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Tick-borne viruses: Epidemiology, pathogenesis, and animal models

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ABSTRACT

Tick-borne viruses, capable of infecting animals and humans, are expanding geographically and increasing in prevalence, posing significant global public health threats. This review explores the current epidemiology of human pathogenic tick-borne viruses, emphasizing their diversity and the spectrum of symptomatic manifestations in humans, which range from mild to severe. We highlight how the infrequent and unpredictable nature of viral outbreaks complicates the precise identification and understanding of these viruses in human infections. Furthermore, we describe the utility of animal models that accurately mimic human clinical symptoms, facilitating the development of effective control strategies. Our comprehensive analysis provides crucial insights into disease progression and emphasizes the urgent need for continued research. This work aims to provide insight into knowledge gaps to mitigate the health burden of tick-borne infections and open an avenue for further study to enhance our understanding of these emerging infectious diseases.

1. Introduction

Tick-borne viruses, encompassing a diverse array of highly pathogenic human viruses, are classified into five taxonomic families: *Flaviviridae*, *Nairoviridae*, *Phenuiviridae*, *Orthomyxoviridae*, and *Sedoreoviridae* (Fig. 1) [1–5]. While many tick-borne infections are asymptomatic, symptoms may appear after an incubation period ranging from 2 to 34 days, depending on the virus (Table 1). Symptoms such as fever, fatigue, headache, diarrhea, muscle or joint pain, and various blood or biochemical abnormalities can occur. In severe cases, infections may progress to bleeding, encephalitis, or meningitis [6].

The spread of these viruses is closely related to the availability of suitable vectors and hosts, with prevalence influenced by myriad environmental factors (Fig. 2). Climate change, ecological shifts, and host and human-induced environmental changes have broadened the range of tick habitats. The ability of some tick species to reproduce parthenogenetically, coupled with the long-distance transport of viruses by migratory birds and animals enhances their dissemination potential. Additionally, co-infections within hosts may accelerate viral evolution, potentially leading to the emergence of viruses [6–8].

Ticks transmit the virus to mammalian hosts during blood meal (Fig. 3). While infections of reservoir hosts tend to be mild or asymptomatic, humans, as accidental hosts, often struggle to effectively contain viral replication, leading to severe illness characterized by uncontrolled inflammation [9]. Developing reliable animal models capable of replicating human symptoms is challenging. Small animal models are used for their genetic homogeneity, which minimizes variability and facilitates controlled studies. In contrast, non-human primate (NHP) models, which share greater genetic relevance with humans and physiological and immunological similarities, are primarily used for preclinical studies. Nonetheless, both models have limitations.

This review covers the current status of tick-borne viruses, focusing on human clinical manifestations. It also discusses the current landscape of virus evolution and the use of animal models to enhance understanding of disease progression and prospective therapeutic approaches.

2. Flaviviridae

Tick-borne flaviviruses belong to the *Orthoflavivirus* genus within the *Flaviviridae* family and possess a positive-sense single-stranded RNA genome. Tick-borne flaviviruses are further categorized into seabird and mammalian groups [10]. The seabird group replicates within seabirds without infecting humans and includes the Tyuleniy virus, Meaban virus, and Saumarez Reef virus. The mammalian group comprises human-pathogenic viruses, the tick-borne encephalitis (TBE) serocomplex, and other viruses with more than 70 % nucleotide homology in the *Envelope* gene. These include TBE virus (TBEV), Powassan virus (POWV), Kyasanur Forest disease virus (KFDV), Omsk hemorrhagic

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fever virus (OHFV), Louping ill virus (LIV), Langat virus (LGTV). Among these viruses, TBEV and POWV are known to cause encephalitis in humans, while OHFV, KFDV, and Alkhurma virus (AHFV) predominantly induce hemorrhagic disease. However, the Royal Farm virus (RFV), Karshi virus (KSIV), Gadgets Gully virus (GGYV), and Kadam virus (KADV) have not been associated with human disease.

2.1. Tick-borne encephalitis virus (TBEV)

TBE is caused by TBEV, with between 10,000 and 13,000 clinical cases reported annually in endemic countries spanning Europe and Asia [11] (Table 1). Based on seroprevalence studies, the TBEV infection rate in humans is 2.9 to 4.6 % among persons living in TBE-endemic areas, indicating that many TBEV infections are asymptomatic or mildly symptomatic [12]. However, severe clinical symptoms can develop in two phases: an initial viremic prodromal phase of non-specific, flu-like symptoms and a secondary neurological phase with recurring fever and central nervous system (CNS) involvement, such as meningitis or meningoencephalitis. Severe cases can lead to persistent neurological effects known as post-encephalitic syndrome or chronic progressive TBEV.

Differential clinical outcomes are partly due to genetic differences among virus strains. There are three main TBEV genotypes: European (TBEV-Eu), Siberian (TBEV-Sib), and Far Eastern (TBEV-FE). The TBEV-Eu subtype has the lowest case fatality rate (1–2 %), while the TBEV-Sib subtype is linked to milder disease (6–8 % fatality). Further, the TBEV-FE subtype often causes severe neurological symptoms and hemorrhagic TBE, with fatality rates between 20 and 40 % [11]. The TBEV-Sib subtype is most prevalent in endemic regions, and unique subtypes have arisen through geographic migration, including TBEV-2871 (TBEV-Ob), Himalayan (TBEV-Him), and two Baikalian (TBEV-Bkl-1, TBEV-Bkl-2) subtypes. However, the genotype of the infecting virus alone does not predict clinical outcomes, as age is also a factor, with older individuals at higher risk for severe disease [13].

TBEV circulates in ticks such as *Ixodes ricinus* and *I. persulcatus*, which become infected by feeding on viremic hosts or co-feeding with an infected tick [14]. Small rodents, insectivores, and wild or domestic mammals play a crucial role in the spread of TBEV. Despite this widespread role, TBE-infected animals are typically asymptomatic, with rare reports of encephalitis in sheep [15]. While human infection mainly occurs through tick bites, like other animals, humans are not major hosts or reservoirs of TBEV. Further, additional virus infection routes were reported, such as consumption of contaminated milk, organ transplants, and blood transfusions, while airborne transmission remains a theoretical risk [16,17].

