Review

Tick-Borne Encephalitis Virus (TBEV): Epidemiology, Diagnosis, Therapeutic Approaches and Some Molecular Aspects - an Updated Review

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Review

Tick-Borne Encephalitis Virus (TBEV): Epidemiology, Diagnosis, Therapeutic Approaches and Some Molecular Aspects—An Updated Review

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Abstract: Tick-borne Encephalitis Virus (TBEV) is a significant public health concern, particularly in rural regions, like the Caucasus, where tick-borne diseases are prevalent. The review contains the comprehensive data on TBEV circulation in the Caucasus region, demonstrating the TBE cases in the North Caucasus and Georgia and identification of new endemic foci in Armenia and Azerbaijan., indicating the need for futher epidemiological studies and surveillance in the Caucasus region. This review provides an updated overview of TBEV, encompassing its status, subtypes, life cycle and circulation in nature, epidemiology, new approaches to TBE treatment and diagnostics, and recent insights into molecular aspects. Understanding the complexities of TBEV transmission, clinical manifestations, and advancements in diagnostic techniques is crucial for effective management and control strategies. Furthermore, exploring the molecular mechanisms underlying TBEV pathogenesis and host interactions can offer valuable insights for developing novel therapeutics and preventive measures. This comprehensive review aims to consolidate recent research findings and enhance our understanding of TBEV, ultimately contributing to improved public health interventions and patient outcomes.

Keywords: encephalitis virus; tick-born encephalitis; molecular aspects; therapies

1. Introduction

Tick-borne encephalitis virus (TBEV) is a critical pathogen of public health concern, known for causing severe neurological diseases across a wide geographical range, with the primary vector being ***Ixodes*** spp. ticks, and it is also referred to as ***Orthoflavivirus encephalitidis*** (family ***Flaviviridae)*** [1,2]. TBEV foci have been found in Japan, South Korea, northern China, Europe, Siberia, and far-eastern Russia and the Caucasus. For a long time, three subtypes of TBEV were identified based on phenotypical features: the European (TBEV-Eu), Siberian (TBEV-Sib), and Far-Eastern (TBEV-FE) [3]. Recent phylogenetic studies have identified two further subtypes: Himalayan (TBEV-Him) and Baikalian (TBEV-Bkl) [1]. The Himalayan and Baikalian subtypes are geographically restricted and were shown to be associated with severe disease [4]. The Siberian subtype was the most common, found in all TBEV foci except Central and Western Europe [4]. The seven TBEV subtypes—TBEV-Eu, TBEV-Sib, TBEV-FE, TBEV-2871 (TBEV-Ob), TBEV-Him, TBEV-178-79 (TBEV-Bkl-1), and TBEV-886-84 (TBEV-Bkl-2) were identified as a result of the genetic distance-based classification [5]. The recombinant nature of the TBEV-Bkl-2 subtype isolated near Lake Baikal in Russia, originating from recombination between the Siberian and Far-Eastern subtypes was demonstrated [6]. The high pathogenetic potential of TBEV-Bkl-2 was confirmed by laboratory tests and its ability to cause lethal

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focal forms of encephalitis [7]. TBEV-Him was detected in a wild rodent, *Marmota himalayana*, at the Qinghai–Tibet Plateau in China [8]. The evolutionary analysis demonstrated that TBEV-Him diverged from TBEV-FE subtypes about 2469 years ago [8]. Subclinical infections, biphasic fever [3], and tick-borne encephalitis (TBE), an acute viral infection of the central nervous system, which can cause severe neurological symptoms such as meningitis or meningoencephalitis [9] are caused by TBEV. Up to 12,000 TBE cases with mortality rates ranging from 0.2% to 20% are recorded each year in countries where the disease has been documented [10]. The Far-Eastern subtype is considered the most pathogenic, with the highest mortality rate [7].

Even though TBE can be prevented through vaccination, the incidence rate has been rising over the past few decades, and since the travel and tourism sector has grown, TBE is now a concern outside of endemic areas. [11]. Given the broad geographical distribution and the diverse subtypes of TBEV, understanding regional variations in the virus's epidemiology and clinical manifestations is critical. The emergence of new subtypes, such as TBEV-Him and TBEV-Bkl, underscores the need for continuous surveillance and research to anticipate potential outbreaks and to understand their unique pathogenic mechanisms. Moreover, the rising incidence of TBEV in non-endemic areas, driven by increased global travel and climate change, further highlights the urgency of improving public health strategies. There is also a pressing need to refine diagnostic tools and therapeutic approaches, as the complexity of TBEV infection presents challenges in early detection and effective treatment. There are several areas of uncertainty regarding TBEV. Thus, the TBEV assembling and maturation, as well as the minimum infective dose for the infection via different routes should be explored. Clarifying the clinical picture of TBE caused by different subtypes of the virus is also required. Therefore, this review aims to provide a comprehensive synthesis of the latest research, addressing both established knowledge and emerging issues in the study of TBEV. The review covers: TBEV subtypes (Introduction), TBEV structure (chapter 2), TBEV life cycle (chapter 3), TBEV transmission and circulation (chapter 4), geographical distribution of TBE subtypes and TBE prevalence in different countries (chapter 5), pathogenesis of TBEV (chapter 6), clinical presentation of TBEV (chapter 7), various aspects of TBEV diagnostics (chapter 8) . In the last part of the review prevention and treatment of TBE, including antiviral compounds, are discussed (chapter 9).

