Tick-borne viruses: A review from the perspective of therapeutic approaches

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Abstract
Several important human diseases worldwide are caused by tick-borne viruses. These diseases have become important public health concerns in recent years. The tick-borne viruses that cause diseases in humans mainly belong to 3 families: Bunyaviridae, Flaviviridae, and Reoviridae. In this review, we focus on therapeutic approaches for several of the more important tick-borne viruses from these 3 families. These viruses are Crimean-Congo hemorrhagic fever virus (CCHF) and the newly discovered tick-borne phleboviruses, known as thrombocytopenia syndrome virus (SFTSV), Heartland virus and Bhanja virus from the family Bunyaviridae, tick-borne encephalitis virus (TBEV), Powassan virus (POWV), Louping-ill virus (LIV), Omsk hemorrhagic fever virus (OHFV), Kyasanur Forest disease virus (KFDV), and Alkhurma hemorrhagic fever virus (AHFV) from the Flaviviridae family. To date, there is no effective antiviral drug available against most of these tick-borne viruses. Although there is common usage of antiviral drugs such as ribavirin for CCHF treatment in some countries, there are concerns that ribavirin may not be as effective as once thought against CCHF. Herein, we discuss also the availability of vaccines for the control of these viral infections. The lack of treatment and prevention approaches for these viruses is highlighted, and we hope that this review may increase public health awareness with regard to the threat posed by this group of viruses.

Keywords: Tick-Borne Disease; Arbovirus; Therapy; Antiviral

Introduction
Tick-borne viruses are a group of viruses with significant worldwide importance in public health and as such a global concern. Currently, there is no effective therapeutic agent or vaccine for most of these viruses. Novel viral mutants and different variants can emerge and may potentially become a public health threat. These new emerging viruses could also pose a biosecurity threat. The aim of this review is to increase the public awareness of this group of viruses, particularly with regard to the possible treatment approaches and antiviral drugs for the management, control, and prevention of the diseases caused by these viruses. Generally, the therapeutic strategies comprise of (i) vaccination; (ii) administration of high-titer antibodies; and (iii) treatment with antiviral drugs. In this review, we have focused on tick-borne viruses that are of public health importance and the antiviral drug perspective for the treatment of the diseases caused by them.
Family Bunyaviridae

Crimean-Congo hemorrhagic fever virus

Crimean-Congo hemorrhagic fever virus (CCHFV; genus: Nairovirus; family: Bunyaviridae) was first identified in 1944 in the Crimean Peninsula (Chumakov et al., 1963; Mourya et al., 2012), and it was then isolated from a patient in Kisangani, Congo, in 1956 (Simpson et al., 1967; Mourya et al., 2012). This virus, which is maintained in nature by ixodid species (Labuda and Nuttall, 2004) and is transmitted by *Hyalomma* ticks (Tekin et al., 2010), has been associated in a series of outbreaks with a large geographical distribution across Europe, Middle East, Asia, and Africa (Hoogstraal, 1979; Whitehouse, 2004; Flick and Whitehouse, 2005; Papa et al., 2010; Tekin et al., 2010; Ergonul, 2012). Besides transmission of the virus by ixodid ticks, CCHFV can be transmitted by contact with tissues and excreta or secreta of infected animals or humans (Keshtkar-Jahromi et al., 2011; Ergonul, 2008; Whitehouse, 2004). Early signs of the disease typically include fever, hypotension, conjunctivitis, and cutaneous flushing or skin rash. Later, patients may have signs of progressive hemorrhagic diathesis, similar to petechiae, and mucous membrane and conjunctival hemorrhage hematuria, hematemesis, and melaena. Disseminated intravascular coagulation (DIC) and circulatory shock may ensue (Ergonul, 2012). The mortality rate of CCHF is between 9% and 50% (Ergonul, 2008).

Issues concerning the treatment and prevention of CCHF

There is currently no effective vaccine available for CCHF, although several vaccine candidates have been developed and evaluated. One example of a candidate vaccine for CCHF is the inactivated mouse brain vaccine, which was used on a small scale in the former Soviet Union and Bulgaria on several hundred human volunteers (Tkachenko et al., 1971; Vasilenko, 1973). Despite the vaccine being able to induce high detectable antibody levels, no sufficient clinical trials were performed as there were concerns about using mouse-brain vaccines, which have the potential to cause autoimmune responses. Additionally, there is a lack of commercial value for the vaccine as CCHF is a disease confined to poor-resource countries.

More recently, a DNA vaccine containing the CCHF genome M segment was developed, and it was demonstrated that it induces neutralizing antibodies in mice, as well as antibodies that immunoprecipitate with the M segment expression products (Spik et al., 2006; Keshtkar-Jahromi et al., 2011). However, the protective effect of the vaccine was not evaluated.

