Am. J. Trop. Med. Hyg., 97(4), 2017, pp. 992–996
doi:10.4269/ajtmh.16-0967

Review Article

The Emergence of Severe Fever with Thrombocytopenia Syndrome Virus

Jesus A. Silvas[1,2] and Patricia V. Aguilar[1,2,3]*

[1]*Department of Pathology, University of Texas Medical Branch, Galveston, Texas;* [2]*Institute for Human Infection and Immunity, University of Texas Medical Branch, Galveston, Texas;* [3]*Center for Tropical Diseases, University of Texas Medical Branch, Galveston, Texas*

Abstract. Severe fever with thrombocytopenia syndrome (SFTS) is a newly recognized hemorrhagic fever disease found throughout Asia with a case fatality rate between 12% and 30%. Since 2009, SFTS has been reported in China throughout 14 Chinese Provinces. In addition, SFTS has been recognized in South Korea and Japan with the first confirmed cases reported in 2012. A similar disease, caused by the closely related Heartland virus, was also reported in the United States in 2009. SFTS is caused by SFTS virus, a novel tick-borne virus in the family *Bunyaviridae*, genus *Phlebovirus*. Unlike other mosquito- and sandfly-borne bunyaviruses, SFTS virus has not been extensively studied due to its recent emergence and many unknowns regarding its pathogenesis, life cycle, transmission, and options for therapeutics remains. In this review, we report the most current findings in SFTS virus research.

INTRODUCTION

Severe fever with thrombocytopenia syndrome (SFTS) is a newly emerging viral hemorrhagic fever that was first recognized in China in 2009.[1] The disease etiological agent, SFTS virus, was isolated from patients presenting fever with thrombocytopenia, leukocytopenia, and gastrointestinal symptoms.[1] During the initial investigations, *Anaplasma phagocytophilum* was suspected as the etiological cause of the outbreaks; nevertheless, further investigation uncovered the presence of the novel bunyavirus, SFTS virus, and confirmed the presence of SFTS virus genetic material and SFTS virus antibodies in most patient sera.[1,2] The virus was genetically and antigenically classified as a new member of the *Phlebovirus* genus.[1,3]

Ecological investigations carried out to identify the vectors involved in the transmission of the virus identified *Haemaphysalis longicornis* ticks as the main vector for SFTS virus.[4] The tick vector has a vast geographic distribution in China, and confirmed cases were initially reported in seven provinces in eastern and central China, which includes a human population of approximately 500 million.[1,2] To date, SFTS cases have been reported in 14 provinces in China according to the surveillance data obtained by the Chinese Center for Disease Control and Prevention and the epidemic areas continue to expand.[5] Notably, SFTS virus cases were also recognized in South Korea and Japan in 2012. Furthermore, a virus closely related to SFTS virus, Heartland virus, was isolated in 2009 in the United States and is associated with fatal disease.[6–9] This has only raised awareness for the public health importance of these newly recognized pathogens.

Epidemiology of SFTS. Although SFTS was first recognized in 2009, the disease first appeared in rural areas of central China in the spring of 2006.[10] Since then, the number of SFTS cases have increased considerably in China from 511 in 2011 to nearly 1,500 cases in 2012.[11] The initial case fatality rate reported was up to 30%; however, recent estimates range between 10% and 12% with the exception of Japan and South Korea where the mortality rate is as high as 32–47%.[1,12–14] The disease is mainly seen among farmers engaged in agricultural activities or forest workers, and the majority of the cases (86%) are detected in subjects 50 years of age or older with fatality rates increasing with age.[5,15] The SFTS case incidence was found to be similar for both females and males,[5] although a female-to-male ratio of 1.58 was reported in an early study in the Xinyang Province based on laboratory-confirmed SFTS cases.[15] It has also been noted that approximately 67% of the cases are reported between the months of May–July in China, May–August in South Korea, and April–August in Japan coinciding with the high tick density during these months.[5,13,15,16]

The SFTS virus antibody prevalence among healthy subjects residing in endemic areas in China ranges between 0.8% and 3.8%.[17,18] Given the limited information available about the duration of antibody responses after exposure to SFTS virus, studies are needed to elucidate if the low prevalence levels are due to low exposure levels, limitation in the sensitivity of antibody detection methods, or short duration of antibody responses after SFTS virus exposure. A recent study in a small cohort of previously SFTS hospitalized patients detected SFTS virus antibodies even 4 years after hospitalization; nevertheless, the antibody levels had decreased overtime among most study subjects.[19] Thus, studies to evaluate the duration of antibody responses in a larger study group after SFTS virus infection are still needed.