Climate changes, including rising temperatures and milder winters, and ecological factors have expanded the geographic range of *I. ricinus* tick, leading to greater abundance and potentially increased TBEV transmission. A study has shown an increase in TBE incidence since the mid-1980s compared to the period 1960–1983 [18]. Additionally, the climate model of the European Union predicts a doubling of the *I. ricinus* distribution range in Europe [19]. Furthermore, Additionally, migratory birds may contribute to the spread of TBEV, as ticks collected from these birds have tested positive for the virus [20]. Therefore, the risk of TBEV infection is continuously increasing.

Animal experimental studies have been conducted to understand viral diseases and their characteristics. TBEV-infected wild rodents, including wood (*Apodemus sylvaticus*) and yellow-necked mice (*A. flavicollis*), are asymptomatic, even though TBEV RNA is detectable in blood and brains. Thus, these wild animal species not suitable for TBEV pathogenesis studies [21]. In contrast, subcutaneously or intracerebrally infected laboratory mice, including type I interferon receptor knock-out (*IFNAR*$^{-/-}$), BALB/c, C57BL/6, and C3H mice, exhibit viral replication in the spleen, liver, and brain, which is accompanied by weight loss and neurological symptoms such as paralysis before death [22]. Moreover, infected *IFNAR*$^{-/-}$ mice can transmit TBEV to co-caged mice [17]. However, BALB/c-c-STS/A (CcS/Dem) and CD1 mice exhibit lower susceptibility to TBEV infection than other laboratory mice [23,24]. Overall, mouse models partially mimic human infections, particularly neurological symptoms; however, they do not exhibit febrile or chronic diseases. Therefore, animal models replicating febrile symptoms and chronic forms of TBEV are still needed. In NHP studies, macaques (*Macaca sylvanus*) showed greater susceptibility than African green monkeys (*Chlorocebus aethiops*), exhibiting higher viral titers in tissues and brain pathology following subcutaneous infection. The observed symptoms were similar to human febrile disease, including viremia, fever, and virus replication in the spleen, lymph nodes, and CNS [25]. Further investigation is needed to determine if the variation between macaques and African green monkeys might be attributed to the genetic differences between species. In addition, TBEV infection can potentially also occur by consuming unpasteurized milk from infected goats. Despite no clinical symptoms, experimental studies have shown that infected goats harbor TBEV in their milk between 8 and 19 days post-infection (dpi). Thus, further investigation is required to determine the propensity of this virus to be transmitted in milk [16,26].

2.2. Powassan virus (POWV)

Since POWV was first isolated in Canada in 1958, cases of infection have been identified in Canada, the United States, and Russia (Table 1) [27]. POWV infection can cause severe symptoms, including neuroinvasive diseases, with a mortality rate of 10–15 %. Additionally, 50 % of survivors experience long-term neurological sequelae. However, seroprevalence studies revealed antibody rates between 0.7 % and 6.1 % in Ontario, British Columbia, New York, Minnesota, and Wisconsin, suggesting undetected infections due to mild or absent symptoms similar to those observed in animals [28].

POWV comprises two lineages: Lineage 1 and Lineage 2, also known as Deer-tick virus (DTV). These viruses are transmitted by different tick species with distinct host preferences. Lineage 1 is found in Canada, the United States, and Russia, while Lineage 2 (DTV) is found in the United States and Canada. Despite 84–85 % nucleotide similarity, Lineage 1 is maintained by *Ixodes cookie, I. maxi*, *I. spinipalpus*, with woodchucks (*Marmota monax*), while DTV is primarily associated with *I. scapularis* and small mammals.

The spread of ticks is influenced by complex interactions involving

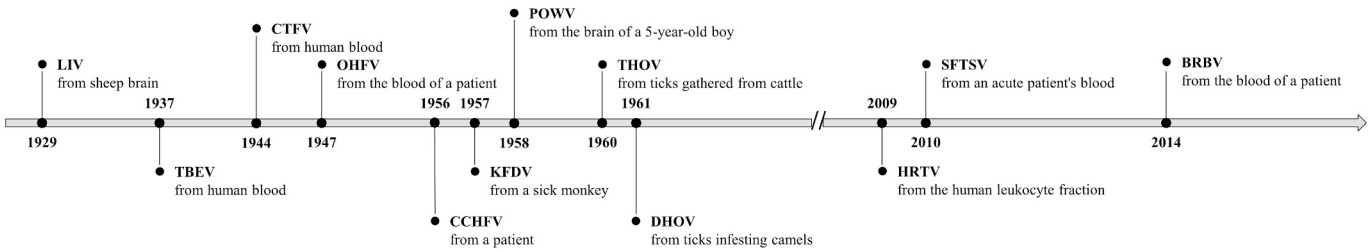

Fig. 1. Timeline for first isolation of tick-borne viruses. This timeline displays the year and source of initial isolation for each virus, arranged from left to right in ascending order of the year of isolation.

climate changes, human activity, and animal movements. Warmer temperatures extend the questing periods of ticks, thereby increasing feeding opportunities and potentially enhancing virus transmission [29]. Moreover, changes in forest ecosystems affect primary hosts and tick density [30]. For example, the policy of reforestation and white-tailed deer (*Odocoileus virginianus*), the primary host for *I. scapularis*, has increased POWV seroprevalence among them from less than 25 % prior to 1996 to 80–91 % between 2005 and 2009 according to a study in Connecticut [31]. The incidence of human infection has also increased from 64 cases between 2004 and 2013 to 276 cases between 2014 and 2023 [32].