Currently, management of CCHF is based on general supportive measures and monitoring of
the patient’s hematologic and coagulation status, with replacement of cells and factors as needed (Ergonul, 2008).

To date the only drug that is placed on the WHO essential medicines list to be used against CCHFV infection is ribavirin (Ergonul, 2006); however, there are many contradictions with regard to the efficacy of this drug for CCHF disease. Ribavirin inhibits the growth of CCHFV in vitro and in experimentally infected mice (Watts et al., 1989; Tignor and Hanham, 1993). There is evidence about the effectiveness of this drug in patients following oral and intravenous administration (Mardani et al., 2003; Elaldi et al., 2009). However, in one randomized controlled trial published on this topic, there was no significant positive effect in the clinical or laboratory parameters after administration of ribavirin in CCHF patients (Koksal et al., 2010). In a meta-analysis of 21 unique studies including one randomized controlled trial of ribavirin to investigate the effect of ribavirin in CCHF patients, it was noted that the current data available are insufficient to understand the efficacy of the drug (Soares-Weiser et al., 2010). For example, studies in which ribavirin was combined with cycloferon, which is an interferon inducer, either in the form of solution or tablets, shortened the period of the fever in CCHF patients, minimized the intoxication syndrome, promoted earlier resolution of hemorrhagic eruption, and lowered the frequency of complications, which improved the disease prognosis (Cherenov et al., 2012; Romantsov et al., 2012). Administration of corticosteroids together with ribavirin was also reported to be useful, particularly during early stages of the disease – however, this experience was limited to an observational study of only 6 patients (Jabbari et al., 2006).

Currently, ribavirin is used in most endemic countries and ethical issues about using a randomized trial have been raised (Arda et al., 2012). Researchers should therefore consider how ribavirin therapy might be further evaluated without violating ethical guidelines. Given the high fatality rate associated with CCHF, well-designed multi-centre and random-controlled trials are urgently needed to provide evidence-based data about the efficacy of ribavirin (Maltezou and Papa, 2011). Besides ribavirin, there are some other studies to find effective antiviral compounds against CCHFV, including the in vitro inhibitory properties of exogenous nitric oxide (NO) on CCHFV replication (Simon et al., 2006). Type-I interferon (IFN) has significant antiviral activity against many hemorrhagic fever viruses in vitro, and in animal models, Karlberg and his colleagues (2010) in an in vitro study showed significant antiviral activity of a natural IFN-α produced in human leukocytes (multiferon) compared to 2 recombinant IFN-α preparations (roferon A and intron A) against CCHFV. However, there are data suggesting that CCHFV possesses mechanisms to defeat the IFN-induced defense
mechanisms by delaying IFN secretion for 48 h post infection (Andersson et al., 2008). In one study using a small interfering RNAs (siRNAs) approach, it was shown that the IFN-induced MxA GTPase is a major factor mediating the antiviral effect against CCHFV, and the IFN-α inhibits the growth of CCHFV in human endothelial and hepatoma cells (Andersson et al., 2006). In addition, IFN-stimulated genes (ISGs) seem to be sufficient for significant CCHFV growth inhibition (Andersson et al., 2006). Proteins such as ISG20, P56, RNA-specific adenosine deaminase 1, promyelocytic leukemia protein, and guanylate-binding protein 1 have also been demonstrated to have antiviral activities against CCHFV (Ergonul, 2008).

Besides the above-mentioned strategies, there was an early recognition of the possible benefits of treatment using serum prepared from the blood of recovered CCHF patients or γ-globulin obtained from immunized horses (Hoogstraal, 1979). Bulgarian scientists reported the fast recovery of 7 severely ill patients treated via passive simultaneous transfer of 2 different specific immunoglobulin preparations, “CCHF-bulin” (for intramuscular use) and “CCHF-venin” (for intravenous use), prepared from the plasma of CCHF survivor donors boosted with one dose of CCHF vaccine (Vasilenko et al., 1990). Prompt administration of CCHFV hyper-immunoglobulin has been demonstrated to be effective and a new treatment approach for high-risk CCHF patients (Kubar et al., 2011). In a recent study, combination of intravenous immunoglobulin (IVIG), high-dose methylprednisolone (HDMMP), and fresh frozen plasma (FFP) seemed to be effective in patients with CCHF associated with reactive hemophagocytic lymphohistiocytosis (HLH) (Erduran et al., 2013). Specifically, the suppression of macrophage activation and treatment of HLH was achieved using HDMP. The DIC was treated using FFP, and IVIG was for suppression of macrophage and cytokine storm development in CCHF associated with reactive HLH patients. However, as HLH is a hemotologic disorder that may occur in association with infection by other microorganisms or in association with diseases such as lymphoma or autoimmune diseases, the therapeutic effect from the combination of IVIG, HDMP, and FFP may not be specific for CCHF, but for HLH.