Due to the increased number of SFTS cases reported in recent years, the presence of SFTS virus within blood donations was assessed from April to October 2012 at multiple blood centers in the Henan Province in China. A modest antibody prevalence of 0.54% among the healthy blood donors was reported.[20] Viral RNA was detected in only two of the 17,208 plasma samples tested and viral load levels were low (less than 20 plaque-forming units/mL).[20] Thus, these findings raise some questions as to whether SFTS virus constitutes a significant threat to blood banks. However, this possibility should not be completely overruled, particularly in endemic areas of SFTS virus circulation.

SFTS cases have also been reported in Japan and South Korea.[7,13,21] In South Korea, the first SFTS case was retrospectively identified on a sample collected in August 2012 from a female with history of insect bites while working on a

*Address for correspondence to Patricia V. Aguilar, Department of Pathology, Center for Tropical Diseases, University of Texas Medical Branch, 301 University Boulevard, Galveston, TX 77550. E-mail: pvaguila@utmb.edu

crop farm and who died of multiple organ failure.[6] Additional cases were later identified by the Korean Center for Disease Control and Prevention in 2013 with a case fatality rate of 47.2%.[13] However, a more recent study including SFTS cases reported from January 2013 to December 2015 described an overall case fatality rate of 32.6%.[22] Retrospective study of SFTS has also been conducted in Japan using serum samples collected from 23 patients suspected of having SFTS and a total of 11 cases were confirmed as SFTS.[7] A map depicting the geographical locations of confirmed SFTS cases is shown in Figure 1.

Ecology and transmission cycle. Ticks were initially suspected as the primary SFTS virus vector because patients recounted being bitten by ticks prior to illness onset and because ticks were frequently found in areas where the patients reside. Further investigations resulted in the isolation of SFTS virus from the ticks *H. longicornis* and *Rhipicephalus microplus* collected in areas with endemic SFTS virus transmission in China.[23–25] Notably, SFTS virus RNA was detected in *H. longicornis* at different developmental stages (i.e., larvae, nymphs, and adults) with minimum infection rates of 0.2–1.4, and also in eggs oviposited by engorged adult females.[24,26] The data suggest that transtadial and transovarial transmission of SFTS virus occurs in ticks. These findings could potentially account for maintenance of the virus in nature. In South Korea, SFTS virus has also been isolated from *Amblyomma testudinarium* and *Ixodes nipponensis* suggesting that they may serve as additional vectors in this country.[21] Nevertheless, laboratory vector competence studies are still needed to conclusively confirm their capacity to transmit SFTS virus.

In China, domestic animals are considered potential reservoir hosts for the virus because antibodies against SFTS virus have been detected in goats, cattle, sheep, pigs, dogs, and chickens.[17,27,28] In these studies, SFTS virus RNA was detected only in a small fraction of animals (1.7%–5.3%) and none of these animals showed signs of illness. Virus isolates were obtained from some of these viremic animals and sequencing analyses revealed that they were closely related to isolates obtained from SFTS patients and ticks.[27] Convincing evidence that ticks and possibly goats participate in the SFTS virus transmission cycle was obtained by Jiao and others.[23] Experimental infection of goats with SFTS virus induced detectable viremia in three of five infected animals on day three postinfection. Interestingly, viremia lasted only 24 hours and no viral RNA was detected from nasopharyngeal or anal