2. TBEV Structure

TBEV is an 11 kilobase-long single-stranded, positive-sense RNA virus [12]. During the TBEV maturation, the infected cells produce at least three types of viral particles: immature non-infectious, partially mature, and mature infectious particles [13]. The chemical composition of viral particles includes 6% ribonucleic acids (RNA), 66% proteins, 17% lipids derived from host cell membranes, and 9% carbohydrates [14]. The mature TBEV virion is spherical and is approximately 50 nm in diameter, similar to other Flaviviruses [15,16]. The TBEV consists of the nucleocapsid (NC) formed by a single RNA copy and multiple copies of the capsid (C) protein (11 kDa), surrounded by the membrane. The membrane is composed of host-derived lipids with embedded small membrane (M) glycoprotein (8 kDa) and large envelope (E) glycoprotein (54 kDa) [17,18] (Figure 1A, B). The E, M, and C proteins are the structural proteins of the virion. The C protein possesses strong basic properties and forms dimers serving as building blocks of the capsid, it is also involved in RNA packaging [14,19]. Recent studies demonstrated that protein C accumulates in the nuclei and nucleoli of infected cells and it can induce translational shutoff and decrease of 18S rRNA [19]. The E and M proteins coat the lipid bilayer, determining the overall morphology of the viral membrane [20]. The E-M-M-E heterotetramer formed by head-to-tail dimerization of two E-M heterodimers represents the main building block of the virion [13]. The glycosylated E protein is fundamental in the entry of TBEV into the cell [12], it is a major antigenic determinant of the virus which triggers immune responses in infected mammalian hosts [3]. The M protein was proposed to act as a 'cement' protein, strengthening the interaction of the E proteins and preventing fusogenic conformation of the E protein before the virus encounters the endosome [12]. The viral RNA genome has one large open reading frame, translated into one polyprotein [21], cleaved by cellular and viral proteases into 3 structural and 7 non-structural (NS) proteins [3]. Non-structural proteins NS1, NS2A, NS2B, NS3,

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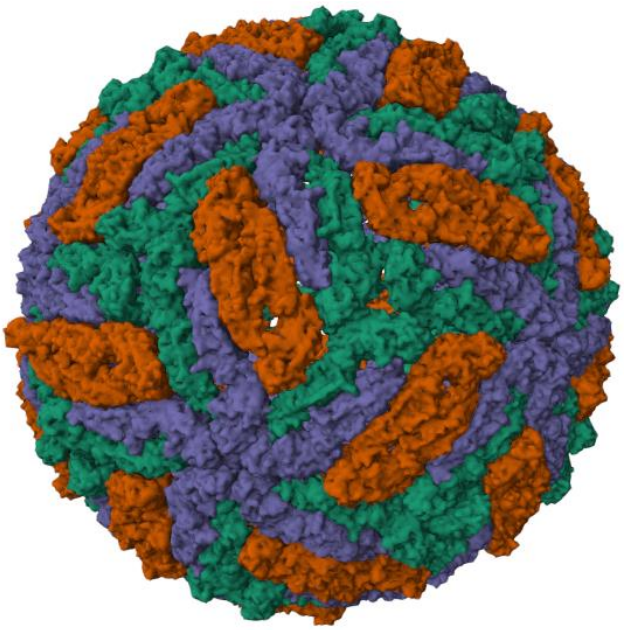
NS4A, NS4B, and NS5 are involved in the assembly and functioning of the virus replication complex [22,23]. Similar to Hepatitis C, the NS2-NS3 proteins exhibit protease and helicase activity, and NS4 and NS5 are involved in the downregulation of the cellular antiviral response [1]. Only NS1 is secreted into the extracellular space among the NS proteins and it is the second most important viral immunogen after the E protein [3].

The immature viral particles contain the precursor M protein (prM) instead of the structural M protein. The prM protein is proteolytically cleaved in the Golgi complex by the host protease furin leading to a conversion from immature to mature fully infectious viral particles [24]. This process results in the release of pr fragment and protein M [25]. Recently, it was demonstrated that prM cleavage, the collapse of E protein ectodomains onto the virion surface, movement of the E and M membrane domains and the release of the pr fragment render the virus maturation and provide an explanation of why the maturation of TBEV is irreversible [26].



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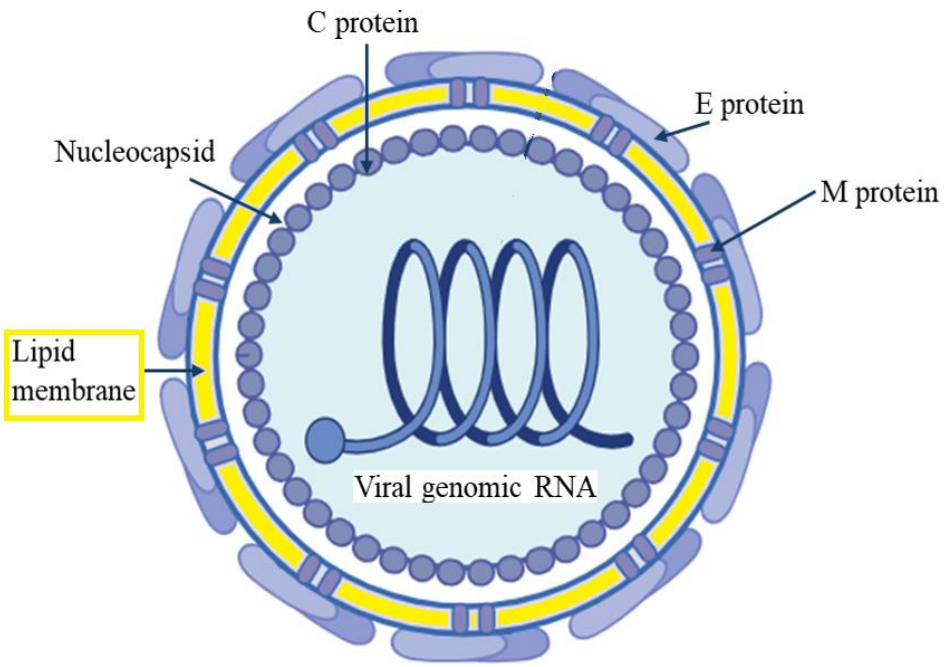