**Severe fever with thrombocytopenia syndrome virus**

Severe fever with thrombocytopenia syndrome virus (SFTSV) also known as Huaiyangshan virus is a new member of the phlebovirus genus from the Bunyaviridae family. This virus was reported for the first time in the vicinity of Huaiyangshan, China (Jin et al., 2012). Later, infections due to SFTSV were reported from 11 Chinese provinces (Lam et al., 2013) with a significant mortality rate of up to 30% (Hofmann et al., 2013). The virus is transmitted by ticks, and the viral genomic RNA has been detected mostly in *Haemaphysalis longicornis*
ticks from endemic regions and *Rhipicephalus microplus* in non-endemic regions (Zhang et al., 2012a; Jiang et al., 2012). However, there is evidence of human-to-human transmission through contact with infected blood samples (Liu et al., 2012).

The clinical manifestation of the disease consists of 3 stages: fever stage, multiple organ dysfunction stage, and convalescent stage (Gai et al., 2012). The first stage persists for approximately 7 days with clinical signs of sudden onset of fever, headache, gastrointestinal symptoms, thrombocytopenia and leukocytopenia and lymphadenopathy (Gai et al., 2012; Zhang et al., 2012b). Then, 7–13 days after disease onset, multiple organ dysfunction will occur with elevation of serum AST, CK, CK-MB, and LDH, and subsequently progresses to hemorrhagic manifestations, central nervous system manifestations, DIC, and multiple organ failure (MOF) (Gai et al., 2012). In some cases, pronounced coagulation disturbances have been reported (Zhang et al., 2012b). In patients who recover, the clinical symptoms and abnormal laboratory parameters gradually return to their normal status (Gai et al., 2012). It seems that the fatal outcome is associated with high viral RNA load during disease progression, and it suggests the role of active virus in determining the clinical outcome of the disease (Gai et al., 2012; Zhang et al., 2012b). Recently, a new virus named Heartland virus was isolated from 2 severely febrile patients in Missouri, USA (McMullan et al., 2012). This virus is classified as a distinct member of the Phlebovirus genus, and it is closely related to SFTSV. Heartland virus is a tick-borne virus, and there are many more tick-borne viruses with unassigned genera. For example, Bhanja virus, which was previously unassigned to a genus, has recently been found to be more closely related to the novel emerging SFTSV and Heartland virus using phylogenetic and serological analyses (Matsuno et al., 2013). These tick-borne phleboviruses are becoming a global concern due to the insufficient information about the pathogenesis, epidemiology, and many other aspects of these viruses, and also the lack of therapeutic and vaccination approaches to control the spread of the disease.

Treatment outlook of tick-borne phleboviruses

The current clinical approaches for treatment of these viruses are on the basis of general supportive measures. It is essential to monitor the hematologic and coagulation status of patients. Intravenous transfusion of FFP, whole blood, platelet cells, albumin, or granulocyte colony-stimulating factor should be conducted as needed. In some severe cases, intravenous ribavirin was administered; however, no clinical studies have been able to confirm the efficacy of this antiviral drug on phleboviruses (Gai et al., 2012). Recently, there has been some development in characterizing molecular aspects of SFTSV infection to find new...
approaches for prevention and treatment of this virus. For instance, in one study, the entry of SFTSV to the host cells has been elucidated, which is the initial insight into cell tropism, receptor usage and proteolytic activation of SFTSV (Hofmann et al., 2013). Further, the crystal structure of the SFTSV's viral nucleocapsid protein has been determined (Jiao et al., 2013). From the protein structure, it was demonstrated that a mutant of SFTSV-N with triple mutations would result in an inhibitory effect on the transcription and replication of the viral RNA. It was also determined that the drug suramin which is commonly used in the treatment of trypanosomiasis and helminthiasis, has an inhibitory effect on SFTSV replication in Vero cells (Zhang et al., 2013). Accordingly, these recent findings can be considered as insights for drug and vaccine development against these novel phleboviruses and will help to prevent its potential as a public health threat.