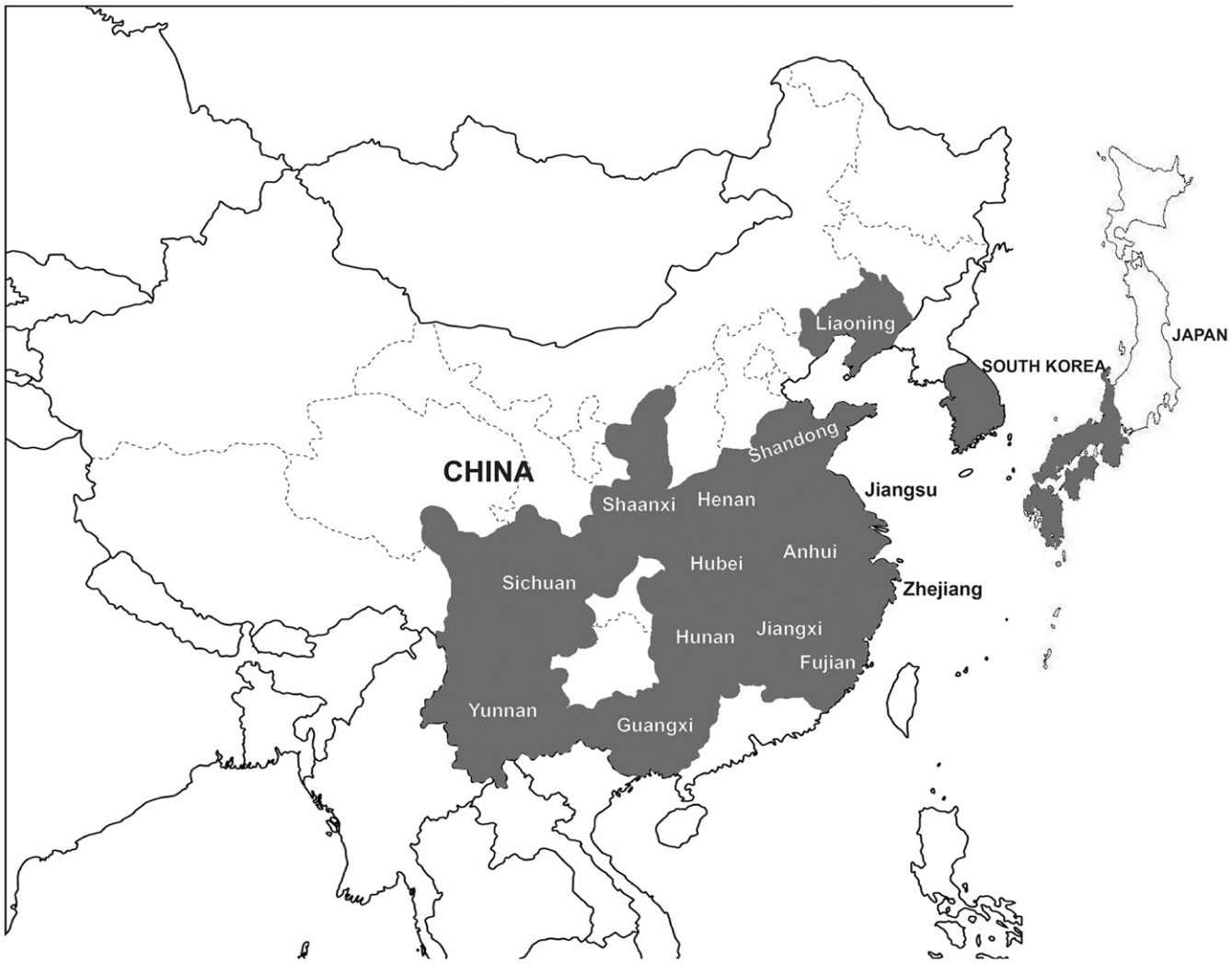

FIGURE 1. Geographic distribution of confirmed severe fever with thrombocytopenia syndrome cases.

swabs suggesting that the virus is not shed through respiratory or digestive routes. Control animals that had close contact with the infected animals did not develop antibody responses indicating that close contact transmission of SFTS virus among goats does not occur.[23] Despite this knowledge, evidence demonstrating that the viremia detected in goats experimentally infected with SFTS virus is high enough to infect ticks was not obtained in the study. In another set of experiments conducted by the same authors, goats were naturally infected by exposure to ticks and seroconversion monitoring and tick collection were performed on a daily basis. All goats were naturally infected by day 34 and viral RNA was detected in the majority of the animals, as well as in *H. longicornis* ticks collected from them. Not surprisingly, virus isolates obtained from both one goat and its parasitic tick samples demonstrated high sequence homology, supporting the conclusion of natural transmission of SFTS virus.[23]

Prevalence in rodents, particularly *Apodemus agrarius* and *Rattus norvegicus*, has also been assessed and approximately 3% were found to be SFTS virus antibody positive.[17] Yet, the role of rodents in the transmission cycle of SFTS virus remains to be elucidated.

