Global epidemiology of severe fever with thrombocytopenia syndrome virus in human and animals: a systematic review and meta-analysis

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Summary

Background Since the initial identification of the Severe Fever with Thrombocytopenia Syndrome (SFTS) in ticks in rural areas of China in 2009, the virus has been increasingly isolated from a diverse array of hosts globally, exhibiting a rising trend in incidence. This study aims to conduct a systematic analysis of the temporal and spatial distribution of SFTS cases, alongside an examination of the infection rates across various hosts, with the objective of addressing public concerns regarding the spread and impact of the disease.

Methods In this systematic review and meta-analysis, an exhaustive search was conducted across multiple databases, including PubMed, Web of Science, Embase, and Medline, CNKI, WanFang, and CQVIP. The literature search was confined to publications released between January 1, 2009, and May 29, 2023. The study focused on collating data pertaining to animal infections under natural conditions and human infection cases reported. Additionally, species names were unified using the National Center for Biotechnology Information (NCBI) database. The notification rate, notification death rate, case fatality rate, and infection rates (or MIR) were assessed for each study with available data. The proportions were pooled using a generalized linear mixed-effects model (GLMM). Meta-regressions were conducted for subgroup analysis. This research has been duly registered with PROSPERO, bearing the registration number CRD42023431010.

Findings We identified 5492 studies from database searches and assessed 238 full-text studies for eligibility, of which 234 studies were included in the meta-analysis. For human infection data, the overall pooled notification rate was 18.93 (95% CI 17.02–21.05) per ten million people, the overall pooled notification deaths rate was 3.49 (95% CI 2.97–4.10) per ten million people, and the overall pooled case fatality rate was 7.80% (95% CI 7.01%–8.69%). There was an increasing trend in notification rate and deaths rate, while the case fatality rate showed a significant decrease globally. Regarding animal infection data, among 94 species tested, 48 species were found to carry positive nucleic acid or antibodies. Out of these, 14 species were classified under *Arthropoda*, while 34 species fell under *Chordata*, comprising 27 *Mammalia* and 7 *Aves*.

Interpretation This systematic review and meta-analysis present the latest global report on SFTS. In terms of human infections, notification rates and notification deaths rates are on the rise, while the case fatality rate has significantly decreased. More SFTSV animal hosts have been discovered than before, particularly among birds, indicating a potentially broader transmission range for SFTSV. These findings provide crucial insights for the prevention and control of SFTS on a global scale.

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Research in context

Evidence before this study

Severe fever with thrombocytopenia syndrome (SFTS) is a zoonotic disease that was first described in rural areas of China. A previous review presented the epidemiology, clinical features, and diagnostic criteria of SFTSV, and another systematic review and meta-analysis listed the animal hosts of SFTSV. We searched 7 databases using a comprehensive search strategy to identify studies on SFTSV published between Jan 1, 2009 and May 29, 2023 and found that the virus has been increasingly isolated from a diverse array of hosts globally, exhibiting a rising trend in incidence.

Added value of this study

In this systematic review and meta-analysis, we defined and estimated the notification rate, notification deaths rate and case fatality rate of SFTS. Our findings suggest that There was an increasing trend in notification rate and deaths rate, while the case fatality rate showed a significant decrease globally. At the same time, we used the NCBI Taxonomy Database to match the species names of SFTS hosts reported in the previous literature, which could help us unify and standardize the naming of species and provide a more comprehensive and detailed host list than the previous literature review.

Implications of all the available evidence

Reports of SFTS are increasing, which means its spread may be expanding, but it has not been fully studied worldwide. Further research should be conducted to monitor SFTSV among migrating birds, explore the mechanism of cross-species transmission of SFTSV, and standardize the reporting of species names. More research and better-quality evidence can help build mathematical transmission models that policymakers can use to develop prevention and control programs in a timely manner, as well as provide a reference for similar virus studies.

Introduction

Severe fever with thrombocytopenia syndrome (SFTS) is a zoonotic infectious disease caused by severe fever with thrombocytopenia syndrome virus (SFTSV), which has been continuously spreading in East Asia in recent years. SFTS was first discovered in rural areas of Hubei and Henan in central China. SFTSV was successfully isolated and sequenced in 2010.[1] SFTSV was named *Dabie bandavirus* by the International Committee on Viruses (ICTV) in 2019, belonging to the genus *bandavirus*, family *Philippines*, Order *Bunyavirales*.[2] SFTSV is a single stranded negative stranded RNA virus, consisting of three segments: large (L), medium (M), and small (S). The L segment encodes RNA dependent RNA polymerase (RdRp); The M segment encodes glycoproteins Gn and Gc, which form the envelope; The S fragment encodes nuclear proteins (Np) and nonstructural proteins (NSs), and the role of Np in the formation of viral RNA envelope interferes with host interferon production.[1,3,4] From 2011 to 2021, 18,902 cases of SFTS were reported from 533 counties in 154 prefecture-level cities in 27 provinces in China, with a case fatality rate of 5.11%. The reported cases mainly concentrated from April to October, especially the highest incidence from May to June, with obvious seasonal characteristics.[5] SFTS was later discovered in South Korea and Japan.[6] As of July 31, 2022, Japan has reported a total of 763 cases and 92 deaths.[6,7] As of 2018, the cumulative number of cases in South Korea reached 866.[6] This trend of continuous diffusion deserves our attention.