The virus infection induces varied pathogenicity in animals. The groundhogs (*Marmota monax*), striped skunks (*Mephitis mephitis*), fox squirrels (*Sciurus niger*), and mice (*Peromyscus leucopus*) do not cause clinical signs or death against POWV infection [33,34]. Therefore, wild animals are not suitable models for the elucidation of pathogenicity. In contrast, BALB/c mice inoculated intraperitoneally or intracranially are susceptible to lethal outcomes, and transmission and pathogenesis of POWV intensified following footpad inoculation with homogenized *I. scapularis* salivary glands [35]. Intraperitoneal inoculation of C57BL/6 mice induced chronic disease with CNS inflammation [36]. Furthermore, infection in 50-week-old mice mirrors human encephalitis and long-term CNS damage, with a high lethality rate (82 %) compared to 7.1 % in 10-week-old mice [37]. These results suggest that BALB/c and C57BL/6 mice are susceptible to POWV infection and mimic the manifestations of pathogenicity and long-term neurological symptoms in humans. Similarly, POWV infection of rhesus macaques (*Macaca mulatta*) resulted in significant neuro invasiveness with symptoms similar to human infection as well as viral replication in the brain and spinal cord [38]. While the rhesus macaque might be a promising animal model due to its high susceptibility, there are still many hurdles to overcome, including that they are extremely hard to handle in laboratories, and the cost of experiments is much higher than that of other animal models.

2.3. Kyasanur Forest disease virus (KFDV)

KFDV was first identified from the Kyasanur Forest in Karnataka state of India and was then found to be endemic in South Asia (Table 1) [39,40]. Since then, 400–500 human cases have been reported annually. Clinical manifestation begins with high fever and headache, body aches, diarrhea, and hemorrhagic symptoms, including gastrointestinal, gum, and nose bleeding [41]. Neurological complications occur in 10–20 % of cases, with an overall mortality rate of 2–10 %. While similar severe clinical symptoms are observed in non-human primates (black-faced langurs (*Presbytis entellus*) and red-faced bonnet monkeys (*Macaca radiata*)), severe manifestations have not been reported in other animal species, including birds, cattle, and bats [42].

Continuous studies have demonstrated that KFDV variants in China are referred to as the Nanjianyin virus, while those in Saudi Arabia and

Table 1
Epidemiological and experimental features of tick-borne viral infections.

Virus	Diversity	Tick (main vector)[†]	Geography	Animal model (susceptible)	Incubation period [‡]
Flaviviridae/Orthoflavivirus					
TBEV	European (TBEV-Eu) Siberian (TBEV-Sib) Eastern (TBEV-FE)	*I. ricinus*, *I. persulcatus*	Europe, Russia, Asia, UK, Netherlands	Mouse (*IFNAR*$^{-/-}$, BALB/c, C57BL/6, C3H, CD1, CcS/Dem), NHP (*Macaca sylvanus*, *Chlorocebus aethiops*)	8 days (range 4–28 days)
POWV	Lineage 1 Lineage 2 (DTV)	*I. cookie, I. maxi*, *I. spinipalpus* *I. scapularis*	Russia, United States, Eastern Canada	Mouse (BALB/c, C57BL/6), NHP (*Macaca mulatta*)	8–34 days
KFDV	Old isolates Recent isolates	*H. spinigera*	Southern India, Asia	Mouse (BALB/c, C57BL/6, A/J, C3H), Palm squirrels (*Funambulus palmarum*), NHP (*Presbytis entellus*)	3–8 days
OHFV	A, B, C, D and E	*D. reticulatus*	Russia, Kazakhstan	Mouse (BALB/c, C57BL/6)	3–8 days
LIV	Northern and southern England, Northern Scotland, Wales, Ireland	*I. ricinus*	UK	Mouse (BALB/c)	4–7 days
Nairoviridae/Orthonairovirus					
CCHFV	Group I-VI	*Hyalomma* sp.	Crimean Peninsula, Europe, Asia, Africa	Mouse (*STAT1*$^{-/-}$, *IFNAR1*$^{-/-}$), NHP (*Macaca fascicularis*)	3–7 days (range 1–13 days)
Phenuiviridae/Bandavirus					
HRTV		*A. americanum,*	the United States	Mouse (*IFNAR1*$^{-/-}$, AG129)	2 weeks
SFTSV	Genotype A-F	*H. longicornis*	South Korea, Japan, Thailand, Pakistan, Myanmar, Vietnam	Mouse (HuPBL-NCG), Ferret (>3 years old)	9–10 days (range 7–13 days)
Orthomyxoviridae/Thogotovirus					
THOV		*R. decoloratus,* *H. longicornis*	Africa, Asia (Iran, Japan), Europe (Italy, Portugal)	Mouse (BALB/c, C57BL/6)	4–5 days
DHOV		*H. dromedarii*	India, Russia, Pakistan, Egypt, Saudi Arabia, Kenya, Portugal	Mouse (C57BL/6)	3 days
BBRV		*A. americanum,* *H. longicornis*	the United States	Mouse (*IFNAR*$^{-/-}$)	2–7 days
Sedoreoviridae/Coltivirus					
CTFV		*D. andersoni*	USA, Canada	No susceptible animal models	3–4 days (range 1–14 days)

[†] Generic tick names abbreviated: *I., Ixodes; H., Haemaphysalis; D., Dermacentor; A., Amblyomma; R., Rhipicephalus.*
[‡] Incubation period, the median or range of time from exposure to onset of initial symptoms.

Egypt are referred to as AHFV [43,44]. Among these viruses, KFDV and AHFV diverged from a common ancestor approximately 700 years ago, indicating that KFDV variants might have a wider geographic distribution than currently known, with potentially undiscovered variants from China to Egypt [45]. Further, continuous circulation of KFDV in India has led to the divergence into two clades, the first from strains isolated between 1957 and 1972 and the second from 2006 to 2017 [46]. Comparative sequence analyses revealed approximately 2.76 % genomic divergence between clades, which may have facilitated the virus spread through vectors or hosts.

KFDV transmission occurs through tick bites, the primary vector being *Haemaphysalis spinigera*, or through direct contact with infected animals [47]. Additionally, other tick species may play a role in disseminating the virus. Especially, transovarial and transstadial transmission of KFDV was confirmed in *Ornithodoros* species, a vector for AHFV [48]. Moreover, KFDV was initially isolated in Karnataka, India. Later, the virus was identified along the Western Ghats region in five states [46]. The expansion to new areas and increasing cases indicate that ecological changes due to deforestation and cattle grazing could spread KFDV [49].

