range	10
	6/48 (10.95%)	Confined-range	20
Cattle	509/842 (60.50%)	Free-range	10
	64/414 (15.50%)	Confined-range	20
	11/510 (2.20%)	Confined-range	22
	62/220 (28.18%)	Free-range	24
	14/19 (73.70%)	Free-range	25
	63/63 (100%)	Free-range	34
	33/88 (37.50%)	Free-range	35
	1/2 (50.00%)	Free-range	37
	4/5 (80.0%)	Free-range	38
	4/5 (80.00%)	Free-range	41
Dogs	136/359 (37.88%)	Free-range	10
	23/311 (7.40%)	Confined-range	24
	59/426 (13.84%)	Confined-range	28
	1/2 (50.00%)	Free-range	30
	4/35 (11.43%)	Confined-range	32
	30/40 (75.00%)	Free-range	34
	6/140 (4.29%)	Confined-range	35
	6/11 (54.54%)	Free-range	38
	6/11 (54.54%)	Free-range	41
	5/47 (10.64%)	Confined-range	42
Pigs	26/839 (3.10%)	Confined-range	10
	17/365 (4.66%)	Confined-range	24
	2/56 (3.57%)	Confined-range	34
	5/220 (2.27%)	Confined-range	35
	4/10 (40.00%)	Confined-range	37
Chickens	250/527 (47.4%)	Free-range	10
	6/501 (1.20%)	Confined-range	24
	1/300 (0.33%)	Confined-range	35
	1/149 (0.67%)	Confined-range	39
	1/78 (1.28%)	Confined-range	40
Geese	2/120 (1.67%)	Confined-range	24
	1/3 (33.33%)	Confined-range	39
	1/3 (33.33%)	Free-range	21
Elk	7/39 (18.00%)	Wild	20
Deer	35/296 (11.82%)	Wild	20
	5/21 (23.81%)	Wild	26
	5/20 (25%)	Wild	42
Shrews	4/89 (4.50%)	Wild	21
	7/102 (6.84%)	Wild	27
Rodents	5/666 (0.75%)	Wild	21
	38/872 (4.36%)	Wild	24
	13/473 (2.75%)	Wild	27
	1/94 (1.06%)	Wild	34
	20/103 (19.42%)	Wild	36
	2/94 (2.12%)	Wild	39
Boars	35/190(18.42%)	Wild	23
	1/54 (1.85%)	Wild	26
	20/93 (12.51%)	Wild	27
	10/40 (25%)	Wild	42
Mink	15/178 (8.42%)	Confined-range	31
Hedgehogs	2/75 (2.67%)	Wild	24
	9/14 (64.28%)	Wild	29
Anser cygnoides	5/70 (7.14%)	Wild	27
Streptopelia chinensis	2/85 (2.35%)	Wild	27

SFTSV, severe fever with thrombocytopenia syndrome virus.

Table 3
Seroprevalence of total antibodies (IgG/IgM) against SFTSV in different animal species.

Species	Characters	No. studies	Prevalence (%)[a]	95% CI for prevalence[a]	Heterogeneity		Model[c]
					p-Value[b]	I^2 (%)	
Goats and sheep		15	45.70	28.40–63.00	<0.001	99.2	R
	Confined-range	4	8.30	6.60–10.10	0.025	67.8	F
	Free-range	11	58.60	42.00–75.20	<0.001	98.1	R
Cattle		7	36.70	13.00–60.30	<0.001	99.6	R
	Confined-range	2	8.70	−4.30–21.80	<0.001	98.0	R
	Free-range	5	49.00	28.50–69.50	<0.001	97.0	R
Dogs		10	27.00	16.60–37.50	<0.001	96.60	R
	Confined-range	5	9.70	5.20–14.30	0.001	79.6	R
	Free-range	4	55.20	31.90–78.50	<0.001	88.9	R
Rodents		6	3.20	1.10–5.20	<0.001	89.1	R
Chickens		5	9.60	3.50–15.60	<0.001	99.1	R
	Confined-range	4	0.60	0.20–1.10	0.483	0.00	F
Pigs		5	3.20	2.3–4.10	>0.05	51.80	F

SFTSV, severe fever with thrombocytopenia syndrome virus; CI, confidence interval.
[a] Seroprevalence of total antibodies (IgG/IgM) against SFTSV.
[b] *p*-Value of *Q*-test for heterogeneity. When the *p*-value was <0.05, the random-effects model was used to assess the summary seroprevalence.
[c] F: fixed model; R: random model.