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Figure 1. 3D molecular (A) and schematic (B) structure of the Tick-Borne Encephalitis Virus (TBEV) virion. The nucleocapsid formed by a single RNA copy and multiple copies of the capsid (C) protein is surrounded by a lipid membrane (yellow). In this membrane, (M) and envelope (E) proteins are embedded. The structure 1A corresponding to the inactivated mature tick-borne encephalitis virus is freely available online at the link (https://www.rcsb.org/3d-view/8R8L/1; [27] accessed on 3d September 2024) and uses Mol* [28]; while 1B was produced by the authors using the BioRender platform (**https://www.biorender.com/**) (basic license terms).

In summary, the structure and maturation of TBEV involve a complex interplay of viral and host-derived components, with the mature virion featuring a spherical shape and a lipid membrane embedded with the E and M glycoproteins, and the transition from immature to mature particles being driven by precise proteolytic cleavage and structural rearrangements. It should be noted, that in comparison with mosquito-borne flaviviruses, the data on the maturation steps of TBEV are limited and the process of maturation has mainly been studied in mammalian cells, but limited evidence shows there may be differences between the mammalian and tick systems [12].

3. The Life Cycle of the Virus

Similarly, the TBEV life cycle was mostly studied in mammalian cells, even though the tick is a central part of the biology of the virus [12]. The virus's life cycle starts with the binding of the virion to the host cell's surface (Figure 2). Interestingly, despite the ability of TBEV to infect multiple cell types, the virus is characterized by significant neuronal tropism, the comparison of neuronal and epithelial cells revealed that neuronal cells exhibit 10,000-fold higher TBEV replication [2]. It is agreed that receptor-mediated endocytosis is the main mechanism of TBEV entry into the cell [29] but the entry via micropinocytosis was also proposed [30]. Laminin-binding protein (LBP) and the $\alpha V\beta 3$ integrin were proposed as two major receptor candidates for TBEV in mammalian cells, but receptors in tick cells have not been elucidated yet [31]. It is known, that the TBEV also utilizes the attachment factor, glycosaminoglycan heparan sulphate, present on the membranes of various vertebrate and tick cells [32,33] and the viral envelope E protein mediates the binding. It was demonstrated that the invasiveness of TBEV in the nervous system depends on the glycosylation of the E protein [34,35] and it was further supported by the finding that in Louping ill virus, closely related to TEBV, a mutation in the glycosylation site reduced neurovirulence [36]. As the result of endocytosis or pinocytosis virions are transported into prelysosomal endocytic vesicles of the host cell with acidic pH [12]. The acidic pH triggers conformational changes in viral envelope protein E [37], leading to the formation of trimmers of E proteins, which provide the fusion of the viral membrane with the membrane of the endocytic vesicle [38]. The result of the fusion is the viral nucleocapsid release in the host cell's cytosol, uncoating of RNA, and protein translation, followed by replication. RNA replication involves the production of full-length negative strand copies serving as the templates for the synthesis of positive-strand RNA [29]. The virus replication occurs in close contact with the endoplasmic reticulum (ER) membrane, rearranged by NS1, NS2B, NS4A, and NS4B proteins [39,40]. The rearrangement of the membrane was revealed in both tick and mammalian cells [12]. The package of RNA into nucleocapsid by protein C occurs on the cytoplasmic side of the ER membrane. The package is coordinated with the assembly of a viral envelope, consisting of prM and E proteins translocated into the lumen of the ER. This process yields immature virions, containing heterodimers of prM and E [24]. Then, the cleavage of prM by host protease takes place in the cisternae of the trans-Golgi network, yielding mature virions [41]. Mature virions are transported in vesicles to the plasma membrane and released by exocytosis, together with partially mature and immature particles [42]. However, immature particles are non-infectious since they are incapable of fusion, and, therefore, only the mature and partially mature particles can start a new infection cycle [12].

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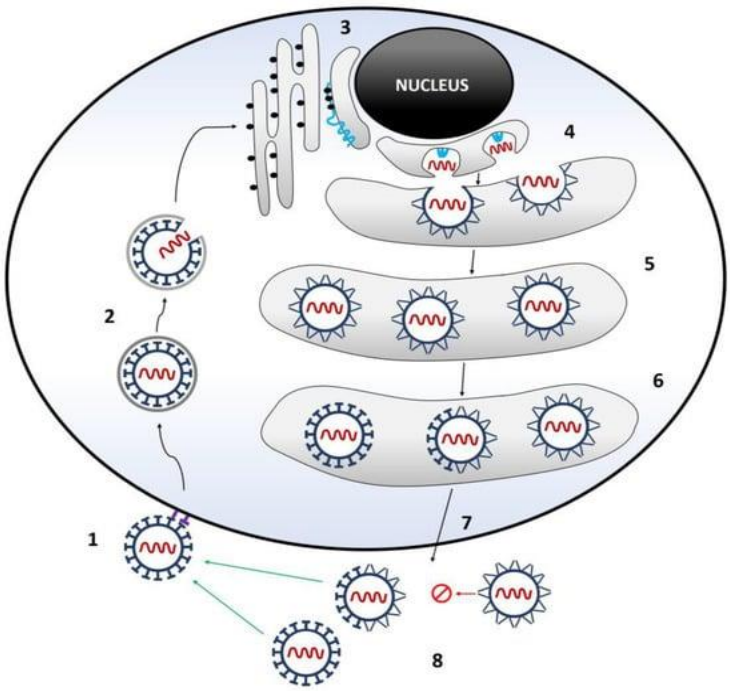

Figure 2. Overview of the TBEV life cycle. This figure has been adapted from the work of Pustijanac et al. [43].