Ticks are considered as carriers of SFTSV transmission.[8] *Haemaphysalis longicornis* is considered the main vector tick, and its distribution is strongly correlated with the distribution of SFTS cases.[9] Additionally, evidence suggests that SFTSV could be transmitted from human to human,[10–13] adding another critical layer of complexity to controlling the spread of this virus. A previous systematic review pointed out that anti-SFTSV antibodies (IgG or IgM) or SFTSV RNA were detected in 16 animals (excluding ticks).[14] At present, the spread of SFTS continues to expand, and there is no vaccine available for prevention or specific drugs available for treating infections.[3,15–17] A deep understanding of the human infection status and potential hosts of SFTSV is crucial for drug developers, vaccine manufacturers, clinicians, and policy makers. This understanding can not only provide key information for early monitoring and prevention of the epidemic, but also guide the formulation of public health policies, in order to establish a more sensitive disease monitoring system and emergency response mechanisms on a global scale. Previously, data on human infections were mostly published at the level of individual countries,[5,15,18,19] and data comparisons from a global perspective were only updated until 2018.[20,21] Further updates are needed on the reporting status of SFTS in human. Additionally, there was evidence that SFTSV can be transmitted directly from domestic cat to human.[22] Therefore, to obtain a more comprehensive screening of infection in animal hosts, we collected global literature and reclassified the reported species in the study.

Methods

Search strategy and selection criteria

We identified the search term (Appendix 1 p 2) and searched seven database, PubMed, Web of Science, Embase, Medline, CNKI, Chinese WanFang Database, and CQVIP. Considering that SFTS was first reported in 2009, we have limited the date to January 1, 2009 to May 29, 2023 (search date). We have not made any restrictions on the language of the article. Previously, we submitted the Protocol on PROSPERO with registration number CRD42023431010.

For human studies, our inclusion criteria are as follows: (1) Epidemiological studies reported by government public health agencies or case outcomes reported by hospitals that can represent a regional level; (2) Reports that included the time, location (at least at the level of secondary administrative divisions or above), number of cases, or number of deaths; (3) Clear diagnostic criteria. For animal studies, our inclusion criteria are (1) Specimens collected from the natural environment; (2) Reports that included the time of collection, location, testing object, and testing method. The following studies will be excluded: (1) The data was not sufficient to calculate the indicators; (2) The detected object is not SFTSV; (3) The infection rate obtained from animal infection treatment under laboratory conditions; (4) Species could not be matched to NCBI Taxonomy Database.

Data extraction and risk of bias assessment

Zotero (version 6.0.2) is used to remove duplicate literature. After deduplication, the literature was imported into Endnote (version X9, Clarivate) and the titles and abstracts of the identified studies were screened to exclude unrelated articles that clearly did not meet the inclusion criteria. This step will be independently performed by two individuals (HC and LC) to ensure consistency and minimize deviations. The differences during the screening process are resolved through consensus or submitted to the third responsible person (YX). Data extraction using Excel 2021 (Microsoft Corp). We will extract the following information: the author, the year of publication, the region of the study, the number of reported cases or reported incidence rate of humans, the number of reported deaths or reported mortality of humans, the sample size of animals, the number of positive animals, the infection rate (or the minimum infection rate) of animals, the test object, and the test method. The data will be extracted by two individuals (HC and LC). If the population data of the area where the infection case is located is missing, we will actively query the official report. The sources of these reports include the China Economic and Social Big Data Research Platform (https://data.cnki.net/),[23] website of Japan Bureau of Statistics (https://dashboard.e-stat.go.jp/en/),[24] website of South Korean Bureau of Statistics (https://kosis.kr/eng/).[25] Due to the heterogeneity of species names in different literatures, we have conducted species reclassification work to improve the classification information of animal orders, families, genus, and species in the records, using the NCBI Taxonomy Database as a standard reference. This part of the work is carried out by one person in charge (HC). Considering the large number of literatures, we use Endnote software to generate a unique Paper ID for each article. All data validation is carried out by two individuals (ZF and QW). Throughout the process of literature selection and data extraction, team members will hold regular meetings and discussions to ensure consensus is reached and any differences are resolved. The research will follow the PRISMA guidelines to ensure transparency and quality of the review process report.

