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Review Article

Severe Fever with Thrombocytopenia Syndrome Virus, Crimean-Congo Haemorrhagic Fever Virus, and Migratory Birds

Keun Hwa Lee[1*], Jolyon M. Medlock[2] and Sang Taek Heo[3]

[1]Department of Microbiology and Immunology Jeju National University School of Medicine, Jeju; [2]Medical Entomology & Zoonoses Ecology, Microbial Risk Assessment, Emergency Response Dept., Public Health England, Porton Down, Wiltshire SP4 0JG, UK, and [3]Department of Internal Medicine, Jeju National University School of Medicine, Jeju, Korea

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Severe Fever with Thrombocytopenia Syndrome (SFTS) and Crimean-Congo Haemorrhagic Fever (CCHF) are tick-borne diseases belonging to the family Bunyaviridae. Since SFTS was first reported in China in 2009, the virus was isolated and confirmed in 2011, with additional reports of SFTSV expanding its geographic range from China to South Korea and Japan. CCHFV has the widest geographic distribution of any tick-borne virus, encompassing around 30 countries from eastern China through Asia, the Middle East, and southeastern Europe to Africa. During the past decade, CCHFV has emerged in new areas of Europe, Africa, the Middle East, and Asia and has increased in endemic areas. Migratory birds are considered to play a role in dispersing CCHFV vectors, and the virus. This review summarises SFTSV and CCHFV, highlighting the role of migratory birds in the transmission of tick-borne disease.

Key Words: Severe Fever with Thrombocytopenia Syndrome Virus, Crimean-Congo Hemorrhagic Fever Virus, Migratory Birds

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I. Introduction

Severe Fever with Thrombocytopenia Syndrome (SFTS) and Crimean-Congo Haemorrhagic Fever (CCHF) are tick-borne hemorrhagic fever diseases caused by SFTS and CCHF viruses respectively. Migratory birds acting as long-distance carriers of ticks containing various human pathogens have been reported globally and several studies have highlighted the role of migratory birds in the dispersal of CCHFV-carrying tick vectors (1~4). This review summarises the most recent findings on SFTSV in East Asia and CCHFV in Europe, to highlight the role of migratory birds in the transmission dynamics of tick-borne diseases.

II. Severe fever with thrombocytopenia syndrome virus (SFTSV)

SFTS is a tick-borne haemorrhagic fever caused by SFTSV (5). The first suspected SFTS case was found in rural areas of Hubei and Henan provinces in Central China in 2009 and the virus was isolated and confirmed in 2011 (5). SFTSV is an envelope, segmented (L, M, S), negative-strand RNA virus and a new additional member of genus *Phlebovirus* in the family Bunyaviridae (5). Although phleboviruses have been found in Africa and Europe for

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[*]Corresponding author: Keun Hwa Lee, Ph.D. Department of Microbiology and Immunology, Jeju National University School of Medicine Jeju, 690-756, Korea.
Phone: +82-64-754-8111, Fax: +82-64-705-2687, e-mail: yomust7@ jejunu.ac.kr

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Figure 1. Geographic Distribution of SFTS in China. Since March 2010, SFTSV was isolated from patients are shown in red. SFTS has been reported in at least 13 provinces in the central, eastern, and northeastern regions of the People's Republic of China. Most patients are farmers living in wooded, hilly, or mountainous areas, and the epidemic season is from March through November, with the peak incidence usually in June and July (5).

many years, SFTSV is the first phlebovirus isolated in China (Fig. 1) (5). SFTSV RNA was detected in the ixodid tick *Haemaphysalis longicornis* collected from animals (5). Studies in China between June 2009 and September 2010, detected viral RNA in 10 of 186 (5.4%) *H. longicornis* collected from domestic animals in areas where SFTSV RNA was also detected in human patients of SFTSV. Consequently *H. longicornis* has been identified as a possible candidate vector of SFTSV (5).

Common hosts of *H. longicornis* include most mammals, including goats, cattle, sheep, yak, donkeys, pigs, deer, cats, rats, mice, hedgehogs, weasels, brushtail possums, and humans, along with some birds (5).