The virus attachment to the receptor and entrance inside the cell via endocytosis (1).

The acidic pH triggers the fusion of the viral membrane with the membrane of the endocytic vesicle, leading to the uncoating of the virus (2).

The ribosomes of the rough ER start to synthesize viral proteins (3).

The TBEV replication in invaginations in the ER and the package of RNA into nucleocapsid by protein C on the cytoplasmic side of the ER (4).

The package is coordinated by assembling a viral envelope, consisting of precursor M protein (prM) and E proteins translocated into the lumen of the ER (5).

The formation of mature virions via cleavage of prM by host protease in the cisternae of the trans-Golgi network (6).

Mature virions are released by exocytosis, together with partially mature and immature particles (7).

The immature particles are non-infectious since they are incapable of fusion (8).

4. TBEV Transmission and Circulation

4.1. TBEV Circulation in Nature

According to Pavlovsky's theory, TBEV is the focal pathogen, e.g., the virus is associated with specific landscapes, which is called the natural focus of infectious disease. [44]. Further development of this theory determined natural foci as any natural ecosystem where the pathogen population is an essential component. [45,46] and the natural focus consists of three main elements: vector, vertebrate host, and susceptible recipients (humans or animals). The vector of TBEV is the tick, which acquires the virus during feeding on TBEV-infected vertebrate host [47], or via several possible routes of transmission between ticks [48]. In Europe, the most important tick vector is *Ixodes ricinus*, whereas in Russia and Asia it is *Ixodes persulcatus* [49]. The *Haemaphysalis concinna* is one of the major vectors for the transmission of TBEV in Asia [50]. In addition to main vectors, another 22 tick species of genera *Dermacentor, Hyalomma*, and *Rhipicephalus* can transmit the virus [49,51,52]. The main vectors for TBEV-Eu are *Ixodes ricinus* ticks [11], the most common tick species in Europe, which in addition to TBEV can transmit *Borrelia burgdorferi* sensu lato (causative agent of Lyme borreliosis), *Anaplasma phagocytophilum* (causative agent of human anaplasmosis), and *Borrelia miyamotoi*, causative agent of

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hard tick relapsing fever [53]. The main vector for TBEV-Sib and TBEV-FE, is *Ixodes persulcatus* [11], which was shown to be the dominant species in Siberia, forming about 95% of the tick population [54] and high activity of this species was also demonstrated in Mongolia [51].

TBEV can be transmitted to other animals or humans during subsequent feeding [48]. The life cycle of ticks consists of four stages: the egg, the larva, the nymph, and the adult tick. The TBEV is maintained in the tick population via vertical transmission (Figure 3), which includes transovarial transmission from infected fertilized female to egg and transstadial transmission from one developmental stage to another, as well as transmission between male and female ticks [55]. Since the life span of ticks usually takes 4–6 years, the transstadial transmission contributes to retaining the virus in the same place, since TBEV chronically infects ticks for the duration of their life [56–58]. Another possible way is TBEV transmission between infected and uninfected ticks is co-feeding on the same animal, where the vertebrate host serves as a bridge for the transmission [48]. Tick can acquire virus also via horizontal transmission when an uninfected tick feeds on an infected vertebrate host [59]. Such hosts are small rodents, insectivores, large mammals, birds [18] and lizards in the Caucasus region [60]. There is a consensus that each tick stage has a certain range of targeted animals, nymphs and larvae stick to small and medium-sized animals and birds, while adult ticks target large animals [18]. The necessary precondition for TBEV transmission is a level of viremia that is equal to or higher than the threshold required for infection, which occurs in such mammals as sheep, goats, horses, dogs, and rodents [18]. In voles, collected from 2 sites in Finland, the persistence of TBEV during two subsequent winters, contributing to virus overwintering was demonstrated [61]. Experimentally infected voles developed a persistent TBE infection [62].