Family Flaviviridae

Tick-borne flaviviruses with encephalitis manifestations

Tick-borne encephalitis virus

Tick-borne encephalitis virus (TBEV) is a member of the Flavivirus genus. TBEV is a neurotropic virus endemic in central, eastern, and northern Europe, and north-eastern Asia (Gritsun et al., 2003b; Heinz et al., 2007; Toporkova et al., 2008; Süss, 2008; Lu et al., 2008; Takashima et al., 1997). Russia is reported as being the country with the highest incidence with 3721 clinical cases during 1990–2009 (Süss, 2011). The principal vectors for this virus are *Ixodes ricinus* for the European subtype (Gritsun et al., 2003b) and *Ixodes persulcatus* for the Siberian and the Far-Eastern subtypes (Süss, 2003). In the life cycle of TBEV, the virus is mainly maintained in nature by transmission between ixodid ticks, wild mammalian hosts and, in some cases, migrating birds (Gray, 1991; Süss, 2003; Charrel et al., 2004; Mansfield et al., 2009; Waldenström et al., 2007). Infection with this virus is usually initiated by a bite from an infected tick, while the other infection route is due to consumption of raw, unpasteurized milk and dairy products (Grešíková et al., 1975; Dumpis et al., 1999).

Typically, the symptoms of patients with TBE have a biphasic pattern starting with influenza-like symptoms such as fatigue, headache, pain in neck, high fever, and vomiting. In 20–30% of the patients, there will be an asymptomatic period of 2–10 days, followed by the second phase where there is neurological involvement (meningitis, encephalitis, myelitis, and radiculitis) (Andzhaparidze et al., 1978; Monath and Heinz, 1996; Gritsun et al., 2003a; Süss et al., 2007).
There has been an upward rise of clinical cases related to TBEV infection, and this increase is likely due to urbanization and increased human activities like agriculture in the wild (Gritsun et al., 2003b). Other factors that had increasing effects on TBE prevalence can be exemplified by increase of ticks population due to global warming, moving of ticks to higher altitudes, and emergence of new TBE foci (Randolph et al., 2000; Lindgren et al., 2000; Lindgren and Gustafson, 2001; Bröker and Gniel, 2003). The prevention of TBE can be achieved by avoidance of exposure to the bite of an infected tick and by not drinking non-pasteurized dairy products (Dumpis et al., 1999). An effective alternative for TBE prevention is vaccination (Kunz, 1980; Kunz et al., 2003). To date, there are at least 4 formaldehyde-inactivated vaccines available against TBEV infection: the Austrian FSME-IMMUN, German Encepur Adult and Children, and 2 Russian vaccines manufactured in Moscow and Tomsk (EnceVir and TBE vaccine Moscow) (Levkovich et al., 1960; Bock et al., 1990; Harabacz et al., 1992; Hayasaka et al., 2001; Barrett et al., 2003, 2004). Following vaccination, there is efficient cross-protection against different TBEV strains with a reduced, but still protective, neutralization capacity against more distantly related viruses such as Omsk hemorrhagic fever virus (Orlinger et al., 2011). This was clearly demonstrated by quantitatively comparing the cross-protection profiles of vaccines, FSME-IMMUN (derived from European subtype), EnceVir and IPVE (both derived from Far Eastern subtype), and there was no significant difference on the degree of protection (Fritz et al., 2012). However, it also showed that TBE vaccine Moscow and Encepur had a high immunogenicity compared to EnceVir and FSME-IMMUN (Leonova et al., 2009). As a result, more studies are required to determine and evaluate the vaccine-induced cross-protection against different TBEV strains.