Haemaphysalis longicornis ticks have been implicated as vectors of SFTSV, and high seroprevalence to SFTSV has been reported in goats (6). However, the host range of the virus has not been determined, and the role of domesticated animals in the circulation and transmission of SFTSV remains unclear (6). Therefore, Niu *et al.* investigated SFTSV in 3,039 domesticated animals in 2 counties in Shandong Province, China, from April to November 2011, reporting that SFTSV-specific antibodies were detected in 328/472 (69.5%) sheep, 509/842 (60.5%) cattle, 136/359 (37.9%) dogs, 26/839 (3.1%), pigs, and 250/527 (47.4%) chickens, SFTSV RNA was detected in all sampled animal species, but the prevalence was low, ranging from 1.7% to 5.3%. The authors concluded that SFTSV is circulating among several species of domesticated animals and between animals and humans in disease-endemic areas of China and the domesticated animals with high infection rates of SFTSV may act as amplifying hosts for the virus during the epidemic season (6).

In Korea, five species incriminated as Tick-Borne Encephalitis Virus (TBEV) vectors (*Haemphysalis longicornis*, *Haemphysalis japonica*, *Haemaphysalis flava*, *Ixodes persulcatus*, and *Ixodes nipponensis*) have been reported (7) and ten Ixodidae species have been reported on Jeju Island; *Haemaphysalis campanulata* Warburton, *H. phasiana*, *H. flava*, *Ixodes persulcatus*, *I. vespertilionis* Koch, *I. pomeranzevi* Serdyukova, *I. turdus*, *I. nipponensis*, *Boophilus microplus* (Canestrini), and *H. longicornis* (3, 8, 9). Recently *Haemaphysalis formosensis* was reported as a new species to Korea and *Haemaphysalis concinna* a new species to Jeju Island, found on migratory birds. *H. longicornis* and *H. flava* collected in Jeju Island have both tested positive by PCR for TBEV (3, 7, 10).

H. longicornisis is widely distributed in the Asia-Pacific region, including China, Korea, Japan, Australia, the Pacific Islands, and New Zealand (3, 7, 11). This distribution matches the bird migration route between China, Korea, and Japan (3, 7, 11~14), and therefore the coincident occurrence of SFTSV raises questions as to the role of migratory birds in the dissemination of both the putative vector (*H. longicornis*) and the virus (SFTSV).

The major clinical symptoms and signs in patients infected with SFTSV are acute and high fever (temperatures of 38℃ or more), thrombocytopenia (platelet count, <100,000 per cubic millimeter), leucopenia, elevated levels of serum hepatic enzymes, and multi-organ dysfunction (SFTS clinical case 1 and 2) (5, 6, 15).

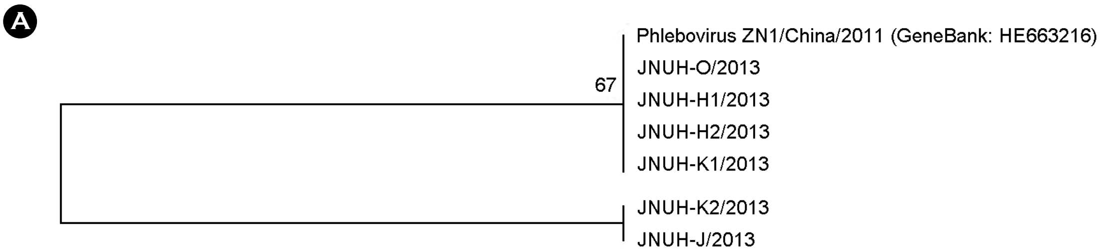
The first SFTSV was isolated from a 42-year-old man from Henan Province China (5). Since SFTS was first reported in China in 2009, SFTS has been reported in at least 13 provinces in the central, eastern, and northeastern regions of the People's Republic of China. Most patients are farmers living in wooded, hilly, or mountainous areas, and the epidemic season occurs from March through November, with the peak incidence usually in June and July (5). During early 2013 SFTS was also confirmed in Korea and western regions of Japan (16, 17).

In China, SFTSV has caused an approximately 12% case fatality rate, retrospective cases in Japan have an even higher case fatality rate, with four deaths reported from out confirmed cases (additional suspected cases still need to be confirmed) (17). In Korea in 2013, 21 cases were reported including 10 fatalities (~48% case fatality rate), with 7 of the 21 cases on Jeju Island (18).

