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Tick borne viral zoonotic diseases: a review

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Abstract
Ticks are the important arthropod vectors for transmission of numerous infectious agents and are responsible for causing human and animal diseases. Among the world's tick fauna, 80% are hard ticks and remaining 20% are soft ticks. However, only 10% of the total hard and soft tick species are known to be involved in disease transmission to domestic animals and humans. The global loss due to ticks and tickborne diseases (TTBDs) was estimated to be between US$ 21.38- 28.76 billion annually, while in India the cost of controlling TTBDs has been estimated as US$ 498.7 million/annum. A number of tick species have been recognised since long as vectors of lethal pathogens, viz. Crimean-Congo haemorrhagic fever virus (CCHFV), Kyasanur forest disease virus (KFDV), Nairobi sheep disease virus, Tick borne encephalitis virus etc. and the damages caused by them are well-recognised. *Hyalomma anatolicum anatolicum* and *Haemaphysalis spinigera* are the two important species of ticks present in India, which are responsible for causing CCHF and KFD respectively. There are about 400-500 cases of KFD, 10000-15000 cases of CCHF with 500 deaths are reported annually. Generally tick-borne viral diseases manifest three different clinical conditions: encephalitis, haemorrhagic fevers and acute febrile illness. The diagnosis of TBDs is challenging and information exchange from physician to veterinarians and vice versa is beneficial for both sides but mainly for patients. There is a need for improved diagnostic facilities and laboratories.

Keywords: Ticks and Tick borne disease, CCHF, KFD

Introduction
Ticks are the important arthropod vectors for transmission of numerous infectious agents and are responsible for causing human and animal diseases [1]. Various wild and domestic animals are reservoir hosts for tick-borne pathogens of livestock, pets and humans [2]. Ticks are obligatory blood sucking ectoparasites that infest mammals, birds, reptiles and amphibians. Among the world's tick fauna, 80% are hard ticks and the remaining 20% are soft ticks. However, only 10% of the total hard and soft tick species are known to be involved in disease transmission to domestic animals and humans. Tick-borne diseases are prevalent only in specific risk areas where favourable environmental conditions exist for individual tick species [3].
The global loss due to ticks and tickborne diseases (TTBDs) was estimated to be between US$ 13.9 and 18.7 billion annually, while in India the cost of controlling TTBDs has been estimated as US$ 498.7 million/annum [4].
Tick borne diseases (TBDs) have been growing and spreading worldwide consequent to the increase in movement in tick-infested areas like forests, grasslands, pastureland and fields. In addition, different human behaviors including sitting on logs, visiting tick-infested parks and sitting along trees are further adding to the potential risk factors for acquiring tick borne infections [5].
Many bacterial, viral and rickettsial diseases are transmitted through ticks as they act as a vector for pathogenic organisms. Generally tick-borne viral diseases manifest three different clinical conditions: encephalitis, haemorrhagic fevers and acute febrile illness. *Hyalomma anatolicum anatolicum* and *Haemaphysalis spinigera* are the two important species of ticks present in India, which are responsible for causing the fatal tick-borne viral diseases of Crimean Congo hemorrhagic fever (CCHF) and Kyasanur forest disease (KFD) respectively [6].

Tick associated pathogens
Current comprehensive listing of tick associated viral pathogens, their hosts and geographical distribution across the globe are presented in table

Table 1: Important tick borne viral zoonotic diseases

S.N.	Disease	Organism	Vector	Host	Region	Referances
1.	CCHF	CCHFV	*Hyalomma marginatum*	Humans, ruminant and ostrich	India, Northern Africa, Southern Europe, Southern parts of Asia	[7]
2.	KFD	KFDV, Group-B Toganvirus (*Flavidiridae*)	*Haemaphysalis spinigera*	Rats, Squirrels,mice,shrews,porcupines, humans	South asia, India	[8]
3.	Nairobi sheep disease	*Bunyaviridae*	*Rhipicephalus appendiculatus*	Sheep and Goat	East and Central Africa, India	[9]
4.	Tick-borne meningo encephalitis	Tick-borne encephalitis virus (TBEV) (Flaviviridae)	*Ixodes scapularis*, *Ixodes ricinus*, *Ixodes persulcatus*	Rodents, humans	Europe, Russia, Asia	[10]
5.	Louping ill	Louping ill virus (Flaviviridae)	*Ixodes ricinus*	Sheep, red grouse, humans	Scotland, America	[11]
6.	Powassan disease	Powassan virus (Flaviviridae)	*Ixodes cookei*, *Ix. marxi*, *Ix.spinipalpusm*, *Ix.scapularis*, *Dermacentor andersoni*, *D. variabilis*	Humans, squirrel, mice	Eastern Russia, North America	[12]
7.	Colorado tick fever	Colorado tick fever virus(CTFV) Coltivirus	*Dermacentor andersoni*	Humans, elks, Marmots, deer Colorado, Idaho	Canada	[13]
8.	Alkhurma haemorrhagic fever	Alkhurma virus	*Ornithodorus savignyi*, *Hyalomma dromedary*	Camel, Sheep	Saudi Arabia, Egypt	[14]
9.	Heartland virus disease	Heartland virus	Lone star tick (*Amblyomma americanum*)	White tailed deer, Racon	U.S., Missouri and Tennessee	[15]
10	Bourbon virus disease	Bourbon virus (*Orthomyxoviridae*)	Lone star tick		Midwest and Southern united states	[16]