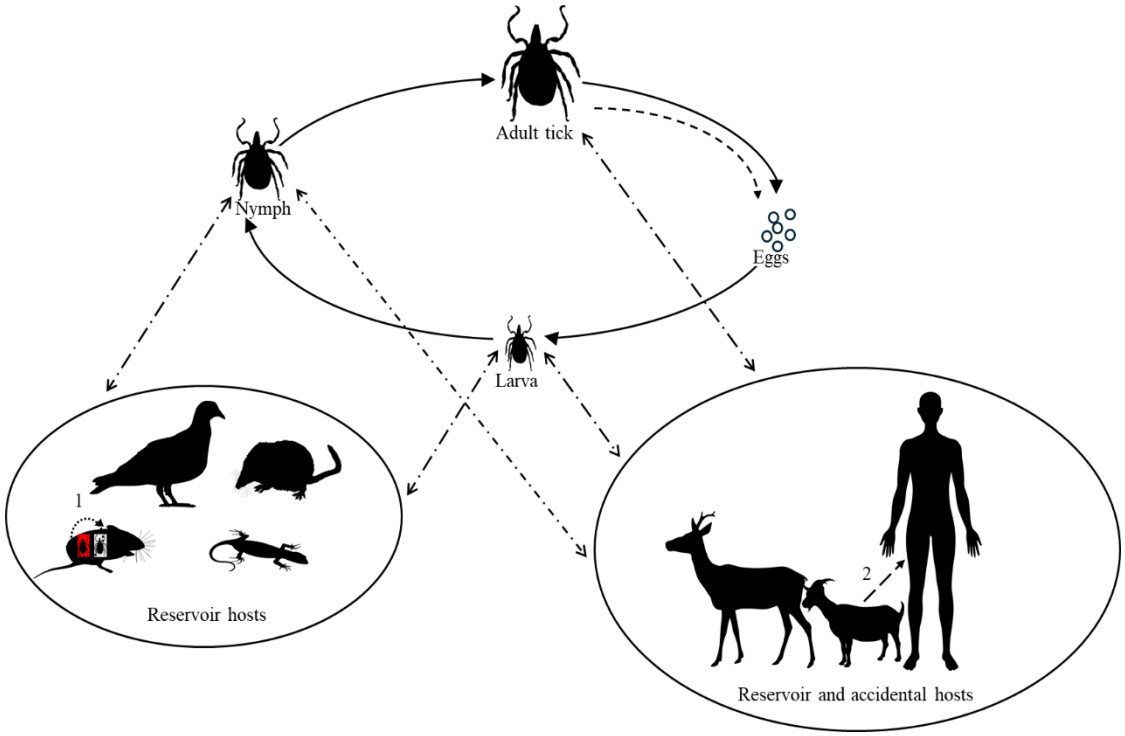

Figure 3. Pathways of TBEV transmission within the life cycle of ixodid ticks. The host groups for different developmental stages of ticks are shown in ovals. ——→ Vertical transstadial transmission occurs between tick developmental stages. – – → Vertical transovarial transmission occurs via eggs of infected female ticks. – · – → Horizontal transmission occurs when uninfected ticks feed on infected vertebrate hosts. 1—Co-feeding, transmission occurs when infected and uninfected ticks feed simultaneously on an animal host. 2—Foodborne transmission of TBEV occurs via unpasteurized dairy products.

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The presence of antibodies against TBEV was revealed in several rodent species caught in various countries: *Myodes glareolus, Apodemus flavicollis, Apodemus sylvaticus* and *Apodemus agrarius* from Slovenia [63] and Switzerland [64], *Apodemus agra*rius from Slovenia [63], in *Clethrionomys glareolus* from the Czech Republic [65]. TBEV RNA was identified in *Apodemus agrarius, Apodemus flavicollis, Microtus arvalis*, and *Myodes glareolus* collected in Hungary [66]. In South-Western Siberia *Myodes rutilus, Sicista betulina*, and *Sorex araneus* were identified as the most important reservoir hosts of TBEV [67]. Two TBEV strains were isolated from *Apodemus speciosus* and *Clethrionomys rufocanus* from Japan [68]. Larger animals, mainly wild cervids, like deer *Capreolus ca*preolus are important hosts, providing blood meal for adult ticks [69], however, these mammals develop only a short period of viremia with low viral concentrations or no detectable viremia [43] and therefore are not capable of efficient transmission of the virus [62]. Birds also contribute to the spread of the virus [38,39] to new endemic areas [49,70]. Thus, the involvement of migrating birds in the transmission of TBEV in the United Kingdom [71] and Finland [72] was demonstrated. Also, the role of migratory birds in the TBEV transmission from Far East Russia to Japan via the East Asian-Australian flyway was demonstrated [73].

4.2. TBEV Transmission to Human

Humans become infected via a tick bite (mostly nymphs) and alimentary by the consumption of raw milk products from TBEV-infected ruminants [74]. According to Pavlovsky's theory, humans are susceptible recipients or, according to modern theory, they are accidental hosts of TBEV, since they do not develop high viremia [75], allowing virus transmission to tick and thus do not participate in the circulation of the virus in nature. Therefore, humans are considered the dead end of the TBEV cycle [76]. TBEV is mainly transmitted to humans via bites of infected hard ticks. The tick attaches to the hair-covered portion of the head, to the arm and knee bends, hand, feet, and ears in the dense vegetation of forests and TBEV is transmitted by saliva during the first minutes of feeding [76]. The TBE cases correlate with the activity of ticks, driven by temperature and depending on geographical location. Thus, the two peaks of *I. ricinus* activity are usually revealed: the spring peak in June and the much lower autumn peak in September [77]. Accordingly, the analysis of TBE cases and tick *I. ricinus* abundance showed a similar bimodal distribution [78]. Interestingly, the study of TBEV prevalence in *I. ricinus* revealed higher prevalence in questing nymphs in autumn than in spring [79]. The *I. persulcatus* has only one abundance peak from the end of April to the beginning of June [80]. The ratio of TBE cases to *I. persulcatus* questing nymphs was highest in the summer-autumn period, which was explained by the effect of temperature on the rate of virus replication in the ticks [78].

In addition to the main vectorial transmission by different tick species, several non-vectorial transmission routes were described. Thus, the transmission of TBEV could occur as the result of consumption of unpasteurized milk from infected goats, sheep, and rarely from cows [81]. Single cases of TBEV transmission due to handling infected material [82], by transplantation of solid organs [83] and during blood transfusions were reported [84]. The probable transmission of TBEV from mother to baby via breast milk was also described [85]. Despite the several reported cases, the risk of TBEV infection via substances of human origin remains uncertain, including the infectious dose and viremia level in asymptomatic individuals. Also, the amount of virus uptake necessary for the infection via different routes (e.g., tick bites, alimentary route and blood transfusion) is unknown [86].Taking into account available data it would be advisable for organ donors from endemic regions, discussed in the next section, to be screened for TBEV [83].