To assess the risk of bias, the Joanna Briggs Institute risk of bias assessment tool will be used.[26] This tool consists of ten questions (Appendix 2 p 3), with answer options of "Yes", "No", or "Unclear". We give each item a score of 1 (answer "Yes") or 0 (answer "No" or "Unclear"). The overall risk of research bias is divided into low risk (defined as 8–10), medium risk (4–7), or high risk (≤3).[27]

Data analysis

In the study of human infection, we defined and estimated three indicators, namely notification rate, notification deaths rate, and case fatality rate. The notification rate is defined as the proportion of reported cases in the population of a certain region to the total population within a certain period of time. The notification mortality rate is defined as the proportion of deaths in reported cases to the total population of a certain region during a certain period of time. Case fatality rate is defined as the proportion of deaths reported in a certain region to the total number of cases during a certain period of time. In research on animal infections, some studies confirm infection through RNA detecting, while others confirm infection through antibodies detecting. RNA detection, also known as nucleic acid detection, is based on the RNA sequence of SFTSV as the detection target. The virus gene is amplified in vitro through PCR, and the amplified virus target gene is identified, labeled, and judged to detect virus infection in the early stage, providing direct evidence of virus infection.[28,29] Antibodies detecting is based on the principle of SFTSV entering the animal body and producing antibodies in the body. It is determined by whether antigen-bound antibody proteins are produced in the collected samples.[30] Antibody detecting reflects current or historical infection with SFTSV.[28] Due to the inconsistent significance of RNA detecting and antibodies detecting, the infection indicators of the two cannot be combined. We focus on two indicators, infection rate and minimum infection rate (MIR). MIR is defined as the ratio of the number of positive test tubes or pools to the number of

tested animals, and is only reported in the results of RNA detecting. Infection rate is defined as the proportion of positive animals to the number of tested animals. The specific calculation formula is shown in the Supplementary (Appendix 3 pp 3–4).

Data analyses were performed using R statistical software (version 4.3.0) with the package meta-6.5.0[31] for these analyses. The notification rate, notification deaths rate, case fatality rate and infection rates (or MIR) were assessed for each study using available data. The rates were pooled using a generalized linear mixed-effects models (GLMMs),[32] which include random effects to account for the variability in true effect sizes between studies. Meta-regressions (using the Restricted Estimation of Maximum Likelihood [REML] method) were conducted to determine whether there were statistical differences between different subgroups within each group. Subgroup analysis would only be conducted when the number of studies was no less than 10.[33] Additionally, we conducted a meta-regression to analyze annual trends in notification rates, notification death rates, and case fatality rates across countries. First, we analyzed the overall trends by combining data from all countries. Second, we analyzed trends for individual countries. Finally, to further explore trend differences between countries, we included interaction terms between country and year in the analysis.[34–36] We used the Knapp Hartung (KH) adjustment method to calculate the confidence interval of the effect value.[37] τ^2 quantifies this variance in true effects. I^2 statistic will be used to measure the heterogeneity of different studies.

Results

We identified 5492 studies and removed 3136 duplicates (Fig. 1). After screening 2356 titles and abstracts, a further 1931 studies were excluded. We assessed 425 full-text studies for eligibility, of which 187 studies were excluded. We therefore included a total of 238 full-text studies in this systematic review, of which 234 studies were included in meta-analysis. Among the 238 studies, 132 studies had a low risk of bias, 102 were moderate, and 4 were high (Appendix 4 pp 6–35).

Between 2009 and 2021, the global incidence of Severe Fever with Thrombocytopenia Syndrome (SFTS) was predominantly observed in East and Southeast Asia. The first documented cases of SFTS emerged in Henan Province, China, in 2009.[38] South Korea[39] and Japan[40] reported their first cases in 2012 and 2013, respectively. Vietnam joined the list of affected countries with confirmed cases in 2017.[41] Co-infection with SFTSV and *Orientia tsutsugamushi*, the causative agent of scrub typhus, was first reported in South Korea in 2013,[42] and subsequently documented in Myanmar in 2018.[43]

138 studies were used to estimate the notification rate. The overall pooled notification rate was 18.93 (95% CI 17.02–21.05, I^2 = 99.57%) cases reported per ten million people in all studies (Table 1; Appendix 5 p 36). The notification rate showed an upward trend from 2009 to 2021 ($\beta_{unadjusted}$ = 0.12, 95% CI 0.08–0.16, P < 0.001, Appendix 5 p 39). Analysis of individual countries indicated that only the upward trend in China was statistically significant (Fig. 2). However, the interaction terms showed no significant differences in trends between countries ($P_{Country[Japan\ vs.\ China]\times Year}$ = 0.942, $P_{Country[South\ Korea\ vs.\ China]\times Year}$ = 0.593, Appendix 5 p 39). The highest pooled notification rate was in South Korea, with 48.49 (95% CI 29.80–78.89, I^2 = 98.28%) cases notified per ten million people, while the lowest is Japan, reporting 2.46 (95% CI 0.93–6.49, I^2 = 94.21%) cases per ten million people (Table 1; Appendix 5 pp 36–37). The pooled notification rate was higher in women than in men, but the difference was not statistically significant (Table 1; Appendix 5 p 38). Among all age groups, the group aged 70–79 had the highest pooled notification rate, reporting 283.27 (95% CI 24.88–3224.95) cases per ten million people (Table 1). The highest notification rate was concentrated between April and September (Table 1).