SFTSV isolates from Japan and China are similar but not identical (17). Our phylogenetic analysis of the S segment of SFTSV, which were isolated from SFTS patients in Jeju Island, showed that these isolates were same or closely related to the viral isolates found in China (19) (Fig. 2A). These findings concur with another study that showed that the SFTSV isolates in the northern part of South Korea were closely related to the Chinese isolates (Fig. 2B) (16). This suggests therefore that there is some degree of commonality between these endemic foci, one hypothesis being a dissemination of virus by migratory birds. This argument is strengthened on account of the fact that the putative SFTSV tick vector *H. longicornis* is commonly found infesting migratory birds that are known to breed and migrate between the endemic foci in China, Korea, and Japan (3, 11~14).

III. SFTS clinical case 1

A 66-year-old farmer presented to a community hospital on Jeju Island on May 28, 2013, with a 6-day history of fever and myalgia. Because of a sudden drop in blood pressure, she was transferred to a tertiary care hospital on Jeju Island on May 31. On admission to the intensive care unit (ICU), she had a temperature of 36.9℃, blood pressure of 79/49 mmHg, an APACHE II score of 27, and a Glasgow coma scale (GCS) score of 15. Laboratory tests revealed a white blood cell (WBC) count of 2.3×10^9/l, platelet count of 72×10^9/l, aspartate aminotransferase (AST) level of 242 U/l, lactate dehydrogenase (LDH) level of 900 U/l, and creatine phosphokinase (CPK) of 88 U/l. She was treated with intravenous fluids, norepinephrine, and broad-spectrum antibiotics. She suddenly showed an altered mental status on hospital day 3 (GCS score, 11). Ribavirin (4.0 g/day) was administered orally after a positive SFTSV result from a reverse transcriptase PCR (RT-PCR). On hospital day 4, plasma exchange was performed using a COBE Spectra Apheresis System (Terumo BCT, Lakewood, CO, USA). Based on her weight and hematocrit, approximately 2,200 ml of plasma was removed and replaced with fresh frozen plasma obtained from healthy volunteer donors each time (speed of blood output, 23~33 ml/min; maximum quantity of vitro blood circulation, 170 ml; interval of plasma



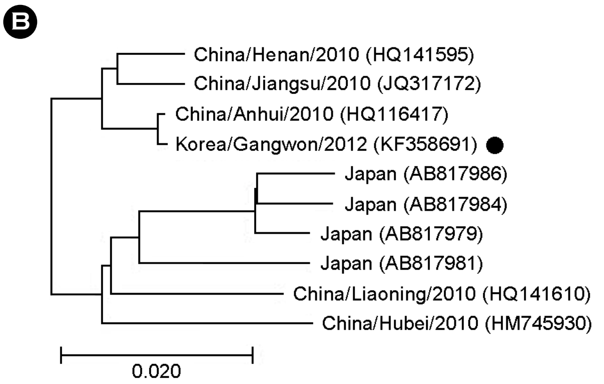


Figure 2. Phylogenetic tree of S segment of isolates obtained from SFTS patient in Jeu Island in 2013 and phylogenetic tree of the RNA-dependent RNA polymerase gene of an isolate obtained from a SFTS patient in South Korea in 2012 (B). The tree was constructed using the neighbor-joining method in MEGA4 (19). JNUH-O/2013, JNUH-H1/2013, JNUH-H2/2013, JNUH-K1/2013, JNUH-K2 /2013, and JNUH-J/2013, were isolated from SFTS patient in Jeju Island in 2013 respectively, and Phlebovirus ZN1/ China/2011 (GeneBank: HE663216), which were isolated from China in 2011 (A) and phylogenetic tree for the RNA-dependent RNA polymerase gene sequences of the large segment of an isolate obtained from a SFTS patient in South Korea (black dot) compared with representative SFTSV strains from China and Japan (B) (16).

exchange, 24 h). The following night, her blood pressure began to rise, even after discontinuing the norepinephrine infusion. Blood pressure was maintained within the normal range, and the GCS score increased to 13 on hospital day 6. Plasma exchange was discontinued (frequency of plasma exchange, three times; total volume of exchanged plasma, 6,737 ml). She had recovered fully by hospital day 9, with an APACHE II score of 5 and a GCS of 14 (20).