5. Geographical Distribution of TBE Subtypes and TBE Prevalence in Different Countries

Globally, TBE is endemic in Eurasia, mainly in Southern Central and Northern Europe [87] in Russia, Eastern and Central Asia [88]. Data on the burden of TBE in different countries and the geographical distribution of viral subtypes are presented in Table 1. In Europe, out of EU/EEA countries, twenty reported 3 650 TBE cases in 2022, of which 3 516 (96.3%) were confirmed (Table 1). For 2022 the following EU countries reported zero cases: Bulgaria, Iceland, Ireland, Liechtenstein, Luxembourg, Malta, and Spain and no data were available for Cyprus and Romania [89]. The TBEV

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cases were also not revealed in Albania, Kosovo, Macedonia, and Montenegro [10] (countries with zero cases were not included in Table 1). In Europe, the highest number of confirmed cases for 2022 was reported for Czechia (n=709), Germany (n=554), and Sweden (n = 465, Table 1). The number of confirmed cases for 2022 was also high in Lithuania (n = 377) and Poland (n = 446, Table 1).

Another indicator used to assess TBE prevalence is TBE incidence per 100,000 population. Based on this index countries with a high incidence (> 5/100,000 inhabitants), countries with an intermediate incidence (1–5/100,000) and countries with a low incidence (< 1/100,000) are distinguished [90]. Similarly to the number of confirmed cases, this indicator does not reflect the situation in regions of individual countries. Thus, according to this system, Germany is a low-incidence country (incidence of 0.7). However, Bavaria and Baden-Württemberg have incidence rates of 10 and 6.2 respectively [90]. For many decades, it was believed that TBEV is endemic only in southern Germany, however, recently autochthonous human clinical cases increased in north-western Germany (Lower Saxony), and several natural foci of TBEV transmission have been revealed in this region [91].

Based on TBE incidence, Czechia, Estonia, Latvia, Lithuania and Slovenia are countries with the high incidence rate among European countries (Table 1, Figure 4). The high number of TBEV cases in Czechia and the trend for the continuous increase of this indicator were associated with the gradual infiltration of TBEV into montane biocenosis due to climate warming [92]. Similarly, the high incidence of TBE rate in Baltic countries (Estonia, Lathia, Lithuania) was explained by an increase in spring-time daily maximum temperatures and the promotion of the transmission of TBE virus between larval and nymphal ticks co-feeding on rodents by the warming [93]. Several studies have shown that all three subtypes of TBEV are present in Estonia and Latvia [94,95], while only the TBEV-Eu subtype has been detected in Lithuania and Poland [96]. Such distribution of TBEV subtypes between neighboring countries is determined by the ranges of the two species of TBEV vectors, *I. ricinus* and *I. persulcatu, which* overlap in the Eastern parts of Estonia and Latvia [97], while only *I. ricinus* was revealed in Lithuania.

Figure 4. World map indicating the TBE incidence rate per 100,000 individuals in 2022.

Also, the study of the dynamics over several years revealed a systematic increase in TBE incidence in Austria, the Czech Republic, Germany, Lithuania, Latvia, Estonia, southern Scandinavia, northeastern Poland [98]. In Southern Scandinavia, Sweden has the highest incidence of human cases, with a continuous increase of cases: 520 cases in 2021 and 465 cases in 2022 [89,99], (Table 1).

Many European countries with low TBE cases and low incidence rates are active natural focus of TBEV. Thus, two new natural micro-foci have emerged in Croatia in the central mountainous

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region since 2019 [100]. The Netherlands was long considered a non-endemic country for TBEV, however, in 2015 TBEV was first detected in ticks and this study demonstrated that the virus might have been circulating in the Netherlands as far back as 2010 [101]. The study of TBEV RNA in rodents and tick pools in the Netherlands revealed 3 different variants of the TBEV-Eu subtype [102]. Similarly, despite low TBEV prevalence in Denmark, the presence of TBEV in tick populations in most parts of Denmark was reported [99]. In Poland, TBEV was demonstrated in all parts of the country [103]. The TBEV is endemic in Slovakia with increasing incidence over the past 50 years [104] and up to 16–17% of all TBEV cases were due to milk consumption [74] and in Slovenia [105], where a high degree of TBEV variability was revealed in patients, ticks and rodents [106]. The high incidence rate of TBEV in Slovenia was correlated with the appearance of new foci in forest and agricultural areas, which are influenced by human activity [107]. A risk assessment report described two probable and two confirmed cases of tickborne encephalitis in the UK since 2019 [108] and a potential TBEV focus [109].

The high number of confirmed cases for 2022 was reported by Russia (n=1779, Table 1, Figure 4), where all three TBEV subtypes are circulating. TBEV-Sib is dominant in the Middle Urals [4], this subtype in Russia originated twice from different foci in Western Siberia. The rapid distribution of strains in this region was associated with human economic activity during the colonization of Siberia [110]. TBEV-Eu is widely distributed in the European part of Russia while TBEV-FE is characteristic for the Far East of Russia [111]. The incidence rate for the whole country does not reflect the real situation in Russia, since part of Siberia (Tomsk, Krasnoyarsk, Kemerovo) have incidence rates of more than 30 [90]. In the Russian Far East TBEV-FE is the dominant strain [112] and three separate clusters (Sofjin, Senzhang and Shkotovo-like strains) of TBEV-FE were identified [113]. Similarly, all three TBEV subtypes were revealed in Ukraine, and it was identified as a potential endemic area [105]. In Belarus, circulation of the TBEV-Eu subtype has been established and the continuous increase of TBE cases was reported [114]. Single TBEV-FE isolates have been also reported in Belarus, probably due to the presence of two species of ixodids: *I. ricinus* and *I. persulcatus* [114,115].