Kyasanur Forest Disease (Kfd)

Kyasanur Forest Disease (KFD) is a re-emerging zoonotic disease associated with sudden onset of high grade fever, prostration, nausea, vomiting, diarrhea and occasionally neurological and haemorrhagic manifestations. The virus was initially suspected as a Russian spring–summer (RSS) complex of viruses since isolates from monkeys and human showed relatedness to this virus. KFDV is classified in risk group 4 pathogens and causes endemic disease [17].

History

This disease was first discovered in 1957 from Kyasanur forest area, Shimoga district of Karnataka state in southern India, when an illness occurred in monkeys- Black faced langures (*Semnopithecus entellus*) and Red faced bonnet monkeys (*Macaca radiata*) and in humans [18]. It derives its name from the forest range where the virus was first isolated. It is also known as **"**monkey disease/monkey fever" because of its association with monkey deaths.

Global situation

As of now, KFD is only reported from India. The other viruses which are closely related to KFD are Omsk hemorrhagic fever virus in Siberia, Alkhurma virus in Saudi Arabia and Nanjianyin virus in China.

Indian scenario

Since 1957, the estimated incidence of KFD in India has been 400–500 cases per year [19]. Since 1957, after the discovery of KFDV many sporadic cases have been observed in the endemic state of Karnataka every year, mostly in five major districts Shimoga, Chikmagalur, Udupi, Uttar Kannada, and Dakshina Kannada [20]. Between 2003 and March 2012, there were 3263 reported human cases and of these 823 were laboratory confirmed and 28 deaths due to KFDV have been reported [21].

From 2012 to 2013 KFD outbreak was reported in the Bandipur Tiger Reserve in Chamarajanagar among the forest workers. During the same period, the virus was detected in ticks and monkeys in Nilgiri and Wayanad [22]. During 2016, KFD cases were reported from Dodamarg and Sindhudurg districts of Maharashtra and Dharbandora taluk of Goa [23]. The number of cases increased in 2017 from Dodamarg, Sawantwadi, Sindhudurg districts of Maharashtra and Valpoi, Pernem, Dharbandora taluk of Goa state.

Recently first case of suspected KFD in latest outbreak came to light on 24 november 2018 from Aralagodu, around 18 residents of the village are now suspected to have been

affected by the virus. This year 2018-19 about 3,548 fever cases were tested for KFD and of which 341 cases were positive.

Epidemiological determinants

Agent

The KFD virus (KFDV) is a member of the genus *Flavivirus* and family *Flaviviridae*. The KFD virus (KFDV) is immunologically close to Alkhurma virus. This RNA virus measuring about 25nm in diameter. The positive-sense RNA genome of the KFDV is about 11 kb in length and encodes a single poly protein that is cleaved post translationally into three structural (C, M and E) and seven nonstructural (NS1, NS2a, 3 NS2b, NS3, NS4a, NS4b and NS5) proteins.

Life cycle of KFD tick with seasonal incidence of KFD

The epidemic period usually begins in October or November and peaks from January to April, then declines by May and June. The epidemic/ outbreaks relates to the activity of nymphs, which is very high during November to May. Adult fed female ticks lay eggs which hatch to larvae under the leaves. The larvae further infest and feed on small mammals and monkeys, drop on the ground and change into nymphs. Nymphs feed on small mammals, birds, (as well as accidentally infesting humans), drop on the ground and mature in to adults. Adult ticks usually feed and mate on large animals such as cattle and monkeys.