In South Korea, feral cats may also play a role in SFTS virus transmission since 17% of the samples obtained from feral cats had detectable viral RNA present.[29] In Japan, SFTS virus antibodies were also detected in cattle as well as wild boars.[30,31] Recent studies have also suggested a link between the occurrence of SFTS virus and migratory birds.[32] The distribution of *H. longicornis* and the migratory birds route between mainland China, South Korea, and Japan suggest that water fowl are responsible for the dispersal of SFTS virus-infected ticks.[32] As expected, phylogenetic studies performed on isolates from Japan and South Korea have also demonstrated genetic similarities with SFTS virus strains isolated in mainland China.[33,34] Although tick to human is believed to be the main route of SFTS virus transmission, evidence supporting possible person-to-person transmission of SFTS virus has also been documented.[10,35–37] Given the fact that SFTS virus RNA is found in bodily secretions, this further supports the potential for human-to-human SFTS virus transmission without the involvement of the tick vector; nevertheless, risk factor analyses did not detect being in close contact with SFTS patient as one of the main risk factor for infection.[38]

SFTS pathogenesis. Due to its recent emergence, the pathogenesis of SFTS virus has not been fully defined. We do know that inhibition of innate immune responses is a common feature among the mosquito- and sandfly-borne bunyaviruses and this occurs through a variety of mechanisms, including protein degradation and downregulation of host cell transcription.[39–44] The bunyavirus nonstructural protein (NSs) was found to be the major virulence factor involved in the inhibition of interferon (IFN) responses as well as inhibition of host cell gene transcription.[44,45] Interestingly, SFTS virus-infected patients have almost no detectable IFN-β in their sera suggesting that SFTS virus is also capable of inhibiting IFN responses.[12] Consistent with these observations, studies have demonstrated the ability of the SFTS virus NSs to inhibit IFN responses.[46–49] However, the mechanism by which the tick-borne SFTS virus inhibits IFN responses differs to those described for mosquito-borne phleboviruses (Table 1). In contrast to protein degradation or inhibition of host cell transcription, the particular ability of SFTS virus NSs to inhibit the innate immune response correlates with the spatial relocation or sequestration of key components of the IFN response (i.e., retinoic inducible gene I, tank-binding kinase 1, and the E3 ubiquitin ligase TRIM25) into the SFTS virus NSs positive-cytoplasmic structures.[46,50,51] Interestingly, live cell imaging studies revealed that a portion of the SFTS virus NSs-positive structures were secreted into the extracellular space and were endocytosed by neighboring cells.[52] Ultrastructural analysis of purified extracellular structures revealed that these structures contain SFTS virus-like particles. Further studies demonstrated that these structures were able to efficiently mount and maintain a productive SFTS virus infection even in the presence of neutralizing antibodies raised against SFTS virus suggesting that the virus is capable of receptor-independent transmission.[52] Although these studies have suggested that SFTS virus has the capacity of receptor-independent transmission in vitro, studies are still needed to understand the contribution of extracellular vesicles to SFTS virus pathogenesis in vivo and the potential role that these "infectious" structures play in the dissemination and pathogenesis of SFTS virus. This information will also reveal the challenges that the vesicles may pose in the development of effective vaccines against SFTS virus.

Abnormal production of proinflammatory cytokines has been recently detected in patients with a severe form of the disease and higher serum viral load correlated with elevated cytokine levels.[53] Key immune mediators such as interleukin (IL)-1β, IL-8, macrophage inflammatory protein (MIP)-1α, and MIP-1β were elevated during the acute phase of the disease in patients who succumbed to infection when compared with those who survived SFTS.[53] SFTS virus has been also shown to bind to platelets. This phenomenon has been suggested as the possible cause of thrombocytopenia observed in patients, because virus bound to platelets are recognized by macrophages and phagocytosed, leading to a decrease in platelet count.[54] Decreased levels of $CD3^+$ and $CD4^+$ T lymphocytes have also been reported in SFTS-infected patients, including in those who succumbed to the disease.[14,55] Additionally,

TABLE 1
Summary of the mechanism of inhibition of IFN responses by representative mosquito and tick-borne phleboviruses

	Phlebovirus	NSs distribution	Mechanism of IFN inhibition/target
Mosquito	Rift Valley fever virus	Nuclear	Proteosomal degradation of PKR,TFIIH p62; inhibition of host cell transcription; sequestration of TFIIFH p44 and XPB
	Punta Toro virus	Cytoplasmic	Inhibition of IFN induction
Tick borne	Severe fever with thrombocytopenia syndrome virus	Endosomal	Sequestration of RIG-1, TBK-1/IKKe, TRIM25, STAT 1/2, IRF3 into endosomal structures