Animal models of KFDV infection have been investigated to understand the characteristics of the virus; rats (*Rattus rattus wroughtoni* and *R. blanfordi*) demonstrate nonclinical symptoms without death. However, palm squirrels (*Funambulus palmarum*) and BALB/c, C57BL/6, A/J, and C3H mice are susceptible to virus infections and often succumb to them [50,51]. Moreover, BALB/c and C57BL/6 mice exhibit viral replication in the brain, with symptoms including ataxia, tremors, paralysis, and eventually death in severe cases. In contrast, CD1 mice displayed lower lethality with lower viral replication, primarily in the CNS [51,52]. The virulence of KFDV in NHP models varies depending on the species and virus titers. In endemic areas, natural infection of black-faced langurs resulted in 100 % mortality, while red-faced bonnet macaques developed neurological symptoms but no signs of hemorrhage. Further, rhesus macaques (*Macaca mulatta*) infected with KFDV developed viremia without overt clinical signs [42]. Therefore, mice and black-faced langurs could be helpful animal models of virus infection; however, these animals do not demonstrate hemorrhagic signs seen with human disease. Thus, additional animal models are needed.

2.4. Omsk hemorrhagic fever virus (OHFV)

Since OHFV was first identified in 1945 in Russia, the virus was recently detected in Kazakhstan. Infection with OHFV causes fever, muscle pain, coughing, and hemorrhagic manifestations, as well as occasional neurological involvement, with 0.5–3 % mortality (Table 1) [53]. The continuous evolution of the virus has resulted in six clusters, predominantly in clade A, which diverged from clade B approximately 700 years ago.

The sylvatic cycle of OHFV involves tick species *Dermacentor reticulatus* and water voles (*Arvicola terrestris*); however, the release of nonnative muskrats (*Ondatra zibethica*), which are highly susceptible to OHFV, is thought to have significantly increased infection rates among other animals and humans [54]. There is a report that, without tick bites, family members have become infected through activities such as hunting muskrats and handling their skins despite no reports of person-to-person transmission [55]. Moreover, the endemic OHFV region