Ecological Factors

The Western Ghats provide ideal topographical and climatological conditions for the vector ticks thus making these Ghats as epitome for this tick-borne disease.

Human gets exposed to ticks while visiting the forest for farming or grazing livestock animals, collecting dried leaves or dry woods, hunting or trekking, cashew nut farming and disposal of KFD-infected dead monkeys. Deforestation and encroachment of human dwellings towards forest areas are also responsible for increase in transmission and spread of KFDV in newer regions [24].

Natural host, Reservoirs and Vector

Ticks serve as vectors and main reservoirs of KFDV [25]. A number of forest dwelling small mammals like rodents, shrews, insectivorous bat and many birds maintain the natural enzootic cycle of the virus in the forest ecosystem. The wild primates, black faced langurs (*Semnopithecus entellus*) and red faced bonnet monkeys (*Macaca radiata)* get the virus infection by tick bite and are susceptible to the infection. Man is an incidental dead end host. Cattle are very important in maintaining tick population.

The hard ticks belonging to family *Ixodidae* of the genera *Haemaphysalis* are the reservoirs as well as vectors of the virus. The major vector ticks *Haemophysalis spinigera* and *H. turturis* found to inhabit the forest floors and vegetation and also infest various small mammals and birds.

Mode of Transmission

The transmission cycle involves mainly monkeys and ticks. The disease is transmitted by the bite of infective ticks especially nymphal stage.

Clinical symptoms

Animals

KFD in animals is always fatal with an acute onset. Mortality noticed during high viremic stage. Case fataity rate is 100% noticed in experimental infections. Neurological signs were noticed in 2nd febrile stage in bonnet macaque in experimental infection with KFD.

Humans

The incubation period of KFD is estimated to be about 2 to 7 days after tick bites or exposure [8]. The initial prodormal stage lasts for around one week with sudden onset of fever, headache, gastro intestinal disturbances, insomnia, sore throat, decreased blood pressure and heart rate, pain in muscles and extremities. Humans infected with KFDV have low platelet, white blood cells and red blood cells count. Ophthalmic manifestations of KFD are haemorrhages in conjunctiva, retina and vitreous humour, keratitis, opacity of lens and mild iritis [26].

The next haemorrhagic stage is characterised by irregular epistaxis with blood in vomitus and faeces, blisters on mouth, haemorrhages from the gum and nose. The haemorragic stage is followed by a long convalescent stage. The fever last for 2-12 days. Frequently a second febrile stage of around 2 weeks with same clinical manifestations of first phase along with various neurological complications was reported [27].

Vaccination

Since 1990, in all KFD endemic areas of Karnataka, the State government has initiated vaccination campaign using formalin-inactivated tissue-culture vaccine. Vaccination is usually carried out within a range of 5 km of the affected area. The schedule for vaccine is two doses at baseline and one month to all persons aged 7-65 yr and with a booster dose at 6-9 months. Vaccine efficacy was low with 62.4 per cent for first two doses and 82.9 per cent with booster dose after receiving the first two doses [19]. Hence, there is a need for booster doses annually for five years.

Crimean-Congo Haemorrhagic Fever (Cchf)

Crimean-Congo haemorrhagic fever (CCHF) is a viral haemorrhagic fever caused by *Nairovirus*. The disease is endemic in many regions such as Africa, Asia, Eastern and Southern Europe and Central Asia. The disease has a fatality rate of 3-10% and it affects 400-500 people annually.

Synonyms

CCHF is also referred to as Central Asian hemorrhagic fever, Congo fever, Congo virus disease, Crimean hemorrhagic fever, Hungribta (blood taking), Karakhalak (black death), Khunymuny (nose bleeding) and viral tick-borne hemorrhagic fever disease [28].

History

The virus may have evolved around 1500–1100 BC. In 1944, Soviet scientists first identified the disease they called Crimean hemorrhagic fever in Crimea and later in the Democratic Republic of the Congo in 1956. They established its viral etiology but were unable to isolate the agent at that time.

Etiology

CCHFV belongs to the genus *Nairovirus* and family *Bunyaviridae*. The circulation of CCHFV is dependent upon the distribution of ticks, mainly of the *Hyalomma* genus [29].