IFN = interferon.

gastrointestinal symptoms, gastric ulcerative lesions with hemorrhage, and central nervous system compromise have been described after SFTS virus infection.[56,57]

Therapies. Currently, no vaccine of antiviral therapy is available to treat SFTS. The Chinese Ministry of Health initially approved the use of ribavirin to treat SFTS based on results of in vitro studies; nevertheless, the effectiveness of ribavirin to treat SFTS was evaluated in patients with a clinical diagnosis of SFTS, and no beneficial effect of ribavirin on platelet recovery or viral load reduction was noted among on fatal or nonfatal cases.[58] Supportive treatment, including treatment with plasma exchange followed by convalescent plasma therapy from SFTS survivors, intravenous immunoglobulin, and corticosteroid had been reported[59–61]; however, it is difficult to determine whether these treatments have any positive effect due to the limited data available.

CONCLUSIONS AND FUTURE DIRECTIONS

This review summarizes the main aspects of the epidemiological, ecological, and pathogenesis studies of SFTS virus. Although epidemiological and ecological studies have incriminated ticks as the main vector, the specific reservoir host(s) involved in the transmission of the virus needs further examination. Studies with SFTS virus have revealed certain virus pathogenesis details that differ from what is known about phleboviruses. However, studies to fully understand the mechanism of disease pathogenesis should be further pursued. In particular, the ability of SFTS virus to evade host immune responses and the contribution of extracellular vesicles to virus pathogenesis and dissemination remains to be elucidated. Furthermore, there is an urgent need to develop vaccine and antivirals against SFTS virus, which may help to control the disease.

Received December 9, 2016. Accepted for publication April 11, 2017.

Published online August 7, 2017.

Acknowledgments: We would like to thank Linsey Yeager for critically reading the manuscript and for helpful suggestions.

Financial support: This study was supported by the National Institutes of Health (NIH) grants number F31 AI124662-01 and AI115286-01A1. Patricia V. Aguilar was also partially supported by 5R24AI120942-02.

Authors' addresses: Jesus A. Silvas and Patricia V. Aguilar, Department of Pathology, University of Texas Medical Branch at Galveston, Pathology, Galveston, TX, E-mails: jasilvas@utmb.edu and pvaguila@utmb.edu.