IV. SFTS clinical case 2

A 62-year-old farmer presented to a community hospital on Jeju Island on June 5, 2013, with fever and altered mental status. He had a systolic blood pressure of 50 mmHg and was confused. He was initially treated with intravenous fluids, antibiotic agents, and mechanical ventilation. On June 12, he was transferred to a tertiary care hospital on Jeju Island immediately after a positive RT-PCR result for SFTSV. On admission to the ICU, he had a temperature of 37.3℃, blood pressure of 67/41 mmHg, an APACHE II score of 30, and a derived GCS score of 3. Laboratory tests revealed a WBC count of 9.5 × 10^9/l, platelet count of 75 × 10^9/l, AST of 184 U/l, LDH of 1,481 U/l, and CPK of 588 U/l. Chest radiography showed bilateral diffuse pulmonary infiltration, indicating pulmonary edema. He continued to be mechanically ventilated with an FiO_2 of 1.0. He was treated with intravenous fluids, norepinephrine, and broad-spectrum antibiotics. Plasma exchange was performed using the same method as described above. Based on his weight and hematocrit, approximately 3,500 ml of plasma was removed and replaced with fresh frozen plasma each time (speed of blood output, 43~52 ml/min; maximum quantity of vitro blood circulation, 170 ml; interval of plasma exchange, 24 h). Oral ribavirin (4.0 g/day) was administrated via a nasogastric tube. His derived GCS score increased to 8, and blood pressure was maintained within the normal range on hospital day 4, even after decreasing the infusion rate of norepinephrine. Consequently, plasma exchange was discontinued on hospital day 4 (frequency of plasma exchange, four times; total volume of exchanged plasma, 14,141 ml). Mechanical ventilation and norepinephrine were stopped on hospital day 6. His condition improved to an APACHE II score of 12 and a GCS of 15 on hospital day 7 (20).

V. Crimean-Congo Hemorrhagic Fever Virus (CCHFV)

CCHFV is an envelope, segmented, negative-strand RNA virus in the genus *Nairovirus* in the family Bunyaviridae (2). It is transmitted to humans through an infected tick bite or by contact with blood or tissues from infected ticks, livestock, or humans. CCHF causes sudden onset of signs and symptoms including headache, high fever, back pain, joint pain, stomach pain, and vomiting, which can progress to severe bruising, severe nosebleeds, uncontrolled internal and external haemorrhages, and multi-organ failure; with a case-fatality rate of approximately 30% (21, 22).

CCHF was diagnosed for the first time in South Africa by isolation of the virus from the blood of a 13-year-old boy who died after attending a nature study camp (23), with the virus having already been isolated from Senegal in the west to Kenya in the east (24). Since the first descriptions of human infections with this virus in 1944-1955 in Crimea, outbreaks of CCHF have been reported in Africa, Asia, and Eastern Europe (23). Nowadays CCHFV has the widest geographic distribution of any tick-borne virus, encompassing at least 30 countries from eastern China through Asia, the Middle East, and southeastern Europe to Africa (21). During the past decade, the virus has emerged in new areas of Europe, Africa, the Middle East, and Asia and has increased in endemic areas (25). Although the virus has been detected or isolated from over 30 species of ticks, this does not denote their active involvement in the transmission and/or maintenance of the virus in natural cycles (23), and is an important consideration when considering the role of *H. longicornis* in the transmission of SFTSV. Only 12 tick species from the genera *Dermacentor*, *Hyalomma*, and *Rhipicephalus* have been confirmed as vectors in the field whereas the remaining only proven in the laboratory setting (26). *Hyalomma marginatum* is considered to be of most important tick for transmission of CCHFV in Europe (23, 24). *H. marginatum*, commonly known as the Mediterranean *Hyalomma*, is widely distributed from North Africa to the Middle East where there are reports from Algeria, Armenia, Azerbaijan, Egypt, Ethiopia, Georgia, Iran, Iraq, Israel, Morocco, Sudan, Syria, Tunisia, and Turkey (21, 23, 24). It is also present in Southern and Eastern Europe having been recorded in Albania, Bosnia and Herzegovina, Bulgaria, Croatia, Cyprus, France, Greece, Italy, Kosovo, Macedonia, Moldova, Montenegro, Portugal, Romania, Russia, Serbia, Spain, and Ukraine (21, 23~26). There are several historical records of *H. marginatum* being imported by migratory birds including Sweden, Czech Republic, Norway, Slovakia, Finland, Germany, the United Kingdom and Spain (26). It is clear that migratory birds play an important role in the dissemination of the main tick vector of CCHFV. Its current inability to establish in northern Europe appears to be climatically linked. However with changes in climate (including warmer temperatures) it may be permissible for *H. marginatum* imported on migratory birds to complete their moult and thus expand their current distribution.