88 studies were used to estimate the notification deaths rate. The overall pooled notification deaths rate was 3.49 (95% CI 2.97–4.10, I^2 = 96.97%) deaths per ten million people in all studies (Table 1; Appendix 5 p 36). The notification death rates showed an upward trend between 2009 and 2021 ($\beta_{unadjusted}$ = 0.08, 95% CI 0.02–0.14, P = 0.009, Appendix 5 p 39). Analysis of individual countries indicated an upward trend in both China and South Korea, while Japan exhibited a downward trend (Fig. 2). However, the interaction terms indicated no significant differences in trends between countries ($P_{Country[Japan\ vs.\ China]\times Year}$ = 0.179, $P_{Country[South\ Korea\ vs.\ China]\times Year}$ = 0.546, Appendix 5 p 39). The highest pooled notification deaths rate was in South Korea, with 7.66 (95% CI 3.13–18.75, I^2 = 85.76%) deaths per ten million people; The lowest is Japan, reporting 0.65 (95% CI 0.19–2.22, I^2 = 39.86%) deaths per ten million people (Table 1; Appendix 5 pp 36–37). The pooled notification deaths rate was higher in males than in females, but the difference was not statistically significant (Table 1; Appendix 5 p 38). In existing studies, the 80+ years old group reported the highest pooled notification deaths rate, with 340.85 (95% CI 153.99–754.44) deaths reported per ten million people (Table 1). The highest notification deaths rate was concentrated between July and September (Table 1).

There were 78 studies used to estimate the case fatality rate. The overall pooled case fatality rate was 7.80% (95% CI 7.01%–8.69%, I^2 = 89.76%) in all studies (Table 1; Appendix 5 p 36). The case fatality rate exhibited a declining trend from 2009 to 2021 ($\beta_{unadjusted}$ = –0.10, 95% CI –0.14 to –0.07, P < 0.001). Individual country analyses revealed that all three countries demonstrated a significant downward trend (Fig. 2). Further examination through interaction effect

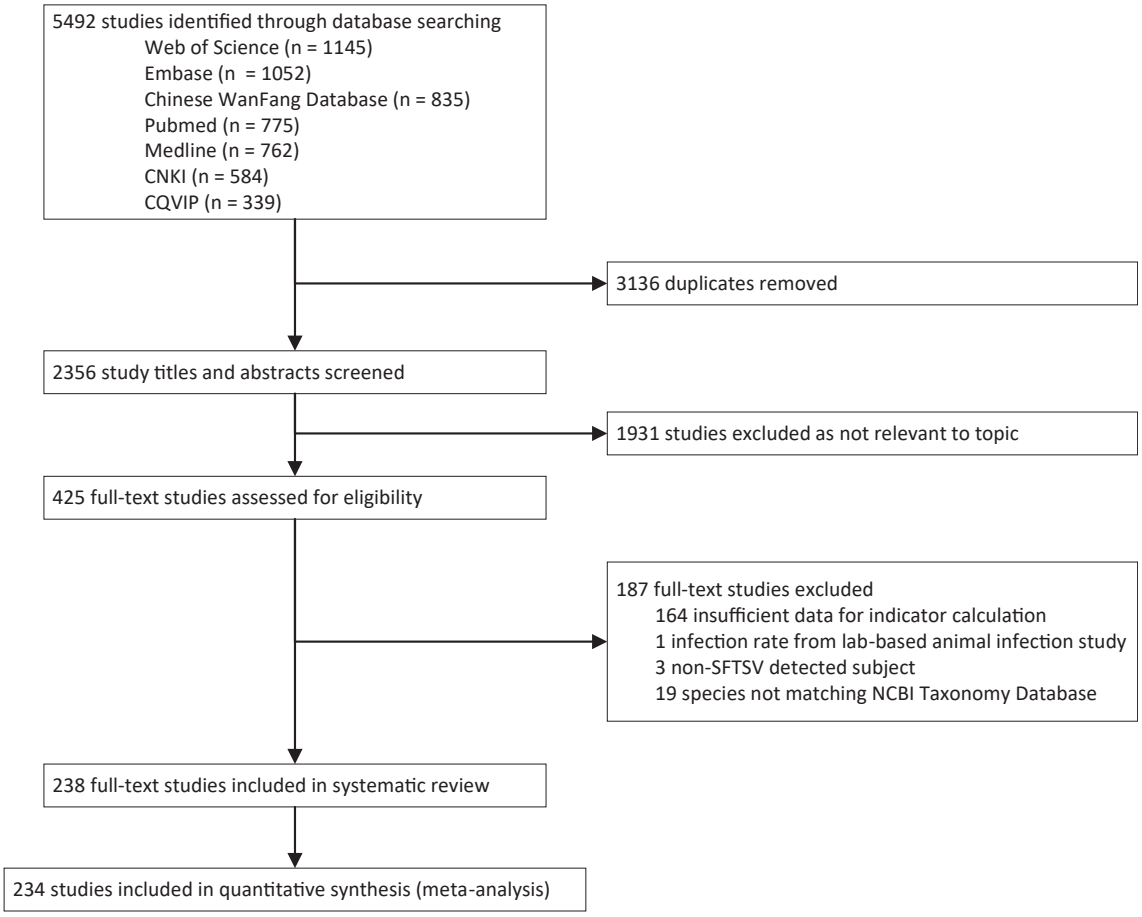

Fig. 1: Study selection.