REFERENCES

1. Yu XJ, et al., 2011. Fever with thrombocytopenia associated with a novel bunyavirus in China. *N Engl J Med 364:* 1523–1532.
2. Zhang YZ, et al., 2011. Hemorrhagic fever caused by a novel tick-borne Bunyavirus in Huaiyangshan, China. *Zhonghua Liu Xing Bing Xue Za Zhi 32:* 209–220.
3. Palacios G, Savji N, Travassos da Rosa A, Guzman H, Yu X, Desai A, Rosen GE, Hutchison S, Lipkin WI, Tesh R, 2013. Characterization of the Uukuniemi virus group (*Phlebovirus*: *Bunyaviridae*): evidence for seven distinct species. *J Virol 87:* 3187–3195.
4. Luo LM, et al., 2015. *Haemaphysalis longicornis* ticks as reservoir and vector of severe fever with thrombocytopenia syndrome virus in China. *Emerg Infect Dis 21:* 1770–1776.
5. Liu K, et al., 2015. A national assessment of the epidemiology of severe fever with thrombocytopenia syndrome, China. *Sci Rep 5:* 9679.
6. Kim KH, Yi J, Kim G, Choi SJ, Jun KI, Kim NH, Choe PG, Kim NJ, Lee JK, Oh MD, 2013. Severe fever with thrombocytopenia syndrome, South Korea, 2012. *Emerg Infect Dis 19:* 1892–1894.
7. Takahashi T, et al., 2013. The first identification and retrospective study of severe fever with thrombocytopenia syndrome in Japan. *J Infect Dis 209:* 816–827.
8. Savage HM, Godsey MS, Lambert A, Panella NA, Burkhalter KL, Harmon JR, Lash RR, Ashley DC, Nicholson WL, 2013. First detection of heartland virus (*Bunyaviridae*: *Phlebovirus*) from field collected arthropods. *Am J Trop Med Hyg 89:* 445–452.
9. Muehlenbachs A, Fata CR, Lambert AJ, Paddock CD, Velez JO, Blau DM, Staples JE, Karlekar MB, Bhatnagar J, Nasci RS, Zaki SR, 2014. Heartland virus-associated death in Tennessee. *Clin Infect Dis 59:* 845–850.
10. Liu Y, Li Q, Hu W, Wu J, Wang Y, Mei L, Walker DH, Ren J, Yu XJ, 2012. Person-to-person transmission of severe fever with thrombocytopenia syndrome virus. *Vector Borne Zoonotic Dis 12:* 156–160.
11. Ding F, et al., 2013. Epidemiologic features of severe fever with thrombocytopenia syndrome in China, 2011–2012. *Clin Infect Dis 56:* 1682–1683.
12. Liu Q, He B, Huang SY, Wei F, Zhu XQ, 2014. Severe fever with thrombocytopenia syndrome, an emerging tick-borne zoonosis. *Lancet Infect Dis 14:* 763–772.
13. Park SW, Han MG, Yun SM, Park C, Lee WJ, Ryou J, 2014. Severe fever with thrombocytopenia syndrome virus, South Korea, 2013. *Emerg Infect Dis 20:* 1880–1882.
14. Hiraki T, et al., 2014. Two autopsy cases of severe fever with thrombocytopenia syndrome (SFTS) in Japan: a pathognomonic histological feature and unique complication of SFTS. *Pathol Int 64:* 569–575.
15. Liu K, et al., 2014. Epidemiologic features and environmental risk factors of severe fever with thrombocytopenia syndrome, Xinyang, China. *PLoS Negl Trop Dis 8:* e2820.
16. Kato H, Yamagishi T, Shimada T, Matsui T, Shimojima M, Saijo M, Oishi K; SFTS Epidemiological Research Group-Japan, 2016. Epidemiological and clinical features of severe fever with thrombocytopenia syndrome in Japan, 2013–2014. *PLoS One 11:* e0165207.
17. Zhao L, et al., 2012. Severe fever with thrombocytopenia syndrome virus, Shandong Province, China. *Emerg Infect Dis 18:* 963–965.
18. Cui F, Cao HX, Wang L, Zhang SF, Ding SJ, Yu XJ, Yu H, 2013. Clinical and epidemiological study on severe fever with thrombocytopenia syndrome in Yiyuan County, Shandong Province, China. *Am J Trop Med Hyg 88:* 510–512.
19. Huang YT, Zhao L, Wen HL, Yang Y, Yu H, Yu XJ, 2016. Neutralizing antibodies to severe fever with thrombocytopenia syndrome virus 4 years after hospitalization, China. *Emerg Infect Dis 22:* 1985–1987.
20. Zeng P, et al.; International Component of the NHLBI Recipient Epidemiology and Donor Evaluation Study-III (REDS-III), 2015. A study of seroprevalence and rates of asymptomatic viremia of severe fever with thrombocytopenia syndrome virus among Chinese blood donors. *Transfusion 55:* 965–971.
21. Yun SM, Lee WG, Ryou J, Yang SC, Park SW, Roh JY, Lee YJ, Park C, Han MG, 2014. Severe fever with thrombocytopenia syndrome virus in ticks collected from humans, South Korea, 2013. *Emerg Infect Dis 20:* 1358–1361.
22. Choi SJ, et al.; for Korea SFTS Clinical Network, 2016. Severe fever with thrombocytopenia syndrome in South Korea, 2013–2015. *PLoS Negl Trop Dis 10:* e0005264.
23. Jiao Y, Qi X, Liu D, Zeng X, Han Y, Guo X, Shi Z, Wang H, Zhou M, 2015. Experimental and natural infections of goats with severe fever with thrombocytopenia syndrome virus: evidence for ticks as viral vector. *PLoS Negl Trop Dis 9:* e0004092.
24. Wang S, et al., 2015. SFTS virus in ticks in an endemic area of China. *Am J Trop Med Hyg 92:* 684–689.
25. Zhang YZ, et al., 2011. The ecology, genetic diversity and phylogeny of Huaiyangshan virus in China. *J Virol 86:* 2864–2868.
26. Li Z, et al., 2016. Ecology of the tick-borne *Phlebovirus* causing severe fever with thrombocytopenia syndrome in an endemic area of China. *PLoS Negl Trop Dis 10:* e0004574.