The virus is spherical in shape with a diameter of 80-100 nm, the lipid envelope is 5-7 nm thick and glycoprotein spikes are

8-10 nm in length. The genome consists of single-stranded RNA with negative polarity, divided into three segments: Small, medium and large segments. These three segments form a complex with nucleocapsid proteins to become a ribo-nucleocapsid. The virion contains three structural proteins: i) A nucleocapsid protein, ii) glycoproteins (Gn and Gc) and iii) a large polypeptide protein, which is a virion-associated RNA-dependent RNA polymerase with a size of 200 kDa [30]. The virus can be differentiated from other members in the *Bunyaviridae* family under electron microscopy [31].

There are 7 CCHFV genotypes: Asia-1, Asia-2, Euro-1, Euro-2, Africa-1, Africa-2, and Africa-3 recognized by the region in which they originated and still circulate. More than one genotype, however, can be found throughout multiple countries.

Host

A wide variety of domestic and wild vertebrates, including birds, may experience subclinical infection. Host preference of ticks carrying CCHF vary by life stage, with larvae and nymphs preferring small mammals and ground birds whereas adults may more likely be found on large mammals, such as livestock [32]. Other wild vertebrate hosts, such as hares and hedgehogs are considered amplifying hosts [33].

Reservoirs

Reservoirs of CCHF include various domestic and wild animals. Common examples include livestock (cattle, sheep, and goats), hares, hedgehogs and other small vertebrates [34]. CCHFV remains in livestock for up to a week.

Vectors

CCHF is a tick-borne disease. The major vectors are ticks of the genus *Hyalomma*. Other viable tick vectors include, but are not limited to: *Amblyomma, Rhipicephalus* and *Dermacentor* spp. [35].

Birds (excluding ostriches) are resistant to CCHF infection, they have the potential to serve as mechanical vectors. Migratory birds, along with ungulates and livestock, can carry attached ticks great distances into new, previously unpopulated areas [28].

Transmission to humans

CCHFV infection is most common in rural areas where exposure to ticks is high and people become infected when bitten by infected ticks. Physical contact with infected body fluids or blood can transmit the virus from person to person within 7-10 days of illness. This type of transmission is extremely common in butchers' shops [36].

The virus is transmitted within tick populations through, Trans-stadial transmission **(**larvae to nymphs to adults), Vertical transmission **(**adult females to their eggs), Venereal transmission **(**male ticks to female ticks during reproduction) and Non-viremic transmission infected to uninfected ticks feeding on the same host [37].

Environmental Persistence of CCHF

CCHFV can survive for a short time in the environment, especially in some organic material infectious virus was found for upto 10 days and occasionally longer in blood kept at 4^0 C (39^0F). Viral RNA was detected for as long as 30 days in serum at 4 ^{0}C. CCHF is susceptible to both heat and disinfectants.

Global distribution

CCHFV has been reported in over 30 countries covering Africa, South-Eastern Europe, the Middle East and Western Asia. India has always been considered at high risk for CCHF, owing to its borders with affected countries such as China and Pakistan. In the 1960, the virus was first isolated from ticks in Pakistan and first reported human case occurred in Rawalpindi in 1976 [38]. An outbreak with 19 cases and 12 deaths was reported from Takhar Province in the northern part of Afghanistan in March 1998. In Iran, CCHF was first isolated in 1978 and the disease re-emerged in 1999 with high case fatality. In China, CCHF was first isolated in 1965 from a human case and later, in 1984, from *H. asiaticum* ticks from the same region of Xinjiang province in north-western China, which is considered to be the most CCHF affected area in the country.

Indian scenario of CCHF

Until 2011, the existence of CCHF was not known in India, apart from some serological evidence recorded in the past. During December 2010, just prior to the CCHF outbreak blood samples were collected by NIV, Pune, to examine livestock from abattoirs in the northern adjoining state of Rajasthan and some more distant areas of Maharastra and West bengal [22]. The outbreak was followed by report of resurgence of CCHF in Amreli and Ahmedabad district of Gujarat [39]. The NIV, Pune reported the seroprevalence of CCHFV in domestic animals from Sirohi district of Rajasthan [22].

In 2013, a cluster of human cases were reported from Karyana, Surendra Nagar, Patan, Kutch and Amreli district of Gujarat [40]. In 2014, three death were recorded in Bayadtaluka and village Madhapur of Kuch district in Gujarat, three death in Jaiselmer and Jodhpur district of Rajasthan and one case reported from Himachal Pradesh.