analysis indicated no significant disparity in trends between countries ($P_{Country[Japan\ vs.\ China]\times Year}$ = 0.323, $P_{Country[South\ Korea\ vs.\ China]\times Year}$ = 0.330, Appendix 5 p 39). The highest combined case fatality rate was in South Korea, at 18.54% (95% CI 10.92%–31.48%, I^2 = 77.21%); The lowest is China, at 7.40% (95% CI 4.64% –8.25%, I^2 = 89.20%) (Table 1; Appendix 5 pp 36–37). The pooled case fatality rate was higher in males than in females, but the difference was not statistically significant (Table 1; Appendix 5 p 38). In existing studies, the 80+ year old combination has the highest pooled case fatality rate, which is 17.40% (95% CI 8.45%–35.81%) (Table 1). The highest concentration of pooled case fatality rate was from July to September, which was 20.3% (95% CI 6.10%–69.71%) (Table 1).

94 animal species were subjected to testing for the presence of RNA or antibodies, of which 46 animal species did not show evidence of these target agents (Appendix 5 pp 40–43). Notably, the remaining 48 animal species were found to test positive for either RNA or antibodies detecting. Among them, 14 belong to the phylum *Arthropoda*, 34 belong to the phylum *Chordatata*, including 27 *Mammalia* and 7 *Aves* (Appendix 5 pp 40–43). Among the studies that were measured by infection rate and determined to be positive by RNA detection, the highest of *Mammalia*, *Aves* and *Arachnida* were *Cricetulus migratorius* (50.00%, 95% CI 5.89%–94.11%), *Gallus* (1.57%, 0.76%–3.20%) and *Amblyomma testudinarium* (13.62%, 95% CI 2.09%–53.80%), respectively. Among the studies that were determined to be positive by antibodies detection and measured by infection rate, the highest of *Mammalia* and *Aves* were *Mustela sibirica* (91.11%, 95% CI 78.59%–96.62%), and *Phasianus colchicus* (42.86%, 95% CI 20.65%–68.37%), respectively. Among the studies confirmed positive by RNA detection and measured by MIR, only *Ovis aries* in *Mammalia* had a MIR of 3.06% (95% CI 0.00%–98.19%), while *Haemaphysalis hystricis* (6.90%, 95% CI 0.20%–73.55%) had the highest MIR in *Arachnida* (Fig. 3).

Based on available studies, we performed subgroup analysis of *H. longicornis*, *Haemaphysalis flava*, *Sus scrofa*, *Canis lupus* by country (Appendix 5 pp 44–47). No matter measured by infection rate or MIR, the positive

	Notification Rate (Per 10,000,000 persons)		Notification Deaths Rate (Per 10,000,000 persons)		Case Fatality Rate (Per 100 persons)	
	Number of Studies	Pooled Estimate (95% CI)	Number of Studies	Pooled Estimate (95% CI)	Number of Studies	Pooled Estimate (95% CI)
Overall	138	18.93 (17.02–21.05)	88	3.49 (2.97–4.10)	78	7.80 (7.01–8.69)
Country						
China	127	18.59 (16.68–20.72)	83	3.51 (2.97–4.13)	73	7.40 (6.64–8.25)
Japan	5	2.46 (0.93–6.49)	2	0.65 (0.19–2.22)	2	19.42 (9.39–40.16)
South Korea	9	48.49 (29.80–78.89)	5	7.66 (3.13–18.75)	5	18.54 (10.92–31.48)
Gender						
Female	41	20.69 (15.18–28.20)	14	3.12 (2.11–4.61)	14	7.90 (6.61–9.43)
Male	41	19.36 (14.21–26.39)	14	3.46 (2.34–5.10)	14	9.56 (8.05–11.36)
Age group						
0–9	1	0.08 (0.00–8.25)	..	..	..	..
10–19	1	0.22 (0.00–16.41)	..	..	..	..
20–29	1	0.42 (0.01–27.70)	..	..	..	..
30–39	1	1.01 (0.02–64.44)	..	..	..	..
40–49	2	17.66 (0.86–362.94)	..	..	..	..
50–59	3	77.37 (6.72–890.55)	2	25.98 (9.82–68.75)	3	5.77 (2.93–11.37)
60–69	3	150.98 (13.08–1743.33)	2	75.55 (34.13–167.22)	3	8.23 (4.70–14.43)
70–79	3	283.27 (24.88–3224.95)	2	136.08 (61.48–301.20)	3	10.81 (6.18–18.90)
80+	3	257.50 (21.55–3076.60)	2	340.85 (153.99–754.44)	3	17.40 (8.45–35.81)
Month						
1–3	19	0.91 (0.54–1.53)	2	0.02 (0.00–0.37)	1	1.43 (0.05–43.87)
4–6	26	14.96 (9.85–22.72)	2	1.33 (0.21–8.31)	2	10.65 (0.79–143.61)
7–9	26	16.25 (10.71–24.64)	2	3.71 (0.80–17.29)	2	20.63 (6.10–69.71)
10–12	1	8.73 (0.20–390.86)	..	..	..	..