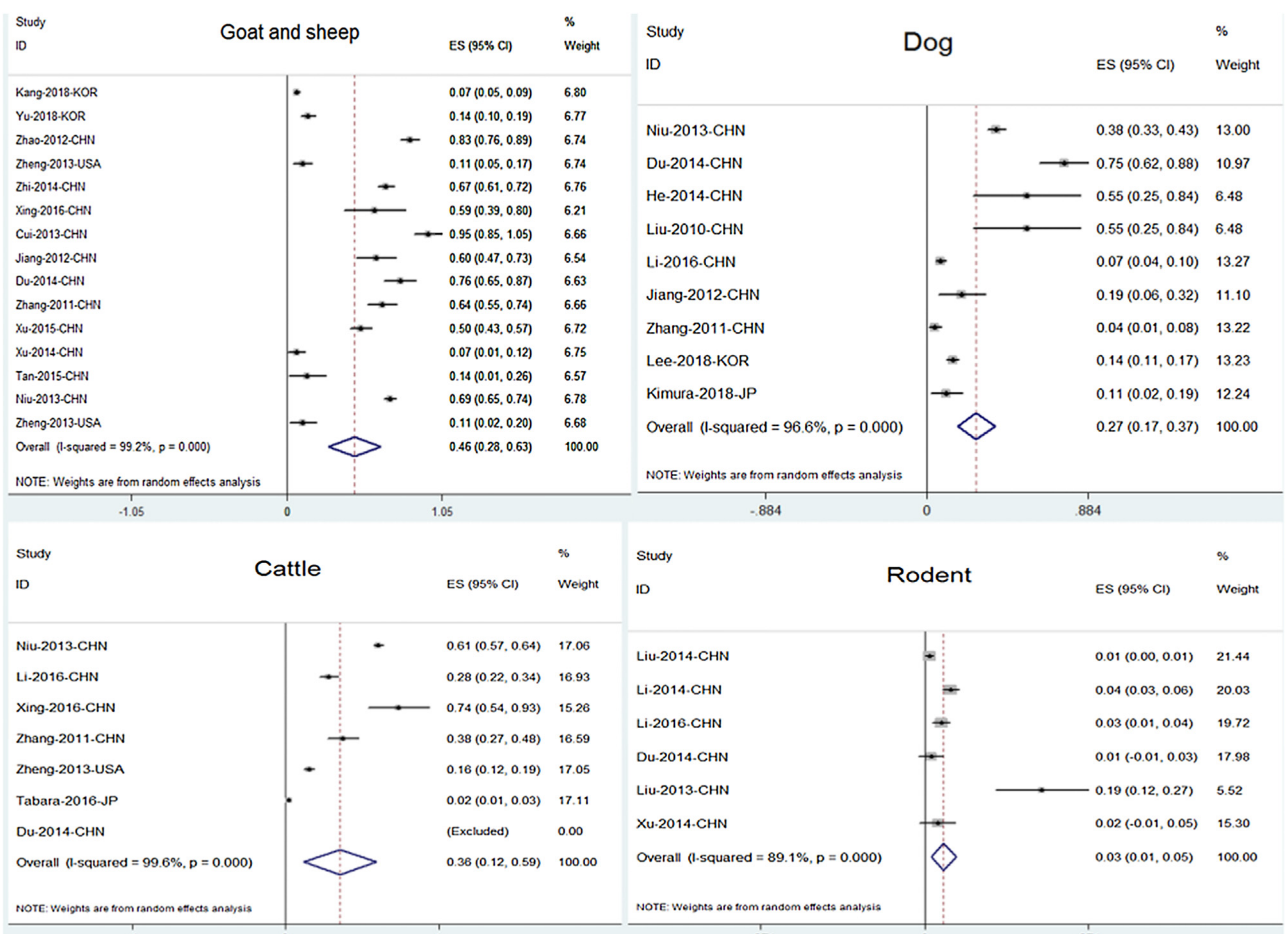

Figure 2. Forest plots of seroprevalence for total antibodies against SFTSV in the six main animal species.

study. This study has several limitations. First, significant heterogeneity was detected across studies. Second, many unmeasured factors, such as the epidemic strength of SFTSV in the study area, may have influenced the results.