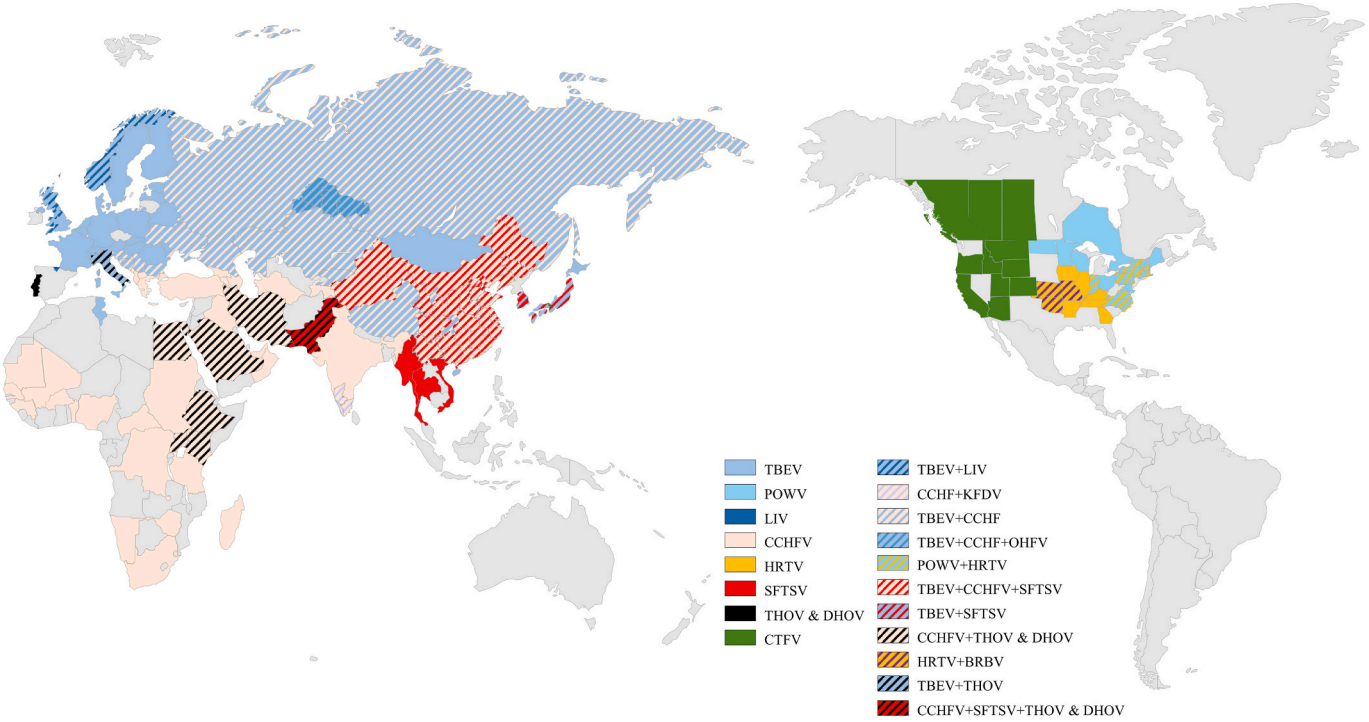

Fig. 2. The global geographic distribution of tick-borne viruses. TBEV, POWV, KFDV, OHFV, LIV, CCHFV, HRTV, SFTSV, THOV, DHOV, BRBV and CTFV are pathogenic viruses distributing globally across regions using vectors or reservoirs, respectively. TBEV is predominantly distributed across regions such as Europe, Russia, and Asia, while POWV, KFDV, and OHFV are limited to certain areas of the Eastern United States, Southern India, and parts of Russia. The global geographic distribution of tick-borne viruses includes TBEV, POWV, KFDV, OHFV, LIV, CCHFV, HRTV, SFTSV, THOV, DHOV, BRBV and CTFV. These pathogenic viruses are distributed across various regions. TBEV is predominantly found in Europe, Russia, and Asia. POWV, KFDV, and OHFV are limited to specific areas in the Eastern United States, Southern India, and parts of Russia, respectively. Additionally, LIV is present in some regions of Western Europe. CCHFV has a wide distribution across Asia, Africa, Eastern Europe (including the Balkans, Spain, and Turkey), and Russia. Similar to POWV, HRTV, CTFV, and BRBV are mainly found in certain regions of the United States. SFTSV is found in South Korea, Japan, Thailand, Pakistan, Myanmar, and Vietnam. THOV and DHOV have been reported in Italy, Portugal, Iran, Pakistan, Egypt, Saudi Arabia, Kenya, and Japan. Regions where a single virus species is distributed are indicated by a a single color (TBEV, sky blue; POWV, light blue; LIV, blue; CCHFV, Apricot; HRTV, yellow; SFTSV, red; THOV & DHOV, black; and CTFV, green), while areas with overlapping viruses are marked with diagonal lines. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

overlaps with the TBEV endemic region, and *I. persulcatus*, the primary TBEV vector, exhibits overlapping geographic ranges, suggesting the possibility of co-infection in animals [56]. *D. reticulatus* has expanded in Northwestern and Central Europe, reaching areas beyond its endemic range, facilitated by an increased population of deer and policies promoting fallow land [57,58].

To understand the virus characteristics, BALB/c and C57BL/6 mouse models, both susceptible to OHFV infection, have been utilized [59,60]. In BALB/c mice, infection leads to elevated neutrophil levels, and a significant inflammatory response with viral replication primarily in the spleen and liver, resulting in hemorrhage [59]. Conversely, C57BL/6 mice exhibit only minor changes in neutrophil levels. Unlike in humans, neurological symptoms in BALB/c mice vary, possibly due to strain differences. However, another group reported that the BALB/C mice are not susceptible to OHFV infection [61]. The variation in results might be due to differences in infectious dose or strain. Thus, further investigation is necessary to identify a suitable animal model for OHFV infection.

2.5. Louping ill virus (LIV)

Louping ill disease has caused neurological illness and death, with 5–60 % morbidity in livestock, mainly sheep (*Ovis aries*) and red grouse (*Lagopus scoticus*), with occasional cases in humans [62]. Primarily isolated in the United Kingdom, 44 cases of LIV infections have been reported in humans (Table 1). Out of the 44 reported human cases, most had occupational exposure to domestic animals and were at risk of bites from *I. ricinus*. While most human patients are asymptomatic or develop only mild febrile illness, severe cases involve neurological symptoms resembling poliomyelitis. No new cases have been reported in 20 years; however, a suspected LIV infection case was reported with headaches and febrile illness progressing to seizures in 2013 [63].

Genetically, LIV demonstrates limited diversity, with a mean nucleotide identity of 96 % across the whole genome. However, phylogenetic studies based on the E gene have identified four distinct geographic lineages in Northern England, Northern Scotland, Southern England, Wales, and Ireland [64]. The habitat of *I. ricinus*, a primary vector of LIV, has spread through tick migration, and it has now been detected in Norway, Spain, and Russia, which links it closely to the geographically widespread TBEV [62,64].

Climate change has significantly impacted the distribution and density of tick populations, with rising temperatures leading to more tick activity in the winter, further extending the active periods of ticks throughout the year. In Sweden, milder winters have resulted in more active tick days, enabling their expansion from 61° to 66° north [65]. Ticks require various hosts for different life stages and are primarily found in deciduous and mixed forests, where the presence of rodents and deer is particularly important for *I. ricinus* [66]. Additionally, *I. ricinus* can adapt to various climatic conditions including colder climates, facilitating the expansion to different environments [67].

Despite the possibility of continuous virus spread, limited pathogenicity studies have been conducted. In mouse models, infection with LIV results in significant neuropathological lesions and eventually mortality, although disease progression varies by LIV strain, while lambs exhibited moderate disease severity [68]. Therefore, mice are a more susceptible animal model than lambs. Further studies are needed to elucidate the factors influencing virus pathogenicity in humans and better understand the mechanisms involved.

3. Nairoviridae

The family *Nairoviridae* includes the tick-borne *Orthonairovirus* genus, which possesses three segments of a negative-sense single-strand RNA genome [2]. The *Orthonairovirus*, including the Crimean-Congo Hemorrhagic Fever Virus (CCHFV), Dugbe virus, Nairobi sheep disease virus, Hazara orthonairovirus, Kasokero virus, and Erve virus, is primarily transmitted by ticks to various animals. Human infections by some viruses within this genus have been detected through ELISA and cause only mild symptoms [69]. However, most human *Nairoviridae* infections are associated with CCHFV, which can lead to high mortality.

3.1. Crimean-Congo hemorrhagic fever virus (CCHFV)

CCHFV was first identified in 1944 on the Crimean Peninsula, and subsequently, CCHFV infections were identified in over 30 countries,