Table 1: **The estimated notification rate, notification deaths rate and case fatality rate of human by country, gender, age group and month.**

number of *H. longicornis* in Japan was 0, and the infection rate and MIR among the three countries showed great heterogeneity, with I^2 being 97% and 94%, respectively (Appendix 5 p 44). *Sus scrofa* tested positive in all three countries, but the differences among the three countries were not statistically significant ($P_{subgroup} > 0.05$) (Appendix 5 p 46). The positive rate of *C. lupus* was higher in China (18.78%, 95% CI 8.95%–35.22%) than in Japan (1.44%, 95% CI 0.10%–17.02%) and the difference was statistically significant ($P_{subgroup} = 0.008$) (Appendix 5 p 47).

Discussion

To our knowledge, this is the first study to find that the notification rate of SFTS worldwide shows an upward trend. This increasing trend has sparked our attention to possible influencing factors. We speculate that the increase of the notification rate of SFTS and the expansion of their transmission range may be influenced by the increasing finding of host animals and the expansion of ticks distribution.[44] Ticks may expand the spread of SFTS through the migration of migratory birds.[45,46] Encouragingly, despite the increase in the notification rate of SFTS, we observed a significant decrease in the case fatality rate of SFTS in three countries. This indicates that the improvement of the medical system and the advancement of treatment methods have played a positive role in reducing patient mortality rates. China has carried out nationwide SFTS monitoring and required online reporting according to Class B statutory infectious diseases.[47] In addition, Chinese clinical experts have proposed a consensus on the diagnosis and treatment of SFTS,[48] improving the recognition ability of early patients, developing appropriate disease monitoring plans, and timely identifying critically ill patients. Furthermore, Chinese experts have placed significant focus on the management of severe SFTS cases. They have integrated scientific evidence through extensive practice and discussion and published an expert consensus on the diagnosis and treatment.[49]

The SFTS notification rate and deaths rate in South Korea are significantly higher than those in China and Japan, similar to previous research results by Miao et al.,[20] who used machine learning methods to predict high-risk areas, with the vast majority of the Korean Peninsula located within it. Our research found that notification rate, notification mortality rate and mortality rate were high from April to September, which may be related to the increase in the number of vector ticks during this period.[50–52] Besides, outdoor activities such as human cultivation, tea picking, grazing, and travel are also mostly carried out in summer and autumn, increasing opportunities for contact with SFTSV hosts