27. Niu G, et al., 2013. Severe fever with thrombocytopenia syndrome virus among domesticated animals, China. *Emerg Infect Dis 19:* 756–763.
28. Li Z, et al., 2014. Seroprevalence of antibodies against SFTS virus infection in farmers and animals, Jiangsu, China. *J Clin Virol 60:* 185–189.
29. Hwang J, Kang JG, Oh SS, Chae JB, Cho YK, Cho YS, Lee H, Chae JS, 2016. Molecular detection of severe fever with thrombocytopenia syndrome virus (SFTSV) in feral cats from Seoul, Korea. *Ticks Tick Borne Dis 8:* 9–12.
30. Hayasaka D, Fuxun Y, Yoshikawa A, Posadas-Herrera G, Shimada S, Tun MM, Agoh M, Morita K, 2016. Seroepidemiological evidence of severe fever with thrombocytopenia syndrome virus infections in wild boars in Nagasaki, Japan. *Trop Med Health 44:* 6.
31. Tabara K, Fujita H, Hirata A, Hayasaka D, 2016. Investigation of severe fever with thrombocytopenia syndrome virus antibody among domestic bovines transported to slaughterhouse in Shimane Prefecture, Japan. *Jpn J Infect Dis 69:* 445–447.
32. Yun Y, et al., 2015. Phylogenetic analysis of severe fever with thrombocytopenia syndrome virus in South Korea and migratory bird routes between China, South Korea, and Japan. *Am J Trop Med Hyg 93:* 468–474.
33. Park SW, Song BG, Shin EH, Yun SM, Han MG, Park MY, Park C, Ryou J, 2014. Prevalence of severe fever with thrombocytopenia syndrome virus in *Haemaphysalis longicornis* ticks in South Korea. *Ticks Tick Borne Dis 5:* 975–977.
34. Zhang YZ, Xu J, 2016. The emergence and cross species transmission of newly discovered tick-borne *Bunyavirus* in China. *Curr Opin Virol 16:* 126–131.
35. Bao CJ, et al., 2011. A family cluster of infections by a newly recognized bunyavirus in eastern China, 2007: further evidence of person-to-person transmission. *Clin Infect Dis 53:* 1208–1214.
36. Jiang XL, et al., 2015. A cluster of person-to-person transmission cases caused by SFTS virus in Penglai, China. *Clin Microbiol Infect 21:* 274–279.
37. Yoo JR, Heo ST, Park D, Kim H, Fukuma A, Fukushi S, Shimojima M, Lee KH, 2016. Family cluster analysis of severe fever with thrombocytopenia syndrome virus infection in Korea. *Am J Trop Med Hyg 95:* 1351–1357.
38. Xing X, et al., 2016. Natural transmission model for severe fever with thrombocytopenia syndrome *Bunyavirus* in villages of Hubei Province, China. *Medicine (Baltimore) 95:* e2533.
39. Blakqori G, et al., 2007. La Crosse bunyavirus nonstructural protein NSs serves to suppress the type I interferon system of mammalian hosts. *J Virol 81:* 4991–4999.
40. Ikegami T, Narayanan K, Won S, Kamitani W, Peters CJ, Makino S, 2009. Dual functions of Rift Valley fever virus NSs protein: inhibition of host mRNA transcription and post-transcriptional downregulation of protein kinase PKR. *Ann N Y Acad Sci 1171 (Suppl 1):* E75–E85.
41. Kalveram B, Lihoradova O, Indran SV, Lokugamage N, Head JA, Ikegami T, 2013. Rift Valley fever virus NSs inhibits host transcription independently of the degradation of dsRNA-dependent protein kinase PKR. *Virology 435:* 415–424.
42. Leonard VH, Kohl A, Hart TJ, Elliott RM, 2006. Interaction of Bunyamwera Orthobunyavirus NSs protein with mediator protein MED8: a mechanism for inhibiting the interferon response. *J Virol 80:* 9667–9675.
43. van Knippenberg I, Carlton-Smith C, Elliott RM, 2010. The N-terminus of Bunyamwera orthobunyavirus NSs protein is essential for interferon antagonism. *J Gen Virol 91:* 2002–2006.
44. Weber F, Bridgen A, Fazakerley JK, Streitenfeld H, Kessler N, Randall RE, Elliott RM, 2002. Bunyamwera bunyavirus nonstructural protein NSs counteracts the induction of alpha/beta interferon. *J Virol 76:* 7949–7955.