It is worth mentioning that the vaccination coverage differs significantly between countries with TBE endemcity. In Austria, 88% of the population showed immunity against TBEV due to wide vaccination (Heinz et al., 2007). In contrast, neighboring countries such as Germany and the Czech Republic have only 13% and 11% vaccination coverage, respectively (Heinz et al., 2007). This would then increase the risk of acquiring TBE with the recent rise in tourism (Dumpis et al., 1999). This can be illustrated by many TBE reports in travelers to Europe (McNair and Brown, 1991; Aendekerk et al., 1996; Kessels et al., 1999; Bröker and Gniel, 2003) and more recently by the first reported case of imported TBE in Australia, where the patient traveled through Russia on a 6-week trip (Chaudhuri and Růžek, 2013). In addition to the prevention of TBE, an effective treatment and post-exposure management approach is highly needed.
In addition to aforementioned inactivated vaccines, several attempts have been done to develop live attenuated vaccines on the basis of Langat virus (LGTV), which is a member of the tick-borne encephalitis virus (TBEV) antigenic complex (Il’enko et al., 1968; Dubov, 1969; Price et al., 1970; Mayer, 1973; Timofeev and Karganova, 2003; Pripuzova et al., 2009). However, vaccine-associated severe complications in some patients (Dubov, 1969, 1971; Smorodintsev and Dubov, 1986) and delayed progressive subacute sclerosing encephalitis through in vivo studies (Zlotnik et al., 1973; Zlotnik and Grant, 1976; Pogodina et al., 1981) have resulted in attempts to develop more attenuated virus vaccines. This can be illustrated by new types of live attenuated vaccines that use mutagenesis of the viral genome or chimerization of 2 different viruses (Mandl et al., 1998; Pletnev, 2001; Lai and Monath, 2003; Kofler et al., 2004). In 1998, Pletnev and Men have produced a chimeric virus with the prM and E genes encoding structural proteins of LGTV strain TP21 and remaining part of the genome from dengue virus type 4 (Pletnev and Men, 1998). The attenuation efficacy of the chimera LGT/DEN4 against virulent strains of TBEV has been shown in mice, monkeys, and humans in past years (Pletnev and Men, 1998; Pletnev et al., 2000, 2001; Rumyantsev et al., 2006; Wright et al., 2008; Pripuzova et al., 2009). However, to make a decision about vaccine strain safety, it is required to do more evaluation for the possibility of long-term persistence of attenuated viruses in the recipients and other complications (Pripuzova et al., 2009). More recently, a replication-defective flavivirus mutant platform, RepliVax was used in the construction of RepliVax-TBE variants containing the prM-E genes of TBEV (Rumyantsev et al., 2013). It was demonstrated in mice and non-human primates that the RepliVax-TBEV variants were highly attenuated, immunogenic, and protective, and have potential as a single-dose TBEV vaccine.

Treatment outlook for TBE
Currently, there is no approved antiviral drug available for TBE. Therefore, the treatment of TBE patients is supportive and symptomatic (Kaiser, 2012; Mansfield, 2009). Administration of corticosteroids have been only supported by few studies like a progressive case from Lithuania (Mickiene et al., 2002) and treatment of a group of TBE patients in Germany (Duniewicz and Kulková, 1982). In Russia, specific immunoglobulins have been used against TBE with more than 60% efficacy in the first 96 h post exposure (Kunz et al., 1981; Kreil et al., 1997; Dumps et al., 1999). However, this medicine was withdrawn completely from the market in Europe, as there was a hypothesis about the antibody-dependent enhancement of infection in some cases (Arras et al., 1996; Waldvogel et al., 1996). For example, specific
prophylactic post-exposure immunoglobulins may have caused severe encephalitis and negative effects on the course of the disease in some age group less than 7 years old in Europe (Kluger et al., 1995; Waldvogel et al., 1996). On the other hand, there are many factors that may affect the treatment using immunoglobulins, which is worth more evaluation. This can be illustrated by a significant correlation of the efficacy of immunoglobulins with calculating adequate doses (Vereta et al., 1994) or HLA phenotype of the patients (Chernitsyna et al., 1992). Recently, Růžek and colleagues (2013) have discussed whether early administration of high dose IVIG therapy may have a positive therapeutic effect on severe cases of TBE. Accordingly, obtaining immunoglobulins from blood donors vaccinated against TBE may be a good strategy in TBE treatment. Further study is required to evaluate the possible benefits of this therapeutic approach.

Another approach that has shown promising results in the treatment of TBE trials is using antioxidants such as cytoflavin, emoxypine (mexidol), and panavir (Abramenko and Iu, 2011; Kon’kova-Reidman and Ratnikova, 2012; Skripchenko and Egorova, 2011; Udintseva et al., 2012; Litvin et al., 2009). In a recent study, Achazi and colleagues (2012) demonstrated the in vitro inhibitory effect of siRNAs on TBEV replication. RNAi has been demonstrated to be a useful technique for inhibiting the replication of many different viruses including the human immunodeficiency virus (HIV), hepatitis viruses, dengue virus, West Nile virus, Japanese encephalitis virus, yellow fever virus, and human respiratory syncytial virus (Achazi et al., 2012). Besides the aforementioned approaches, other potent antiviral agents include pancreatic ribonuclease (RNAs) (Glukhov et al., 1976), complementary and non-complementary oligonucleotides (Frolova et al., 1994), and lincomycin (Votiakov et al., 1992). Additionally, combinations of thymalin (immunomodulator polypeptides) and leukinferon (a complex preparation containing alpha-interferon and cytokines of the first phase of immune response such as interleukins 1, 6, and 12, and tumor necrosis factor to activate the phagocytic process) with human leukocytic IFN (Krylova and Leonova, 2001) may be effective as a treatment for TBE.