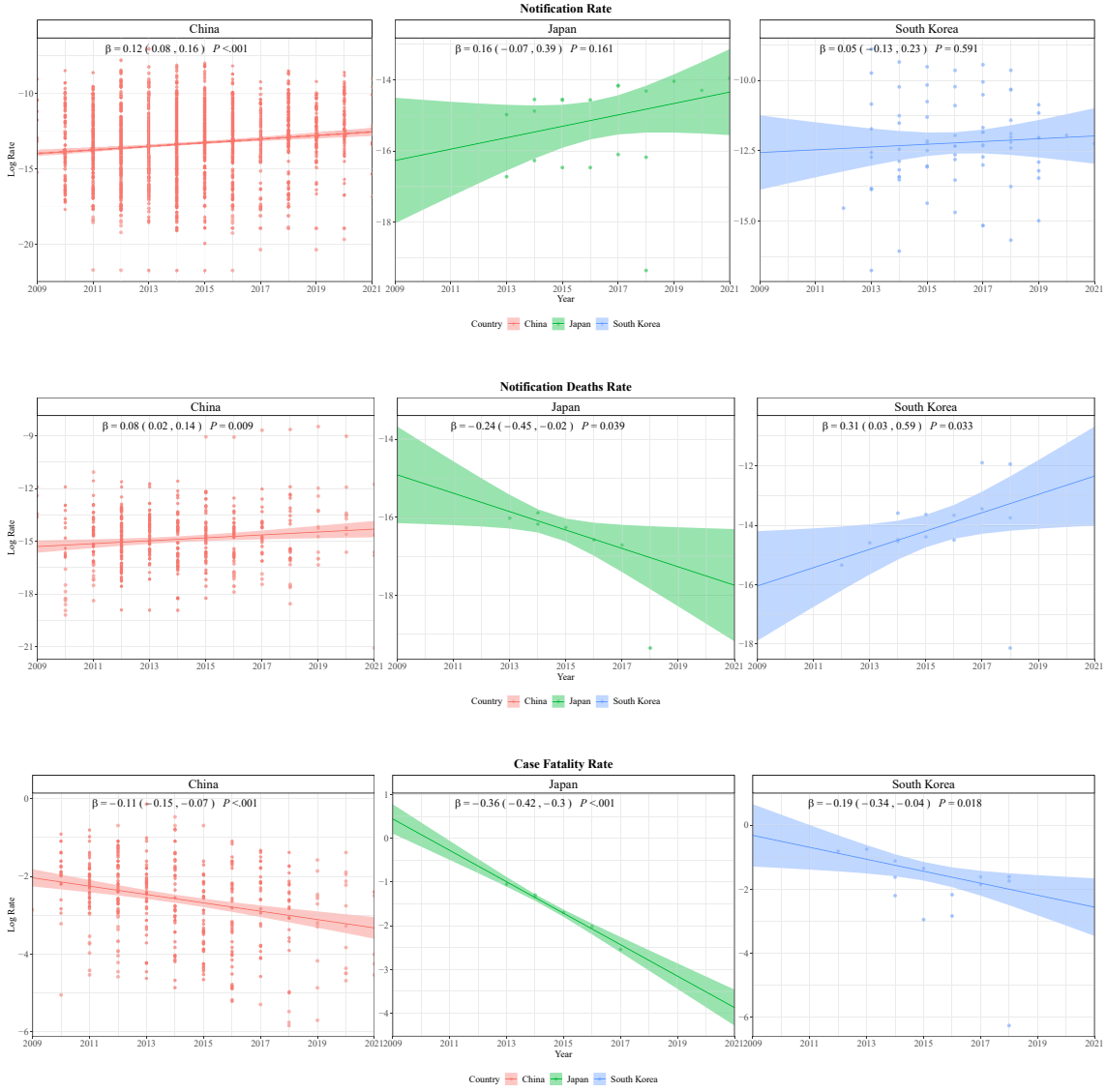

Fig. 2: Trend analysis of the log-transformed notification rate, notification death rate, and case fatality rate across countries using meta-regression. The y-axis represents the natural logarithm of the rates (notification rate, notification death rate, and case fatality rate, without scaling by ten million). The solid lines represent the meta-regression predicted values, and the ribbons represent the 95% confidence intervals.

and vector ticks.[20,52–54] In addition, global warming may create a more favorable environment for the spread of SFTS.[5] Considering the climate and regional factors, it is noteworthy that there are few cases in Myanmar[43] and Vietnam.[41] Antibodies against SFTSV were detected in the serum of farmers in Pakistan.[55] Three patients in Bangkok and surrounding areas tested positive for SFTSV RNA[56] (specific sample details were not provided). We suggest that future research can consider using landscape genetics[57] methods to further explore the transmission patterns of SFTS by combining landscape and genetics, and provide strong support for the formulation of public health policies.

The NCBI Taxonomy database, which is a widely recognized biological taxonomy database[58,59] that provides standardized species names and classification information, was used to match and unifying species names in our study. A total of 48 animals were found to have antibodies or RNA during testing, which exceeds the categories covered by previous review reports.[14] The continuous discovery of the hosts of SFTSV suggests that it may have a wider range of transmission and the potential of crossing species. Animals that tested negative for both RNA and antibodies detecting do not mean they are not hosts of SFTSV.

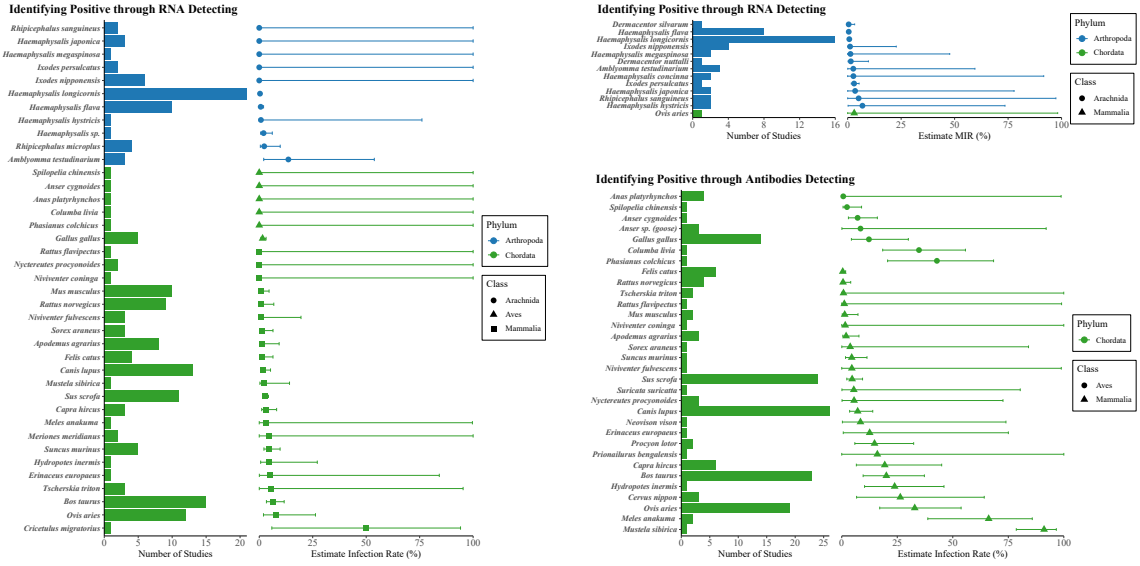

Fig. 3: The estimate infection rate (minimum infection rate) of animals.