VI. Migratory birds and pathogen-carrying tick vectors

Migration remains one of the most compelling aspects of the avian world. Twice a year, billions of birds migrate vast distances across the globe (14). Typically, these journeys follow a predominantly north-south axis, linking breeding grounds in arctic and temperate regions with non-breeding sites in temperate and tropical areas (14). Many species migrate along broadly similar, well-established routes known as flyways. Recent research has identified eight such pathways: the East Atlantic, the Mediterranean/Black Sea, the East Asia/East Africa, the Central Asia, the East Asia/Australasia, and three flyways in the Americas and the Neotropics (Fig. 4A) (14).

Migratory birds acting as long-distance carriers of ticks containing various human pathogens having been reported and several studies showing that migratory birds play a major role in the dispersal of CCHFV-carrying tick vectors (1~4, 22).

Birds are the main hosts for the immature stages of this

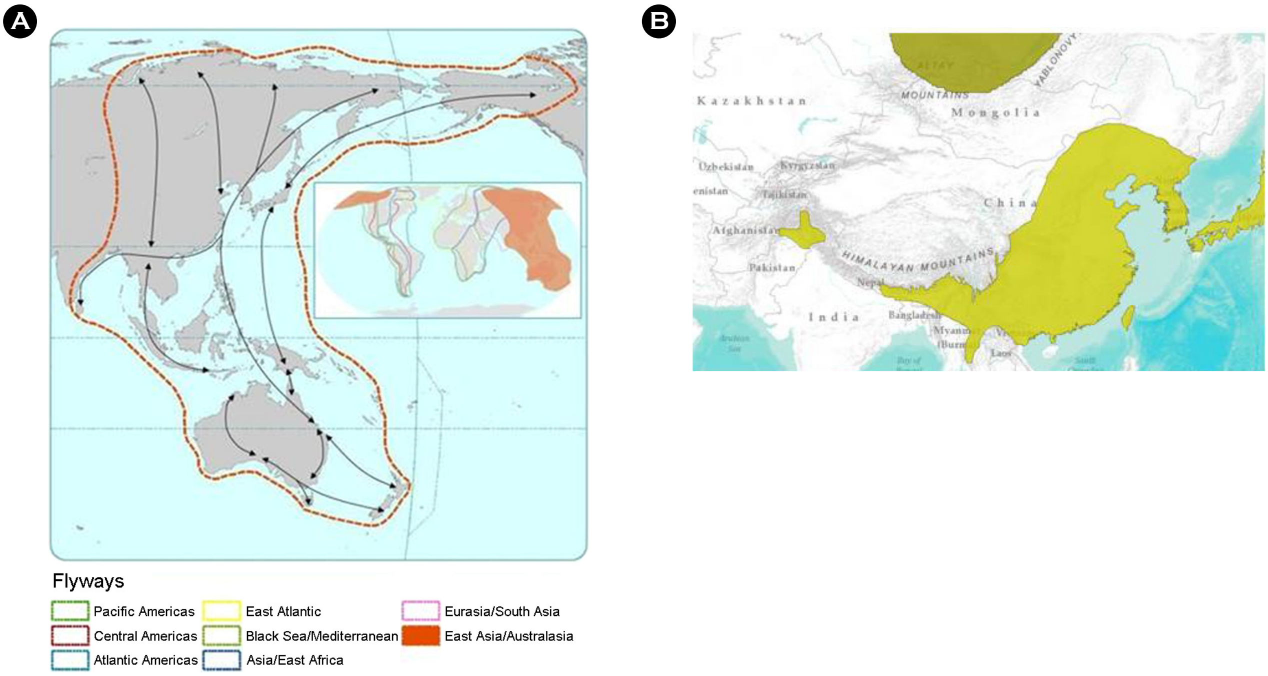
Figure 3. Bird species. Typical feeding sites of *Hyalomma marginatum* nymphs on an *Oenanthe oenanthe* (26).

tick species (27). Pre-adult ticks can stay attached to avian host during migration, thereafter detaching at breeding or stopover sites, where mammalian host can potentially establish new foci (2). This is particularly important in the case of *H. marginatum* that exhibits a two-host cycle with the engorged larva remaining and moulting on the bird to feed again as a nymph. This maximizes the proportion of larvae reaching the adult stage, and also permits long range dispersal on account of the time remaining on the migratory bird.