Among Asian countries, the highest number of cases and the highest incidence rate were revealed for Mongolia (Table 1, Figure 4). The study conducted in Mongolia on serum samples collected from individuals revealed that TBEV infection incidence remained low in most regions but has continuously increased since 1998 in endemic areas [116]. The data on TBE cases for 2022 are unavailable for China. In total 3,364 TBE cases were reported in China from 2007 to 2018, 89.92% of which were revealed in forest areas (in northeast China) [117]. Forestry areas of Northeastern China were epicentres of TBE occurrence, accounting for more than 98% of all reported cases in this country [118]. In Japan, from 1993 all identified TBE cases were caused by TBEV-FE and resulted in two deaths on the island of Hokkaido [119,120]. It was demonstrated that TBEV is endemic in Hokkaido [121]. However, a recent study of serum and cerebrospinal fluid collected in 2010–2021 from 520 patients identified two patients with TBE outside Hokkaido island [122]. Interestingly, in South Korea, TBEV has been detected in ticks [123], but no single human case has been identified. TBEV-Eu foci in South Korea were located approximately 7000 km away from the European range of the TBEV-Eu subtype circulation [10]. In Central Asia, the east area and Almaty region in Kazakhstan were identified as potential endemic areas of TBEV (60 patients in 2004–2006, 22 patients in Almaty from 2004–2006) [124]. For the whole country, in Kazakhstan, the number of TBE cases per year remains stable, with 32 cases in 2022 and 363 cases of TBE revealed from 2011 to 2020 [125]. TBE is also suspected to be endemic in other Central Asia countries, including Kyrgyzstan, Tajikistan, Turkmenistan, and Uzbekistan [126]. TBEV was detected in small mammals and ticks of Kyrgyzstan [127], however, studies on TBEV in ticks of Uzbekistan, Tajikistan, and Turkmenistan were not performed [128]. Recently, the TBEV-Eu was detected in ticks in Tunisia [129], but human cases were not revealed [10].

Table 1. Epidemiology of TBE and geographical distribution of TBE subtypes.

Country	Number of cases in 2022	Incidence per 100,000 individuals in 2022	Circulating subtype	References
Austria	206	2.3	TBEV-Eu	[10,89]

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Belarus	260	4.1	TBEV-Eu, TBEV-FE	[115,130]
Belgium	2	0.02	TBEV-Eu	[10,89]
Bosnia and Herzegovina	n.a., 2 in 2010	n.a.	TBEV-Eu, TBEV-Sib	[131]
China	n.a., 3,364 for 2007-2018	n.a.	TBEV-FE, TBEV-Sib, TBEV-Him	[8,117]
Croatia	23	0.6	TBEV-Eu	[89,132]
Czechia	709	6.7	TBEV-Eu	[89,133]
Denmark	5	0.1	TBEV-Eu	[89,99,134],
Estonia	140	10.5	TBEV-Eu, TBEV-Sib, TBEV-FE	[89,96,135]
Finland	124	2.2	TBEV-Eu, TBEV-Sib	[89,136]
France	37	0.1	TBEV-Eu	[89,137]
Georgia	n.a., 36 in 2008	n.a.	TBEV-FE, TBEV-Sib	[133,138]
Germany	554	0.7	TBEV-Eu	[89,139]
Greece	1	0.01	TBEV-Eu	[89,140]
Hungary	29	0.3	TBEV-Eu	[89,141]
Italy	104	0.2	TBEV-Eu	[89,142]
Japan	n.a., 7 since 1993	n.a.	TBEV-FE	[88,122,143]
Kazakhstan	32	n.a., 0.19*	TBEV-Sib	[144–146]
Kyrgyzstan	n.a.	n.a.	TBEV-Sib	[4,128]
Latvia	240	12.67	TBEV-Eu, TBEV-Sib, TBEV-FE	[95,147,148]
Lithuania	377	13.4	TBEV-Eu, TBEV-Sib, TBEV-FE	[89,96]
Moldova	n.a.	n.a.	TBEV-FE	[149]
Mongolia	240	12.67	TBEV-FE, TBEV-Blk	[10,150]
Netherlands	5	n.a.	TBEV-Eu	[89,102]
Norway	84	1.5	TBEV-Eu	[89,99]
Poland	446	1.18	TBEV-Eu	[151]
Portugal	1	0.01	n.a.	[89]
Romania	n.a., 30 for 2008-2018	n.a.	TBEV-Eu	[152]
Russia	1778	1.34	TBEV-Eu, TBEV-Sib, TBEV-FE, TBEV-Bkl	[111,153,154]
Serbia	1	0.02	TBEV-Eu	[155,156]
Slovakia	158	2.	TBEV-Eu	[89,104]
Slovenia	125	5.90	TBEV-Eu	[89,106]
South Korea	0	0	TBEV-Eu	[10]
Sweden	465	4.4	TBEV-Eu	[89,99]
Switzerland	380	4.3	TBEV-Eu	[157]
UK	n.a., 2 cases since 2019	0	TBEV-Eu	[108,109]
Ukraine	n.a., 459 TBE cases for 1990- 2018	n.a.	TBEV-Eu, TBEV-Sib, TBEV-FE	[10,158]

*Average long-term incidence rate amounted to 0.19 per 100000 people for 2012-2022. n.a.—information is not available.