Recently, Osolodkin and his colleagues (2013) by constructing homology models of envelope glycoproteins of tick-transmitted flaviviruses, have proposed 17 compounds with significant in vitro inhibitory effects on TBEV, Powassan virus (POWV), or Omsk hemorrhagic fever virus (OHFV). Among these compounds, the ones belonging to the series of 1,4-dihydropyridines, had inhibitory effects against TBEV or OHFV, and others from pyridothiadiazines, have a stronger inhibitory effect against TBEV compared to POWV.
In summary, further investigations through in vitro, in vivo studies and clinical trials are required to evaluate the therapeutic efficacy of the above-mentioned approaches on TBE patients in the limitation for the usage of these compounds for treatment purposes.

**Powassan virus**

Powassan virus (POWV) belongs to the genus Flavivirus and was first isolated from the CNS of a 5-year-old boy who suffered from encephalitis in 1958 (McLean and Donohue, 1959). The principal vector for this virus is *Ixodes cookei*, which is found mainly in Canada and the northeastern United States (Birge and Sonnesyn, 2012; Mclean et al., 1967). This virus was found in South Dakota, western United States, western Canada, and Siberia (Lvov et al., 1975; Gritsun et al., 2003a). Additionally, human infection has been documented in the northern United States and Russia (Ebel and Kremer, 2004). Patients infected by this virus present with encephalitis and neurological signs after an incubation period of 1–4 weeks (Briige and Sonnesyn, 2012). The main pathological finding in POWV infection is lymphocytic infiltration of perivascular neuronal tissues with a predilection for grey matter (Gholam et al., 1999), which then leads to long-term neurological sequelae and death in at least 10% of the cases (Hinten et al., 2008; Ebel and Kramer, 2004). Severe encephalitis with a high incidence of neurological sequelae and a mortality rate of up to 60% has been reported in Canada and the United States (Gritsun et al., 2003a).

**Louping-ill virus**

Louping-ill virus (LIV) from the Flavivirus genus was isolated for the first time from sheep brains in England and Scotland (Hubálek and Rudolf, 2012). There are significant antigenic and genomic similarities between LIV and TBEV (Hubálek and Rudolf, 2012). Most of the LIV infections in humans are due to occupational exposure in people who had direct contact with animals (Lawson et al., 1949; Charrel et al., 2004; Dobler, 2010) or through the consumption of raw goat or sheep milk (Reid et al., 1984; Reid and Pow, 1985; Hubálek and Rudolf, 2012). The clinical manifestations of the disease are similar to the western European subtype of TBEV (Charrel et al., 2004; Hubálek and Rudolf, 2012). Antigenic and genetic similarity of this virus to TBEV has suggested that LIV is one of the subtypes of TBEV (Hubálek et al., 1995; Grard et al., 2007; Dobler, 2010). However, this virus rarely infects humans (Grard et al., 2007).

Treatment outlook for POWV and LIV
Due to the lack of antiviral agents against these viruses, the general management of these viral diseases is based on supportive and symptomatic therapy. Diagnosis and management of simultaneous complications such as secondary bacterial infections, aspiration pneumonia, respiratory failure, cardiac abnormalities, and electrolyte imbalance are other aspects to be considered for the treatment (Ferrari et al., 2009).

Concerning specific antiviral agents, there are a few studies on antivirals that directly target POWV and LIV. Examples are given by studies on antivirals like d-[1,2,4] triazole (ETAR) (McDowell et al., 2010) and siRNA (Maffioli et al., 2012), which have an inhibitory effect on LGTV and other flaviviruses; however, no clinical trial has been done to evaluate their therapeutic efficacy. Recently, it has been shown that some compounds belonging to the series pyridothiadiazines have inhibitory effects against POWV (Osolodkin et al., 2013). According to the recent case reports with POWV in the northern United States (Dobler, 2010; Raval et al., 2012), there is an urgent need to do further research to find the safe and effective antiviral agents against POWV as it is becoming a serious public health threat.