A recent study in the United Kingdom reported on the importation of *H. marginatum*, on a range of passerine bird species, but most notably on the northern wheatear *Oenanthe oenanthe* (Fig. 3) (26). During this study nearly 1000 migratory birds were inspected for ticks, 7% were found to be infested, with 21% of all ticks identified as *H. marginatum*. This tick is currently unable to establish in the UK following importation, although this may change with an increased incidence of warmer summer. The predilection of particular bird species to act as long-range dispersers of these ticks is related to two main factors. Firstly the bird must forage in a way that increases their exposure to ticks, through both the habitat they co-exist in and their feeding behaviour. Secondly they must also coincide the timing of their northward migration with the activity of the host seeking ticks. In is noteworthy that the northern wheatear is one of the earliest spring migrants to reach northern Europe from Africa. However, those birds infested with *H. marginatum* were collected at land-fall sites in England towards the end of their migration window. A combination therefore of spring migration times, spring temperature increases and tick activity may vary in such a way that the numbers of ticks dispersing from year to year varies, and will continue to vary with climatic changes in unexpected ways.

In Korea, Choi *et al*. examined 934 migratory birds belonging to 75 species for ticks from 2010 to 2012 in Jeju island (3). A total of 313 ticks of six ixodid species belonging to two genera (*Haemaphysalis* and *Ixodes*) were collected from 74 individuals across 17 avian species (3). The most abundant species was *Haemaphysalis flava* Neumann (226 ticks, 72.2% of the total; 105 nymphs and 121 larvae) followed by *Ixodes turdus* Nakatsudi (54 ticks, 17.3%; 38 nymphs and 16 larvae). The other ticks collected were *H. formosensis* Neumann (14 ticks, 4.5%; 14 nymphs), *H. longicornis* Neumann (12 ticks, 3.8%; 1 adult, 5 nymphs, and 6 larvae), *H. concinna* Koch (4 ticks, 1.3%; 4 nymphs), and *I. nipponensis* Kitaoka and Saito (3 ticks, 1.0%; 3 nymphs). Of the 17 identified host species, thrushes belonging to the genus *Turdus* and *Zoothera* accounted for 82.4% of the infested birds and had higher infestation rates than the birds belonging to the other avian groups. Pale (*Turdus pallidus*; 39 birds, 52.7%), White's (*Zoothera aurea*; 11, 14.9%), Gray-backed (*Turdus hortulorum*; 4, 5.4%) and Eye-browed thrushes (*Turdus obscurus*; 4, 5.4%) were the major avian hosts of the collected ticks (3).

Learning from the scenarios with *Hyalomma* and CCHFV, we may speculate that SFTSV-carrying *H. longicornis* may influx from China to South Korea especially Jeju Island on migratory birds such as *Turdus pallidus* and *T. naumanni*, which are known to breed and migrate among China, Korea, and Japan (Fig. 4B and C) (1~5, 12~14). The East Asia/Australasia Flyway extends from Arctic Russia and North America to the southern limits of Australia and New Zealand includes China, Korea, and Japan (14). It encompasses large parts of East Asia, all of Southeast Asia and includes eastern India and the Andaman and Nicobar Islands (14). The scale of avian movement along the flyway is awesome, with over 50 million migratory waterbirds,