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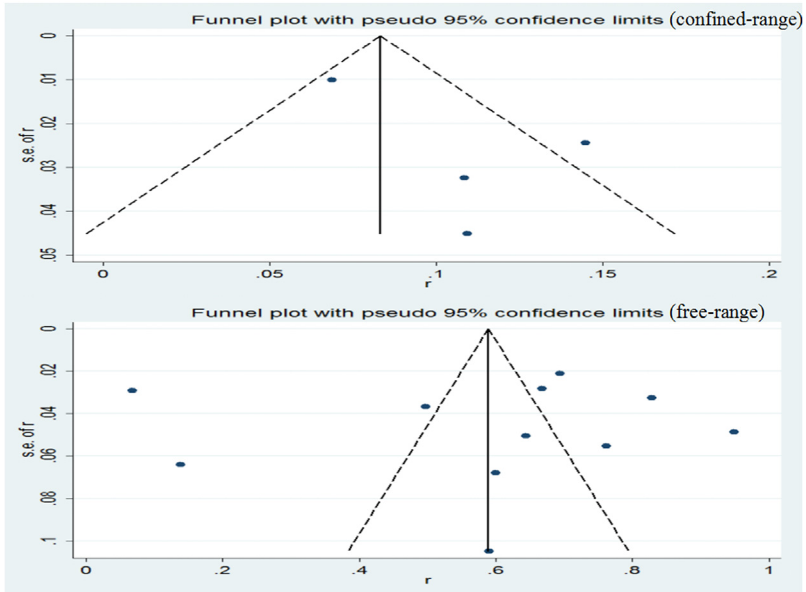

Figure 3. Funnel plot assessing publication bias in studies reporting SFTSV seroprevalence (goats and sheep).

Table 4
SFTSV RNA positivity as detected in the different animal species.

Species	RNA-positive (%)	Feeding model	References
Goats and sheep	18/737 (2.44%)	Confined-range	17
	2/207 (2.00%)	Confined-range	18
	2/22 (9.10%)	Free-range	25
	3/52 (5.77%)	Free-range	32
	18/472 (3.81%)	Free-range	10
Cattle	35/842 (4.16%)	Free-range	10
	5/19 (26.31%)	Free-range	25
	1/21 (4.76%)	Confined-range	32
Dogs	19/359 (5.29%)	Free-range	10
	1/35 (2.85%)	Confined-range	32
	1/426 (0.23%)	Confined-range	43
Pigs	22/839 (2.62%)	Confined-range	10
	4/240 ((1.7%)	Confined-range	44
Chickens	9/527 (1.70%)	Free-range	10
Cats	22/126 (17.46%)	Wild	45
	1/215 (0.47%)	Confined-range	43
Rodents	1/103 (0.97%)	Wild	21
	2/66 (3.03%)	Wild	46
	1/116 (0.86%)	Wild	21
	1/83 (1.20%)	Wild	21
	1/270 (0.37%)	Wild	27
	2/56 (3.57%)	Wild	46
	1/66 (1.51%)	Wild	27
	4/37 (10.81%)	Wild	46
	13/154 (8.44%)	Wild	46
Shrews	2/77 (2.60%)	Wild	21
	3/52 (5.76%)	Wild	46
	3/184 (1.63%)	Wild	27
Deer	1/21 (4.76%)	Wild	26
Boar	2/54 (3.70%)	Wild	26
Hedgehogs	8/159 (5.03%)	Wild	27

SFTSV, severe fever with thrombocytopenia syndrome virus.

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Ethical approval

The study was approved by the Ethics Committee of the Zhoushan Center for Disease Control and Prevention.

Conflict of interest

The authors have declared that no competing interests exist.

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