**Tick-borne flaviviruses with hemorrhagic manifestation**

**Omsk hemorrhagic fever virus**

Omsk hemorrhagic fever virus (OHFV) is a flavivirus that was first isolated from a patient with fever and hemorrhage in the Omsk district, Siberia in 1947 (Dobler, 2010). The virus was also isolated from arthropods, particularly ticks of the species *Dermacentor reticulatus* and vertebrates such as muskrats (Charrel et al., 2004). The Centers for Disease Control and Prevention (CDC) has named several other hosts for this virus. The natural foci of OHFV are in Omsk, Novosibirsk, Tyumen, and Kurgan with a range of fatality rates between 0.5% and 3.0% (Charrel et al., 2004). The transmission routes of this virus are tick bites (Charrel et al., 2004), contact with feces or urine of infected or dead muskrats, contact with viremic blood of infected hosts, and aerosol transmission (Dobler, 2010). The clinical manifestations of OHF include fever, headache, myalgia, cough, and sometimes the appearance of petechial rash or bruises. In the second phase of the infection, meningeal signs with neurological system involvement are noted (Charrel et al., 2004; Růžek et al., 2010). Chronic forms of OHF have not been reported in humans (Charrel et al., 2004; Růžek et al., 2010). The hemorrhagic manifestation is actually due to vascular and circulatory capillary damage (Charrel et al., 2004). To date, there is no licensed vaccine available against OHFV, although there is some evidence that TBEV vaccines have the ability to cross-protect (Růžek et al., 2010; Orlinger et al., 2011; Pripuzova et al., 2013).
Kyasanur Forest disease virus

Kyasanur Forest disease virus (KFDV) was isolated after an outbreak of severe disease in monkeys in Kyasanur Forest and people living near the forest in Karnataka state of India in 1957 (Kasabi et al., 2013; Holbrook, 2012; Pavri, 1989). Transmission of KFDV is mainly through the bites of infected ticks from the genus *Haemaphysalis*, particularly *Haemaphysalis spinigera*. The known natural hosts are Blanford rat (*Rattus blanfordi*), the striped forest squirrel (*Funambulus tristriatus tristriatus*), and the house shrew (*Suncus murinus*) (Dobler, 2010). The annual incidence of KFD in India is estimated to be 400–500 cases with seasonal outbreaks during January to June (Holbrook, 2012; Kasabi et al., 2013). The clinical manifestation of KFD is similar to OHF (Bossi et al., 2004). Since 1990, a formalin-inactivated KFDV vaccine derived from infected cell cultures has been produced and used in India (Dandawate et al., 1994, Holbrook et al., 2012). However, due to insufficient efficacy of the current vaccine protocol, an increasing number of KFD cases were detected in Karnataka state of the Indian subcontinent from 1999 to 2012 (Pattnaik, 2006; Holbrook et al., 2012). There is another genetic variant of KFDV that caused outbreaks in 1994 in Saudi Arabia, and the virus is named Alkhurma hemorrhagic fever virus (AHFV). It has a mortality rate of 25%, and there is a 1.3% seroprevalence in hemorrhagic patients in Saudi Arabia (Charrel and de Lamballerie, 2003; Memish et al., 2011).

Treatment outlook for OHFV, KFDV, and AHFV

These diseases are mostly self-limiting. Strict bed-rest and supportive therapy are important for the management of these patients (Mazbich and Netsky, 1952). Administration of aspirin and other non-steroidal anti-inflammatory drugs with potential side effects should be avoided (Růžek et al., 2010). Despite the potential use of these viruses as biological weapons, according to the list from the CDC, there are only a few studies aiming to develop antiviral agents against OHFV. Some of the antiviral drugs available are virazol (ribavirin), a broad-spectrum antiviral nucleoside, and realdiron, a recombinant human interferon alfa-2b, which binds to cell surface receptors to modulate downstream intracellular signal transduction pathways. Another antiviral agent is interferon inducers, for example larifan and rifastin, which have inhibitory effects against the virus replication (Loginova et al., 2002). Nevertheless, no experimental clinical trials have been done to confirm the effectiveness of these drugs. The compounds belonging to 1,4-dihydropyridines have also shown significant inhibitory effects against OHFV and TBEV in homology models (Osolodkin et al., 2013).
However, further in vitro and in vivo studies are necessary to evaluate their efficacy and safety.

**Family Reoviridae**

**Colorado tick fever virus**

Colorado tick fever virus (CTFV) is a virus of the genus Coltivirus. It was isolated from infected human blood in 1944 (Cimolai et al., 1988). The mountain wood tick,* Dermacentor andersoni,* is the vector of CTFV, and the prevalence of the disease is directly dependent on the seasonal activity and geographical distribution of the ticks (Meagher and Decker, 2012; Rust, 2012; Cimolai et al., 1988). As a result, CTF is mainly prevalent from May to July, and it is mostly localized in the mountainous regions of the western United States and Canada (Meagher and Decker, 2012; Rust, 2012; Cimolai et al., 1988). After West Nile virus, CTFV is the second most important arboviral infection with 200–400 case reports per year in the northern United States (Romero and Simonsen, 2008; Meagher and Decker, 2012).