We noticed that only ticks (*Ixodida*) in the *Arthropoda* phylum can be detected for antibodies or RNA. Both domestic and international studies have shown that the RNA sequence of the virus isolated from ticks has high homology with the SFTSV sequence isolated from SFTS patients.[60,61] *H. longicornis*, which is found in East Asia, Southeast Asia, eastern Australia, and northern North America,[41,62–64] is considered to be the main vector of SFTSV. A new Phlebovirus closely related to SFTSV was identified in Missouri in 2012 and named Heartland virus.[65] *H. longicornis* has also been discovered in the United States,[66] indicating that the USA may be at risk for SFTSV transmission. However, no cases of SFTS have been reported in Australia. In addition to *H. longicornis*, *Ixodes sinensis*, *H. flava*, *A. testudinarium* and *Ixodes nipponensis* are also vectors of SFTSV. Notably, *I. sinensis* has frequently been recorded feeding on residents and tourists in central and southern China.[67] Both *I. nipponensis*[68–70] and *H. flava*[68,71,72] have been documented in China, Japan and South Korea. *A. testudinarium* has been identified in a range of locations including China,[73] Japan,[74] South Korea,[75] India,[76] Bangladesh,[77] Thailand,[78] Malaysia,[79] Singapore[80] and Vietnam.[41] All this evidence may explain why SFTSV has been found in East and Southeast Asia, but it also highlights the risk of cross-regional transmission of SFTSV. Our study found that the infection rate of ticks is very low, whether measured by MIR or Rate. A previous meta-analysis reported a tick infection rate of 8%.[81] Ticks alone are not sufficient to maintain the presence of SFTSV in the natural environment.[46]

It is worth noting that *Anser cygnoides*, which has strong migration ability,[82] can be tested positive. Previous study proposed that ticks may expand the transmission range of SFTS through the migration of migratory birds, but they did not test the birds for SFTSV through neither antibodies detecting RNA testing.[9] We suggest sampling and monitoring migratory birds in epidemic areas to help understand the possible transmission range of SFTSV. The heterogeneity of infection among the same species in different countries may be due to the sampling method used in the study. China conducts regular sampling and testing of animals in and around the location of the case,[83–86] especially domestic livestock such as *Sus scrofa*, *Capra hircus*, *C. lupus*, etc. Japan and South Korea explored whether animals carry SFTSV, selecting samples from potential human case locations.[87,88] This sampling difference may lead to differences in infection rates among different countries. It is worth noting that the high incidence areas of SFTS are usually located at similar latitudes and have similar climate patterns.[20,89–91] Therefore, climate factors may not necessarily be the main factor explaining differences in animal infection rates. In future research, potential biases that may exist in the process of sample collection, testing, and analysis in different countries should be more fully considered to ensure the accuracy and comparability of research results.

Our research faces multiple limitations. Firstly, in regions where only incidence or mortality rates were provided without specific case numbers, we verified that the calculation method was the reported number of cases or deaths divided by the region's total population. We then used the data provided in articles or obtained official population data to calculate the number of cases or deaths. While this calculation method may introduce some bias, it allows us to include data from as many

regions as possible in our study. Secondly, our exhaustive analysis of risk factors for infection in different populations has not yet been completed, and insufficient data on serum infection may limit a deep understanding of the mechanisms of infection. Thirdly, the existing occupational analysis has the problems of inconsistent standards and multiple occupational identities of individuals, and the differences in detection methods are not sufficiently distinguishable, which may affect the accuracy of infection data. In animal studies, due to data limitations, we have not been able to perform a comprehensive subgroup analysis of host animals, and we have not made a clear distinction between geographic levels when analyzing human and animal data, making the pool-rate calculation potentially inaccurate. Finally, the scope of our analysis is limited to the country level and we fail to delve into data at smaller geographic scales, which may affect the understanding of geographical differences. Therefore, we must carefully consider the influence of these limiting factors when interpreting the findings.

Contributors

ZJ, XY and HC designed the study, and all authors oversaw its implementation. HC, LC and XYW coordinated and performed all review activities, including searches, study selection (including inclusion and exclusion of abstracts), data extraction, and quality assessment. All data validation is carried out by ZF and QW. HC and SP did the data analyses. SY, YF, and ZY improved the methods of this study. HC wrote the initial draft of the manuscript. SS, ZW, JZ, JC, BL, TL, XC, and HC contributed to the writing and subsequent versions of the manuscript. All authors reviewed the study findings and read and approved the final version before submission.

Data sharing statement

All datasets generated and analyzed for this work are available by contacting HLC through pkubruce@bjmu.edu.cn.

Declaration of interests

All authors declare no competing interests.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.lanwpc.2024.101133.

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