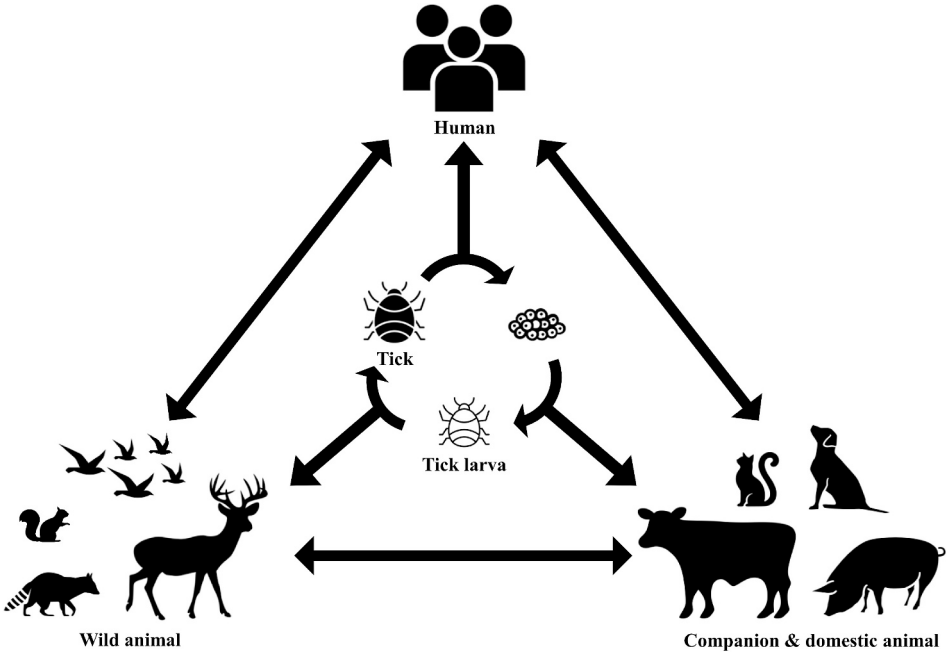

Fig. 3. A schematic diagram showing the host range of tick-borne viruses, including reservoirs and interspecies transmission events. Ticks serve as the natural reservoir of tick-borne viruses, from which they can be transmitted to a variety of hosts, including wild animals, companion animals, domestic animals, and humans through tick bites. Additionally, virus transmission can occur between humans and animals through bodily fluids or direct contact.

including regions of Asia and Africa and parts of Europe (Table 1) [70]. Early symptoms of CCHFV infection include fever, headache, muscle pain, dizziness, and sore eyes, which rapidly progress to hemorrhagic manifestations, including vomiting, skin rashes, and mucosal or gastrointestinal bleeding. Severe cases can lead to sepsis, acute kidney failure, liver dysfunction, and shock, with a fatality rate of 30 % or higher. In contrast, numerous wild and domestic animals do not exhibit significant clinical signs; however, antibodies against CCHFV have been detected, suggesting animals contribute to the transmission cycle of CCHFV by serving as hosts [71].

CCHFV is primarily transmitted through bites from infected ticks, particularly the *Hyalomma* species, which act as vectors and reservoirs. Humans are infected through tick bites or direct contact with blood or tissues of infected livestock, including cattle, sheep, and goats, either during or shortly after slaughter. Human-to-human transmission is possible through direct contact with body fluids or organs from infected individuals [72].

The continuous spread of CCHFV has generated genetic divergence. According to sequence homology of the S segment, the virus is categorized into six genetic lineages with geographic separation of viral isolates: Group I (West Africa), Group II (Democratic Republic of the Congo), Group III (South and West Africa), Group IV (Asia and the Middle East), Group V (Europe and Turkey), and Group VI (Greece). Genetic analysis indicated significant variability and frequent reassortment with high amino acid variation [73].

The circulation of CCHFV is also influenced by environmental changes. Warmer and shorter winter periods contribute to increased *Hyalomma marginatum* tick survival and probably to increased hatching rates of larvae earlier in the year [74]. Further, *Hyalomma* species are better adapted for surviving in drier conditions than other species. Long-distance movement of animals carrying infected ticks, such as migratory birds, also contributes to the spread of CCHFV, as evidenced by isolated cases in Turkey [75].

To date, immunodeficient mice, like signal transducer and activator of transcription (*STAT*) 1 knock-out ($STAT1^{-/-}$) and $IFNAR1^{-/-}$ mice, exhibit clinical signs similar to human disease, including viremia, leukopenia, thrombocytopenia, elevated levels of liver enzymes, and increased inflammatory cytokines as well as lethality [76]. However, due to the absence of innate immune genes in these murine models, studies regarding immune response against CCHFV infection are limited. In contrast, cynomolgus macaque (*Macaca fascicularis*), an immunocompetent model, infected intravascularly with the Kosova Hoti strain of CCHFV, show clinical, biochemical, and hematological symptoms resembling those in humans [77,78]. Therefore, the cynomolgus macaque could be a suitable, albeit expensive, animal model for studying these viruses.

4. Phenuiviridae

Within this *Phenuiviridae* family, the genus *Bandavirus* comprises three segments of the negative-sense (ambisense) single-strand RNA genome. The *Bandavirus* encompasses eight of the nine known tick-borne virus species [79]. Among these, six viruses: Bhanja virus, Guertu virus, Albatross Island virus, Kismayo virus, Lone Star virus, and Razdan virus, either do not infect humans or cause only mild symptoms. However, Heartland bandavirus (HRTV) and Dabie bandavirus (SFTSV) cause potentially fatal infections in humans [80].

4.1. Heartland bandavirus (HRTV)

Since the first isolation in 2009 in Missouri, the United States, more than 60 cases of HRTV have been identified in the Midwest and South, with 3 cases reported deaths (Table 1) [81,82]. The seroprevalence of HRTV in endemic areas is 0.9 %, indicating that asymptomatic infections are present [83]. Although the majority of cases are mild or asymptomatic, severe and lethal cases occur in older patients with weakened immune systems or other underlying conditions [84]. Symptoms of HRTV disease commonly include fever, fatigue, anorexia, diarrhea, vomiting, headache, myalgia, arthralgia, leukopenia, and thrombocytopenia. In vulnerable individuals, complications such as kidney and respiratory system impairment or even organ failure can occur [83].

The *Amblyomma americanum* tick is the primary HRTV vector [80]. While the current range of *A. americanum* encompasses the Southeastern and Northwestern United States, but seropositive testing has shown that white-tailed deer, raccoons (*Procyon lotor*), coyotes (*Canis latrans*), and moose (*Alces alces*) in Central and Eastern United States also possess antibodies against HRTV [85]. HRTV continues to circulate between ticks and a broad range of mammalian hosts; however limited viral diversity and a relatively stable viral population are established. Climate change scenarios predict increased areas suitable for establishing habitats for the *A. americanum* tick [86]. Therefore, continuous surveillance and virus characterization are needed.