Seoprevalence study of domestic animals of Gujarat showed that at least 15 districts are having prevalence of CCHF virus [22, 41] reported a clinical case of CCHF from Moradabad, Uttar Pradesh. In Jodhpur (Rajasthan), 2 male nurse died due to CCHF in 2015. In 2015, Gujarat again witnessed death due to CCHF in Ratadiya village of Mundra taluka of district Kutch.

Symptoms

Four stages are typically observed in CCHFV infected patients: incubation (non symptomatic phase), pre hemorrhagic, hemorrhagic, and convalescent (symptomatic phase). Incubation lasts 1-9 days depending on how an individual was exposed [42].

The disease starts with the pre-hemorrhagic period for 4-5 days. The major symptoms include headache, high fever, abdominal pain, myalgia, hypotension and flushed face [43].

The hemorrhagic phase, typically 2–3 days, consists of bleeding from the nose, gastrointestinal tract, uterus, and/or urinary tract. Neurological symptoms such as reduced alertness, agitation, mood swings and lack of clear thinking or ability to concentrate can develop [42]. When the disease is not treated, patients may succumb due to multiorgan failure.

The convalescent period begins in survivors after 10-20 days of illness [24]. Full recovery can take a complete year in survivors of CCHF. Survivors can expect recovery to start 10–20 days after the first onset of symptoms. Depending on hospitalization and treatment received, mortality rates can range from 5–80% [44].

Ganjam Virus/ Nairobi Sheep Disease

Nairobi sheep disease (NSD) was first observed as acute hemorrhagic gastroenteritis near Nairobi, Kenya in 1910. It was not until 1917 that the causative agent was identified as a virus that infected both sheep and goats. This highly pathogenic, tick-borne virus is a World Organization for Animal Health (OIE) 2013 Listed Disease.

Discovery of the virus

NSD takes its name from where it was originally isolated, Nairobi, Kenya in 1910. For the rest of the 20th Century, it was believed that NSD was endemic to East Africa only until it was shown that Ganjam virus of India and NSDV shared significant sequence homology [45].

GANV was first isolated from *Haemaphysalis intermedia* ticks collected from goats, suffering from lumbar paralysis from Orissa, India, during 1954-55 and named after the place of isolation. Subsequent studies have yielded several isolations mainly from *Haemaphysalis* ticks and a few from mosquitoes, sheep and man. Recently, for the first time, the virus was isolated from *Rhipicephalus hemaphysaloides* [46].

Etiology

Nairobi sheep disease is caused by Nairobi sheep disease virus (NSDV) in Africa or a variant called Ganjam virus in Asia. Despite the two names, NSDV and Ganjam virus are now considered to be the same virus, which belongs to the genus *Nairovirus* in the family *Bunyaviridae*. Currently, its officially accepted species name is Dugbe nairovirus. It shares this name with two viruses, Dugbe virus and Kupe virus, which have been isolated from livestock ticks but are not known to cause any illness in animals.

Virus characteristics

According to the International Committee on the Taxonomy of Viruses, NSDV/Ganjam virus has the following characteristics: Family: *Bunyaviridae*, Genus: *Nairovirus*, Genome: NSDV is an enveloped virus with a segmented, single-stranded, negative sense RNA genome. The three segments of the NSDV genome, the small (S), medium (M) and large (L) segments encode four different viral proteins: the viral nucleocapsid (N) protein, two glycoproteins (G1 and G2) and the viral RNA polymerase (L). Ganjam virus morphology closely mirrors that of NSDV.

Geographical Distribution

Global Scenario

Nairobi sheep disease is found in East and Central Africa. Serological evidence suggests that this virus may also be present in Botswana and Mozambique. Ganjam virus has been reported from parts of Asia including India and Sri Lanka. In 2013, viral RNA of NSDV/Ganjam virus was detected in ticks in northeastern China [47].

Indian scenario

Virus was first reported from *Haemaphysalis intermedia* ticks collected from goats, suffering from lumbar paralysis during 1954-55 from Orissa and named after the place of isolation. Now it has been prevalent in many states of India like Karnataka, Tamil Nadu, Andhra Pradesh, Punjab, Gujarat, Maharashtra, and Arunachal Pradesh and the virus was isolated from sheep, goats, cattle, ticks, mosquitoes and human [48].

Epidemiological determinants

Susceptible Species of domestic livestock

Only sheep and goats are susceptible to NSDV infection. There have been a few fatal cases among duikers (*Cephalophus monticola*) in zoos and in the wild and the African field rat (*Arvicathus abysinicus nubilans*) has been experimentally infected. Ganjam virus primarily infects goats, though serological surveys show that sheep are susceptible as well [49].