45. Le May N, Mansuroglu Z, Léger P, Josse T, Blot G, Billecocq A, Flick R, Jacob Y, Bonnefoy E, Bouloy M, 2008. A SAP30 complex inhibits IFN-beta expression in Rift Valley fever virus infected cells. *PLoS Pathog 4:* e13.
46. Santiago FW, 2014. Hijacking of RIG-I signaling proteins into virus-induced cytoplasmic structures correlates with the inhibition of type I interferon responses. *J Virol 88:* 4572–4585.
47. Qu B, et al., 2012. Suppression of the interferon and NF-κB responses by severe fever with thrombocytopenia syndrome virus. *J Virol 86:* 8388–8401.
48. Ning YJ, Wang M, Deng M, Shen S, Liu W, Cao WC, Deng F, Wang YY, Hu Z, Wang H, 2014. Viral suppression of innate immunity via spatial isolation of TBK1/IKKE from mitochondrial antiviral platform. *J Mol Cell Biol 6:* 324–337.
49. Ning YJ, Feng K, Min YQ, Cao WC, Wang M, Deng F, Hu Z, Wang H, 2015. Disruption of type I interferon signaling by the nonstructural protein of severe fever with thrombocytopenia syndrome virus via the hijacking of STAT2 and STAT1 into inclusion bodies. *J Virol 89:* 4227–4236.
50. Ning YJ, Wang M, Deng M, Shen S, Liu W, Cao WC, Deng F, Wang YY, Hu Z, Wang H, 2014. Viral suppression of innate immunity via spatial isolation of TBK1/IKKE from mitochondrial antiviral platform. *J Mol Cell Biol 6:* 324–337.
51. Wu X, Qi X, Liang M, Li C, Cardona CJ, Li D, Xing Z, 2014. Roles of viroplasm-like structures formed by nonstructural protein NSs in infection with severe fever with thrombocytopenia syndrome virus. *FASEB J 28:* 2504–2516.
52. Silvas JA, Popov VL, Paulucci-Holthauzen A, Aguilar PV, 2016. Extracellular vesicles mediate receptor-independent transmission of novel tick-borne bunyavirus. *J Virol 90:* 873–886.
53. Sun Y, et al., 2012. Host cytokine storm is associated with disease severity of severe fever with thrombocytopenia syndrome. *J Infect Dis 206:* 1085–1094.
54. Jin C, et al., 2012. Pathogenesis of emerging severe fever with thrombocytopenia syndrome virus in C57/BL6 mouse model. *Proc Natl Acad Sci USA 109:* 10053–10058.
55. Sun L, Hu Y, Niyonsaba A, Tong Q, Lu L, Li H, Jie S, 2014. Detection and evaluation of immunofunction of patients with severe fever with thrombocytopenia syndrome. *Clin Exp Med 14:* 389–395.
56. Kaneyuki S, Yoshikawa T, Tani H, Fukushi S, Taniguchi S, Fukuma A, Shimojima M, Kurosu T, Morikawa S, Saijo M, 2016. Ulcerative lesions with hemorrhage in a patient with severe fever with thrombocytopenia syndrome observed via upper gastrointestinal endoscopy. *Jpn J Infect Dis 69:* 525–527.
57. Liu MM, Lei XY, Yu XJ, 2016. Meta-analysis of the clinical and laboratory parameters of SFTS patients in China. *Virol J 13:* 198.
58. Liu W, et al., 2013. Case-fatality ratio and effectiveness of ribavirin therapy among hospitalized patients in China who had severe fever with thrombocytopenia syndrome. *Clin Infect Dis 57:* 1292–1299.
59. Park SY, Choi W, Chong YP, Park SW, Wang EB, Lee WJ, Jee Y, Kwon SW, Kim SH, 2016. Use of plasma therapy for severe fever with thrombocytopenia syndrome encephalopathy. *Emerg Infect Dis 22:* 1306–1308.
60. Oh WS, Heo ST, Kim SH, Choi WJ, Han MG, Kim JY, 2014. Plasma exchange and ribavirin for rapidly progressive severe fever with thrombocytopenia syndrome. *Int J Infect Dis 18:* 84–86.
61. Kim UJ, Kim DM, Ahn JH, Kang SJ, Jang HC, Park KH, Jung SI, 2016. Successful treatment of rapidly progressing severe fever with thrombocytopenia syndrome with neurological complications using intravenous immunoglobulin and corticosteroid. *Antivir Ther 21:* 637–640.