Experiments comparing the susceptibility of vertebrates (raccoons, goats, chickens, rabbits, hamsters, C57BL/6 mice, $STAT1^{-/-}$ mice) as HRTV hosts revealed that all exhibited neutralizing antibodies and limited virus replication [87]. Further, in $IFNAR1^{-/-}$ mice, intraperitoneal infection results in the most severe outcome among inoculation routes, and tick salivary gland extract exacerbates HRTV infections, though it did not induce death [88,89]. Moreover, mice deficient for both type I and II interferon receptors (AG129) showed symptoms of disease and increased mortality [90]. Thus, the AG129 mouse effectively demonstrates HRTV virulence and pathogenesis. However, these results demonstrate the importance of antiviral functions of interferon against HRTV infection. Further studies are needed to elucidate infection mechanisms underlying the host immune response to HRTV infection.

4.2. Dabie bandavirus (SFTSV)

Severe fever with thrombocytopenia syndrome (SFTS) was first discovered in China and subsequently reported in South Korea, Japan, Thailand, Pakistan, Myanmar, and Vietnam (Table 1). The clinical symptoms range from asymptomatic to severe, with complications like high fever, gastrointestinal issues, and thrombocytopenia. These symptoms can progress to increased multiple organ failure, hemorrhage, and central nervous system disorders, contributing to a high fatality rate (5–15 %) [91]. Additionally, individuals aged 60 years and older are more susceptible to SFTSV. Most infection cases are caused by infected tick bites, but animal-to-human and aerosol transmission has also been reported [92,93].

The continuous spread of the virus is driven by its evolution, with at least six SFTSV genotypes (A to F) circulating in endemic regions [94]. Genotype B is most common in South Korea and Japan, while A, D, E, and F are prevalent in China. Genetic diversity in the virus has also been driven by recombination and reassortment.

The spread of SFTSV is primarily transmitted by the *H. longicornis* tick, the primary vector, and facilitated by its wide range of hosts, including livestock and wild animals. Seroprevalence studies have demonstrated positive rates ranging from 3 to 97 % in animals, though these animals do not exhibit symptoms [95]. While *H. longicornis* are dominant tick species in SFTSV endemic regions, ecological niche modeling suggests that *H. longicornis* ticks, adaptable to various hosts and climates and capable of parthenogenetic reproduction, could expand their geographic range [8,95,96]. Further, Migratory birds can transport this tick over long distances, facilitating long-range dispersal [8,97]. Consequently, these ticks have expanded their habitat to new regions, including the United States [96].

Despite the wide circulation of various genotypes and the expanding infection area, studies on SFTSV pathogenesis are limited. Most animals in nature exhibit no or only mild symptoms, limiting the availability of lethal SFTSV infection models. Newborn mice and rodent models are highly permissive due to their undeveloped immune systems; however,

disease progression can change as their immune systems mature, limiting the consistency and relevance of long-term studies [98]. Further, models like *IFNAR1*$^{-/-}$ and *STAT2* knock-out (*STAT2*$^{-/-}$) mice are highly susceptible to the virus but do not show hematological similarities to human cases [99–102]. The humanized immunodeficient NOD-*Prkdc*^{em26Cd52}*Il2rg*^{em26Cd22}/Nju (HuPBL-NCG) mouse, which is engrafted with human PBMC, aged ferrets, and domestic cats, all exhibit similar manifestations to those observed in humans, such as thrombocytopenia and increased liver enzymes with lethality [103–105]. However, HuPBL-NCG mice may produce unstable data due to the need for immune cell injections from donors. Additionally, the use of ferrets and cats is limited by a lack of available immunoreagents.

5. Orthomyxoviridae

The *Orthomyxoviridae* family has six to eight segments of negative-sense RNA [4]. It includes two tick-borne virus genera, *Thogotovirus* and *Quarjavirus*. The *Thogotovirus* genera include Araguari virus (ARAV), Batken virus (BKNV), Bourbon virus (BRBV), Dhori virus (DHOV), Jos virus (JOSV), and Thogoto virus (THOV). The *Quarjavirus* genera includes Quaranfil virus (ORFV) and Johnston Atoll virus (JAV). Among these viruses, THOV, BRBV, DHOV, and ORFV have demonstrated cases of human infection [39,40,106]. However, ORFV caused mild fever in two children in Egypt in 1953, and there are no recent reports of human infection [107].

5.1. Thogoto virus (THOV)

Since it was first isolated in Kenya, two cases of human infection in Nigeria in 1966 were reported (Table 1) [108]. Clinical symptoms of virus infection include febrile illness and encephalitis, and can potentially lead to death in humans. However, no further human infections have been reported since the initial reports. Subsequently, THOV infection has been reported to cause abortions in sheep, and positive seroprevalence has been documented in domestic and wild animals in Africa, Europe (Italy, Portugal), and Asia (Iran) [109]. However, the primary animal hosts are unclear. Initially discovered in the tick species *Rhipicephalus decoloratus*, it has also been identified in *H. longicornis*, which may act as vectors for transmission [110]. This suggests that THOV could circulate in Eurasian regions, as this *H. longicornis* species is predominantly found in Eastern Asia [96]. To date, studies have been conducted in BALB/c and C57BL/6 mice to characterize the pathogenicity of THOV; however, the pathogenicity outcomes vary among different THOV strains from slight weight loss to death [110,111]. Therefore, continuous studies are needed to identify suitable models and pathogenic markers.

5.2. Dhori virus (DHOV)

DHOV was first identified in the *Hyalomma dromedarii* in India in 1961 (Table 1) [40]. Since then, it has been found in India, Russia, Pakistan, Egypt, Saudi Arabia, Kenya, and Portugal [112–114]. Human infections are rare and have only been documented in laboratory settings, with five cases resulting in febrile illness and encephalitis [115]. The presence of antibodies against DHOV in some individuals and domestic animals indicates asymptomatic infections. DHOV has also been isolated from the *Anopheles Hyrcanus* mosquito, although mosquitoes have not been studied as a virus reservoir [116,117]. Further, the continuous spread of tick species suggests a broadened virus spread within these vectors [74,75].