Reservoirs and Carriers

Ixodid ticks are able to maintain NSDV by passing it onto their offspring (trans-ovarial transmission) and maintaining it through life stage changes (trans-stadial transmission).

Environmental Factors

The enzootic areas for NSD are in the moist-forest-derived or natural grasslands and in the contagious moist bushed and wooded grasslands.

Temperature of 15-30^{0}C are optimal for the maturation of the various stages of tick species. A relative humidity of greater than 45% is necessary for maturation and development of the tick vector. However, animals may be infected experimentally with large doses of blood or serum. Experimental infections can also be established by injecting blood, serum or organ suspensions. NSDV survives for only short periods outside the body, its half-life (in 2% serum) is reported to be 1.5 hours at 37°C (99°F) and 7 days at 0°C (32°F).

Disinfection

The OIE does not provide specific guidance on the physical and chemical resistance of NSD but like other bunyaviruses, it is susceptible to hypochlorite, phenolics, 2% glutaraldehyde, and other disinfectants [49]. The Nairovirus Crimean-Congo Hemorrhagic Fever is destroyed by heating at 133° F (56° C) for 30 minutes.

Transmission

Both NSD and Ganjam virus are tick-borne viruses. In East Africa, the most important vector for NSDV is the *Rhipicephalus appendiculatus*. Other Ixodid ticks can serve as vectors: *R. pulchellus*, *R. simus* and *Amblyomma varigatum*. Transovarial transmission passing the virus to offspring has been demonstrated by *R. appendiculatus* and *R. pulchellus*. All tick hosts are able to maintain the virus from life stage to life stage (trans-stadial transmission). Though present in urine and feces, direct contact does not result in infection.

Clinical symptoms

In natural outbreaks, disease usually occurs 5–6 days after susceptible animals move to areas infested with *R. appendiculatus*. Clinical signs begin with a steep rise in body temperature [41°– 42°C (105.8°–107.6°F)] that persists for 1–7 days. Leukopenia and viremia usually coincide with the febrile phase. Diarrhea usually appears 1–3 days after the onset of fever and worsens as infection progresses. Illness is manifest by depression, anorexia, mucopurulent, blood-stained, nasal discharge, occasional conjunctivitis and fetid dysentery that causes painful straining. Pregnant animals frequently abort.

In peracute and acute cases, the time between the appearance of disease and death is usually 2–7 days but may be as long as 11 days in less acute cases.. The clinical signs in goats are similar to those in sheep but less severe, although 80%

mortality has been reported. The presence of colostral immunity not only protects lambs and kids from early exposure to infection but also allows development of active immunity, enabling survival in tick-infested areas.

Vaccination
Two types of experimental vaccines have been developed a modified-live virus vaccine attenuated in mouse brain and an inactivated oil adjuvant vaccine. A single dose of the modified-live vaccine produces rapid immunity however revaccination is necessary to maintain full protection. Two doses of the inactivated vaccine are required to elicit good protection.

Economic significance
Sheep are an important part of global agricultural economy. Small ruminants are reared mainy for four functions, namely meat, milk, skin and wool according to order of importance. Nairobi sheep disease can cause death of the animal, increase cost of preventive programme, threat of spread to new geographical area and protein deficiency. The presence of disease can limit trade and export, import of new breed, loss of animal protein for human consumption and affect people livelihood [50].

Tick Borne Encephelitis (TBE)
Tick-borne encephalitis or TBE is a human viral infectious disease involving the central nervous system in eastern, central and northern European countries and in northern china, Mongolia and the Russian federation.

Global distribution
In 2017, 3079 cases of tick-borne encephalitis (TBE) were reported in EU/EEA countries 2,550 (83%) of which were confirmed. The notification rate in 2017 was 0.5 cases per 100,000 population. The age and gender distribution shows a predominance of cases in 45–64 year-olds and in males. Tick-borne encephalitis shows a seasonal pattern and in 2017, 78% of cases occurred from May–November, while 42% of cases occurred from June-August [51].

Etiology
TBE is caused by the tickborne encephalitis virus (TBEV) a member of the family *Flaviviridae* and was initially isolated in 1937. Three virus sub-types are described: European or Western tick-borne encephalitis virus, Siberian tick-borne encephalitis virus, and Far eastern Tick-borne encephalitis virus (formerly known as Russian Spring Summer encephalitis virus, RSSEV).
TBEV is Enveloped, polyhedral nucleocapsid symmetry, spherical particles, 40-60 nm in diameter, nucleic acid linear, positive-sense, single-stranded RNA, 11.0 kb in length.