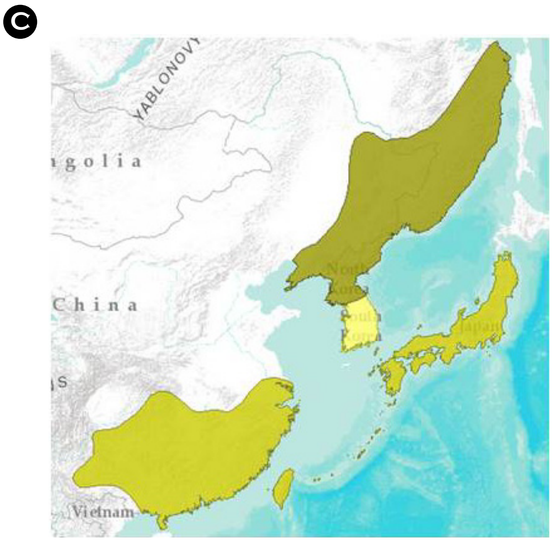


Figure 4. Migratory birds Flyway (A), *Turdus naumanni* (B), and *Turdus pallidus* (C) distribution map of the world. Recent research has identified eight such pathways: the East Atlantic, the Mediterranean/Black Sea, the East Asia/East Africa, the Central Asia, the East Asia/Australasia, and three flyways in the Americas and the Neotropics (A) (14). Native of *T. naumanni* are Bangladesh, Bhutan, Canada, China, Hong Kong, India, Japan, Korea, Democratic People's Republic of Korea, Republic of Mongolia, Myanmar, Nepal, Pakistan, Taiwan, Province of China, Thailand, and Viet Nam and Vagrant of *T. naumanni* are Austria, Belarus, Belgium, Croatia, Cyprus, Czech Republic, Denmark, Faroe Islands, Finland, France, Germany, Hungary, Israel, Italy, Kazakhstan, Kuwait, Montenegro, Netherlands, Northern Mariana Islands, Norway, Oman, Poland, Saudi Arabia, Northern Mariana Islands, Norway, Oman, Poland, Saudi Arabia Serbia (Serbia), Slovenia, United Arab Emirates, United Kingdom, and United States (B) (12). Native of *Turdus pallidus* are Hong Kong, Japan, Korea, Democratic People's Republic of Korea, Republic of Philippines Taiwan, and Province of China and Vagrant of *T. pallidus* are China and Germany (C) (12).

including 8 million waders, using the route annually (14).

Therefore, migratory birds among China to South Korea and Japan, might have a potential role of *H. longicornis*-borne SFTSV transmission from China to South Korea and Japan. However further field work is required to understand better the range of habitats favoured by the putative tick vector, as well as the infestation rates of ticks on migratory birds arriving in Korea from China and Japan. Quantitative data on the infection rates of ticks, migrant birds and the vector competence of ticks for SFTSV is paramount in understanding the eco-epidemiology of the virus in order to better understand the clinical picture in humans, and the spatio-temporal risk across the endemic range of SFTSV.

VII. Conclusion

Migratory birds, known as long-distance carriers of ticks containing various human pathogens (1~4), might have the potential role of disseminating *H. longicornis*-borne SFTSV transmission from China to South Korea and Japan (Fig. 4A, B, and C) (3, 12~14).

Jeju Island is a volcanic island located between 126°00′ and 126°58′ E longitude and 33°06′ and 34°00′N latitude; it is 73 km wide and 41 km long with a total area of 1,847 km^2 (28). This island is located at the southern end of the Korean Peninsula which is the hottest area classified as a subtropical weather zone and represented in the centre of this migration route and, in addition, is home to one of the largest populations of migratory birds on the Korean Peninsula (3, 7, 13, 14, 28).

Thus, it would not be surprising if pathogen-carrying vectors are easily disseminated across the regions, especially Jeju Island through bird migration (3).

Therefore, further research is crucial to elucidate the interaction between migratory birds and ticks in relation to understanding the ecological transmission dynamics and geographic distribution of SFTSV (5, 6). Monitoring the influx of migratory birds carrying SFTSV into Jeju Island (and other sites in South Korea) is a requirement to begin to quantify the infestation rates of ticks on migrant birds, the bird hosts of the putative tick vectors (including *H. longicornis*) of SFTSV and the infection rates of the virus in both migrant birds, endemic birds and imported and endemic ticks.

In addition, it will also be important to understand better how bird species within South Korea especially Jeju Island will be affected by climate change, and what impact this might have in the changing epidemiology of SFTS (3, 28, 29). For South Korea this is particularly concerning given that the vast majority (> 90%) of South Korea's bird species is migratory (13).

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