Transmission routes for this virus include bites of infected ticks, contact with infected animal blood or tissues, and person-to-person transmission via blood transfusion (Emmons, 1988; Cimolai et al., 1988). After an incubation period of 3–5 days, an acute or febrile illness is presented (Meagher and Decker, 2012). The clinical symptoms comprise fever, chills, malaise, lymphadenopathy, headache, conjunctivitis, photophobia, nausea, vomiting, asthenia, myalgia, weakness, and, in some cases, development of meningismus (Rust, 2012). Macular rash has also been seen in about 10% of the cases (Cimolai et al., 1988). “Saddleback” course, which is a recurrence of fever, may occur in some cases (Rust, 2012).

Treatment outlook for CTFV

Due to the sporadic and self-limiting nature of these viral diseases, management is only with supportive care and avoidance of medications that compromise platelet functions, such as aspirin or non-steroidal anti-inflammatory drugs. Currently, there is no antiviral drug or vaccine available for CTFV. However, there are a few studies that focused on specific antiviral drugs for this disease. In 1981, the efficacy of 4 ribonucleic acid virus inhibitors including ribavirin, 3-deazaguanine, 3-deazauridine, and 9-(S)-(2,3-dihydroxypropyl) adenine were evaluated in vivo and in vitro against CTFV (Smee et al., 1981). Findings demonstrated that ribavirin and 3-deazaguanine markedly inhibited CTFV replication in MA-104 cells. In addition, the therapeutic effect of ribavirin triacetate in CTFV-infected mice was reported.
In another study, a nucleoside analog, 3’-fluoro-3’-deoxyadenosine (3’F3’dAdo) was shown to have inhibitory potency against CTFV replication in Vero cells (Smee et al., 1992). On the other hand, ribavirin was less active against CTFV in this study, and this finding was not consistent with the results from the previous study (Smee et al., 1992). Accordingly, the aforementioned studies have demonstrated the availability of some antiviral candidates for CTFV with some contradictions regarding the efficacy of ribavirin; as a consequence, owing to insufficient data on drugs and vaccine development, further study is indispensable to find a potent antiviral agent or vaccine for a better control of these viruses.

Conclusion
According to the aforementioned discussion, it can be concluded that tick-borne viruses are important viruses with many obscure aspects. They are zoonotic agents that pose a serious threat to public health. Therefore, finding and establishing efficient therapeutic strategies is crucial due to the lack of availability of approved antiviral drugs and licensed vaccines. We hope this review will improve the public perception of this menacing viral group and will lead to new insights for future investigations towards finding effective treatment strategies for these viral diseases.

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References


McMullan, L.K., Folk, S.M., Kelly, A.J., MacNeil, A., Goldsmith, C.S., Metcalfe, M.G.,
Batten, B.C., Albariño, C.G., Zaki, S.R., Rollin, P.E., Nicholson, W.L., Nichol, S.T.,
Med. 367, 834–841.

McNair, A.N., Brown, J.L., 1991. Tick-borne encephalitis complicated by monoplegia and
sensorineural deafness. J. Infect. 22, 81–86.

Meagher, K.E., Decker, C.F., 2012. Other tick-borne illnesses, tularemia, Colorado tick fever,

Memish, Z.A., Albarak, A., Almazroa, M.A., Al-Omar, I., Alhakeem, R., Assiri, A., Fagbo,
Alkhurma and other hemorrhagic fever viruses, Saudi Arabia. Emerg. Infect. Dis. 17,
2316–2318.

borne encephalitis in an area of high endemicity in Lithuania, disease severity and


Mourya, D.T., Yadav, P.D., Shete, A.M., Gurav, Y.K., Raut, C.G., Jadi, R.S., Pawar, S.D.,
Nichol, S.T., Mishra, A.C., 2012. Detection, isolation and confirmation of Crimean-
Congo hemorrhagic fever virus in human, ticks and animals in Ahmadabad, India,

Orlinger, K.K., Hofmeister, Y., Fritz, R., Holzer, G.W., Falkner, F.G., Unger, B., Loew-
borne encephalitis virus vaccine based on the European prototype strain induces
broadly reactive cross-neutralizing antibodies in humans. J. Infect. Dis. 203, 1556–
1564.

Osolodkin, D.I., Kozlovskaya, L.I., Dueva, E.V., Dotsenko, V.V., Rogova, Y.V., Frolov,
Inhibitors of tick-borne flavivirus reproduction from structure-based virtual screening.

Papa, A., Dalla, V., Papadimitriou, E., Kartalis, G.N., Antoniadis, A., 2010. Emergence of

Virol. 16, 151–165.


Instituta Poliomieliita i Virusnykh Entsefalitov. vol. XIX. USSR Academy of Medical Sciences, Moscow, USSR, pp. 119–129.


as a live attenuated tick-borne encephalitis vaccine for safety and immunogenicity in healthy adult volunteers. Vaccine 26, 882–890.