Epidemiology
The virus has 3 subtypes, which are closely related:

European virus - transmitted by *Ixodes ricinus* ticks and endemic in rural and forested areas of central, eastern and northern Europe. The European subtype is associated with milder disease than the other subtypes.

Far-Eastern virus - transmitted mainly by *Ixodes persulcatus* and endemic in far-eastern Russia and in forested regions of China and Japan.

Siberian virus - transmitted by *I. persulcatus* and endemic in Urals region, Siberia and far eastern Russia and some areas in north-eastern Europe. *Ixodes ricinus* is the most abundant and widely distributed tick species in the UK and is also the vector for Lyme disease.

Reservoir hosts of TBEV are mainly small rodents (voles, mice) and insectivores (shrews). Other animals support virus circulation indirectly by enabling tick multiplication. These include wild and domestic mammals (especially hares, deer, wild boar, sheep, cattle and goats).

Transmission
The virus can chronically infect ticks and is transmitted both tran-stadially (from larva to nymph to adult ticks) and trans-ovarially (from adult female tick to eggs). Infection also may follow consumption of raw milk from infected goats, sheep, or cows. Laboratory infections were common before the use of vaccines and availability of biosafety precautions to prevent exposure to infectious aerosols. Person-to-person transmission has not been reported with the exception of vertical transmission, from an infected mother to foetus.

Clinical Symptoms
The incubation period of TBE is usually between 7 and 14 days and is asymptomatic. Shorter incubation times have been reported after milk-borne exposure. In contrast to Far-eastern TBE, European TBE is more severe in adults than in children where meningitis is more frequently observed. In approximately two-thirds of patients infected with the European TBE virus, only an early (viremic) phase is experienced, symptoms are nonspecific and may include fever, malaise, anorexia, muscle aches, headache, nausea and or vomiting. After about 8 days of remission, a second phase of disease occurs in 20% to 30% of patients. These patients may experience a clinical illness that involves the central nervous system with symptoms of meningitis (e.g. fever, headache, and a stiff neck), encephalitis (e.g. drowsiness, confusion, sensory disturbances and/or motor abnormalities such as paralysis) or meningo encephalitis.
The convalescent or recovery period can be long and the incidence of sequelae may vary between 30% and 60%, with long-term or even permanent neurologic symptoms.

Public health significance
According to WHO approx 10,000-12,000 Clinical cases of TBE are reported each year.

Vaccination
A vaccine is available in some disease endemic areas (though not currently in the United States). Immunization offers the most effective protection, currently there are 4 widely used vaccines of assured quality.

1. FSME- Immun and Encpur, manufactured in Austria and germany respectively and based on European strain of the virus.
2. TBE- Moscow and Encevir, manufactured in the Russian federation and based on far eastern strain.

The 4 vaccines are considered to be safe and efficacious.

Diagnosis of Tick borne viral diseases
Sample collection and transportation
Collection of serum from suspected patients: Collect 4-5

ml blood in a plain vial. Separate the serum following standard biosafety precaution.

Collection of Monkey viscera: Collect Brain, Lungs, Heart, Liver and Kidney specimens from the dead monkey following standard biosafety precaution.

Tick collection: Collect nymph tick and keep in a sterilised polypropylene container. The tubes should be air tight and sealed in plastic bags so that vial should not open during transportation and infected ticks spread in newer areas.

Sample Storage: Keep serum of human cases/ viscera of monkeys/ tick samples refrigerated (2-8^{0}C) if it is to be processed (or sent to a reference laboratory) within 48 hours. Keep frozen (-10 to -20^{0}C), if it is to be processed after a week. The sample can be preserved for extended periods.

Transportation of the sample to the reference laboratory: Always use triple layer packaging and ship within 48 hours of collection under cold chain (dry ice or at least with cooling gels). The original samples should be packed, labeled and marked. Always include the completely filled out clinical and epidemiological record.

The designated laboratory for diagnosis and isolation of viruses in humans, monkey necropsy samples and ticks is:

1. National Institute of Virology, Pune, India

Also designated laboratories for diagnosis of KFDV in human samples are as follows:

1. Virus Diagnostic Laboratory, Shimoga, Karnataka State
2. Manipal Academy of Higher Education (Deemed to be University), Manipal, Karnataka State, India. The samples for diagnosis of the disease in suspected human cases can be sent to above-mentioned designated laboratories.