Infection of ICR mice with DHOV causes a rapid and fatal disease seen in humans infected with highly virulent strains of *influenza A virus* [118]. However, as noted above, human infection cases are rare, making direct pathogenicity comparisons between ICR mice and human cases challenging.

5.3. Bourbon virus (BRBV)

BRBV was first identified in Kansas, the United States, in 2014, and five human infections have been reported (Table 1) [117,119,120]. The clinical symptoms in humans are similar to those of HRTV disease, including high fever, weakness, nausea, myalgia, arthralgia, fatigue, diarrhea, thrombocytopenia, and leukopenia, often accompanied by a rash [121]. In severe cases, multi-organ dysfunction can occur, including shock, severe cardiac impairment, and pulmonary dysfunction. However, serological studies have shown many asymptomatic cases, with less than 1 % of humans testing positive for the virus [122]. In addition to humans, virus infections have been demonstrated in animals. Serological studies have revealed positive rates of 22–86 % in wild animals, including white-tailed deer, raccoons, and eastern cottontails (*Sylvilagus floridanus*). Therefore, these animals are potential reservoirs for BRBV.

A. americanum is the primary vector, although BRBV has also been detected in *H. longicornis*. Human cases of BRBV infection are currently limited to the Midwestern United States. However, due to climate changes and host expansion, the geographic range of *A. americanum* is expanding, now including the Midwest as well as the Southeastern and Northeastern regions of the United States. Therefore, there is potential for an increase in the geographic spread of the virus [122].

The pathogenesis of BRBV in animals and humans remains unknown. Research involving *A. americanum* ticks engorged on rabbits (*Oryctolagus cuniculus*) indicated antibodies are present, although the virus is not detectable in blood, oral, or rectal swabs [123]. Thus, these wild animals may not be a suitable model for study of human pathogenicity. C57BL/6 mice demonstrated asymptomatic infection with no weight loss, while *IFNAR*$^{-/-}$ mice exhibited susceptibility to BRBV leading to weight loss and 100 % mortality [120]. These findings indicate that the innate immune-related gene is critical for BRBV infection. However, the use of *IFNAR*$^{-/-}$ mice limits the study of viral pathogenesis mechanisms, as their susceptibility is primarily due to their compromised immune system.

6. Sedoreoviridae

The genus *Coltivirus* in the family *Sedoreoviridae* contains a double-stranded RNA genome with 12 segments. Among *Coltivirus* infection cases, human infections with Colorado tick fever virus (CTFV) causing a febrile disease have been reported [124].

6.1. Colorado tick fever virus (CTFV)

CTFV was first isolated in the western United States in 1943 (Table 1) [125]. Since then, CTFV has been continuously reported, indicating a stable presence in endemic regions. Symptoms of CTFV infection typically appear 3–5 days post-tick bite and include high fever, chills, headache, and muscle pain. Although complications like leukopenia, thrombocytopenia, and anemia are common, fatalities are rare (<1 %). Vulnerable populations are at a higher risk of severe complications, including hemorrhagic issues [126].

Currently, the virus shows no divergence into different clades. However, its segmented genome allows for reassortment. For instance, reassortment between strains from the southernmost and northwestern regions in Montana, the United States, at a minimum distance of 30 miles, has been reported, suggesting a possibility of virus evolution through reassortment [127].

CTFV is primarily transmitted by infected *D. andersoni*, with chipmunks (*Eutamias* species), squirrels (*Spermophiles* species), and other rodents serving as natural reservoirs. The virus is prevalent throughout the western United States and southwestern Canada, especially in mountainous areas. However, climate change may enable the tick to expand its range into Northern Canada and the eastern United States [128].

Although human infection cases are continuously reported, no susceptible animal models have been documented. Wild animals such as chipmunks (*Eutamias minimus*), eastern deer mice (*Peromyscus maniculatus*), and golden-mantled ground squirrels (*Spermophilus lateralis*) have demonstrated viremia following infection without succumbing to lethality [129]. Therefore, developing a susceptible animal model that presents human clinical symptoms is necessary for studying virus evolution.

7. Conclusion

Emerging and re-emerging tick-borne viruses are closely linked to the geographic expansion of tick species. Climate change and increased mammalian activity are driving the spread of tick species, including *I. scapularis*, *I. ricinus*, *A. americanum*, *H. longicornis*, and *Hyalomma*. This increased distribution will likely lead to the emergence of virus infections in previously undetected regions. For instance, ticks like *I. ricinus* are now spreading TBEV into new areas such as England and the Netherlands [130,131]. This geographic expansion not only increases the risk of new viral infections, but also creates opportunities for viral sharing among previously isolated tick and animal populations.

The evolution of tick-borne viruses, characterized by various genotypes, further complicates their spread and impact. Outbreaks of tick-borne viral diseases pose a serious threat to public health. Human clinical symptoms against virus infection vary from fatal to asymptomatic, highlighting a critical knowledge gap. Despite extensive studies and the development of animal models undertaken to gain insight into pathogenesis, including immunocompromised mice, wild mice, ferrets, cats, and non-human primates, there remains a critical knowledge gap regarding the complexity and variability of human disease. Current models, while helpful in understanding viral replication, often fail to accurately reflect the natural transmission routes and disease progression observed in human infections.

To advance understanding of tick-borne viruses and mitigate their impact, effective surveillance and monitoring of tick populations, their distribution, and human clinical symptoms are essential. Additionally, developing animal models that more closely mimic human disease outcomes is imperative to improve our understanding of pathogenesis and to guide effective public health responses. Given the unpredictability of virus emergence and re-emergence, ongoing research and adaptation of surveillance strategies will be crucial in managing and mitigating the risks associated with tick-borne viral diseases.

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CRediT authorship contribution statement

Kwang-Min Yu: Writing – review & editing, Writing – original draft, Data curation, Conceptualization. **Su-Jin Park:** Writing – review & editing, Supervision, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

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