Hospital laboratory testing: The following tests should be performed on blood samples from enrolled patients, according to standard hospital procedures complete blood count (CBC), total leukocytic count (TLC)/differential leukocytic count (DLC), haemoglobin level, and platelet counts, liver function tests (aspartate aminotransferase (AST)/ alanine aminotransferase (ALT), serum bilirubin, alkaline phosphatase), serum electrolytes, blood urea, serum creatinine, smear for malaria parasite or malaria rapid diagnostic test.

Virus isolation: Virus can be isolated by inoculation into infant mice or in cell culture (Vero E6, BHK-21 or Chick embryo cells). Virus isolation should be carried out in BSL-3 and BSL-4 laboratory [42].

Enzyme-linked immunosorbent assay (ELISA): KFD IgM antibody can be detected from 5th day of onset of symptoms till 3 months.

Real-time PCR and RT-PCR: Real-time RT-PCR can detect the virus in samples after onset of febrile illness up to the 8th day. Real-time PCR, RT-PCR can be performed from blood/serum of humans, blood and viscera of infected monkeys, or tissues of ticks. The RT–PCR reactions are highly specific and sensitive compared to other conventional methods [53].

Prevention and Control

Quarantine animals before they enter slaughterhouses or routinely treat ruminants with acaricides 4 weeks prior to slaughter. This activity will decrease the risk of the animal being viraemic during slaughter. Wear mask, gloves and gowns when slaughtering and butchering animals in slaughterhouses or at home to prevent skin contact with infected animal tissue or blood [54].

Dead body disposal: Disinfected after use. Thus, control measures should be mainly focused on tick control in outbreak areas and on personal protective measures for persons caring for CCHF patients [55].

Tick control

Safely remove ticks: Use fine-tipped tweezers (or a thread), grab the tick as close as possible to the skin, do not twist or jerk the tick, Gently pull straight up until all parts of the ticks are removed, Wash hands with soap and water. Apply antiseptic on tick bite or clean with soap and water. Never crush a tick with your fingers.

Source reduction: The spraying of insecticide like malathion may be carried out in areas where monkey deaths have been reported within a radius of 50 meters around the spot of the monkey death. It is also effective in forest tracks frequently visited by people for various activities.

Vector control: Vector control may be done by dusting with malathion or by spraying with pyrethroids. Repellents may be used on body/exposed parts during venture into forests. Application of insecticide on cattle can prevent transportation of ticks from forests to dwelling premises.

Personal protection

Application of repellants such as Di methyl phthalate (DMP), N,N-Diethyl meta Toluamide (DEET) and certain other proprietary preparations having these or similar chemicals, e.g. Mylol on the exposed parts is effective from one to a few hours. People living in the forest or visiting forest areas should strictly use tick repellents along with personal protection measures (long clothes by covering neck, chest, back, and legs) before going to the forest.

In the family/community setting: Family members and friends who had direct contact with the patient should be monitored for 14 days, for onset of a febrile illness [56].

Reducing human-to-human transmission: Avoid contact with infected CCHF patients and diseased, Wash hands regularly with soap and water, encourage early treatment in CCHF Treatment Center, use gloves and mask and practice hand-hygiene when caring for suspected CCHF patient at home. Seek health advice.

Information, Education and Communication (IEC)

The IEC can be done by as follows, approaching vaccination campaign in mission mode just like Pulse polio, conducting regular annual sensitization program for Veterinary department, Forest department officials, Accredited Social Health Activist (ASHA), Education department and Gram Panchayath officials, ASHA incentives for assistance during vaccination especially for mobilizing and encouraging public to take vaccine, Pre-vaccination IEC campaigns, Intense and

focused IEC campaign involving all possible media.

Conclusion

The risk of Tick borne disease is increasing worldwide and this situation seems to be driven by several interacting factors. Wildlife populations can naturally migrate, bringing ticks and tick borne pathogens from one area to another. Human travelers may also play a role in the translocation of wildlife species and in the introduction of exotic tick species into previously free areas, which may eventually carry relevant pathogens.

Education is key to controlling TBDs and beyond a shadow of doubt, public health decision makers, researcher, physician, veterinarians, farmers, travelers etc. should be aware of TBDs and how they should be deal with.

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