Data on TBEV in the Caucasus, a large mountain range uniting different regions and countries at the intersection of Asia and Europe are limited and contradictory. Despite many years of large-scale epidemiological and virological research of both people and vectors, the entire area remains

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unanswered as to whether TBEV circulation exists [159]. The investigation of the blood serum of people living in forest-steppe zones of the North Caucasus, collected in 2008-2010 revealed 1.3 % samples with IgG-anti-TBEV [160]. In 2011 TBEV antigen was detected in 7.5% of samples of Ixodid ticks *I. ricinus, D. marginatus, D. reticulates* obtained from eight districts of the North Caucasus [161]. Specific antibodies to the TBEV were detected in five samples of donor blood serum from this region (2.2%). The authors of the study concluded, that cases of TBE disease have not been registered in the area just due to the lack of a laboratory base [161]. In the serological study, performed in the Territory of Caucasian Mineral Waters, specific TBEV antibodies were detected in the blood serum of donors living in the forest-steppe and foothill zones. In this study, positive results were obtained in 2% of samples and the titers of specific antibodies ranged from 1:200 to 1:3200 [162]. In the latter study the TBEV antigen was detected in samples of seven tick species*: Dermacentor marginatus* (7.3%), *Haemaphysalis punctata* (2.5%), *Ixodes ricinus* (2.5%), *Dermacentor reticulates* (2.2%), *Hyalomma scupense* (1.7%), *Haemaphysalis inermis* (0.5%), *Dermacentor niveus* (0.1%) collected in North Caucasus [163]. Five TBEV cases were registered in the non-endemic Stavropol Territory of the North Caucasus Federal District of Russia [164].

In 2024 the TBEV-Sib was confirmed by molecular analysis in the Caucasus region for the first time. The virus was obtained from *Ixodes ricinus* collected from a green lizard host [159]. Another research demonstrated that 4 ixodid tick species, represented mostly by immature stages (larvae and nymphs), known as TBEV vectors and registered for the lizard hosts, were collected in the Caucasian part of Russia, Armenia, Azerbaijan, Georgia (including Abkhazia), Turkey, Iran, and Iraq [60]. These findings for the first time demonstrate the role of lizards as hosts of ixodid ticks in the Caucasus region and indicate the importance of investigating the prevalence of ticks in reptile populations in this region.

In the South Caucasus, TBE cases were reported in Georgia [165] and a hospital-based acute febrile illness surveillance in six hospitals in Georgia revealed 36 TBE cases and indicated tick bites and the consumption of raw dairy products as the major transmission routes [138], (Table 1). Data from literature and results of the epizootological examination of the territory of the Republic of Abkhazia in 2011 and 2012 confirmed the presence of natural TBEV foci [166]. The TBE cases were not reported for Armenia and Azerbaijan [159]. However, in 2009 in Azerbaijan, TBEV has been isolated from *H. turanicus* ticks collected from dogs and *H. plumbatum* from sheep and cows [167]. The authors of the study concluded that there are constant foci of TBEV in the Kura-Araks lowland however, the role of this virus in human pathology in Azerbaijan is unclear [167]. New endemic TBEV foci have been documented in Armenia and Azerbaijan recently [168].

There is clear discrepancy between the statement thatTBE cases were not reported in Turkey [10] and available data. Thus, TBEV genomic RNA was not found in ticks collected in Northern Turkey, however, TBEV IgG antibody was found in cattle (30.8%), goats (6.1%) and sheep (10.2%) [169]. TBEV reactive IgG have been detected by enzyme-linked immunosorbent assay (ELISA) in 1.4% of patients with a history of tick bites and 7 of 39 patients with the preliminary diagnosis of Crimean Congo Haemorrhagic Fever from Central/Northern Anatolia [170,171]. In the study identifying TBEV exposure in healthy blood donors in the Central/Northern Anatolia region of Turkey, 1.9% were reactive for TBEV IgG and TBEV IgM were revealed in 9.2% of the patients [172]. Recently, IgM but no IgG antibodies to the TBEV were revealed by ELISA in five children in Turkey [173] The study of serum samples collected in Iran in 2018-2019 revealed anti-TBEV IgG antibodies in 3.6% of samples and provided the first evidence of the circulation of TBEV in Northern Iran [174]. A recent study revealed a high prevalence of TBEV-Sib in goat and sheep milk collected at farms in North-Western Iran [175]. Data from research performed in the Caucasus region suggest the presence and distribution of TBEV in the region. They also indicate the necessity for implementing routine diagnostics in patients with central nervous system (CNS) infection and intensive research of natural foci in this area.

6. Pathogenesis of TBEV

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Upon attaching to a host, an infected tick will transmit TBEV in its saliva almost immediately, therefore even early tick removal is often ineffective in preventing TBEV transmission [176]. Despite the existence of evidence that ticks saliva facilitates TBEV transmission and infection, the mechanism and active saliva compounds have not been identified for any other tick-borne virus [177]. Such tick saliva properties as antihaemostatic, vasodilatatory, and local immunomodulatory activity contribute to the facilitated transmission of TBEV [178]. After a tick bite, TBEV replication occurs locally in dendritic skin cells (Langerhans cells), which are the primary site of replication and the transport of TBEV to local lymph nodes occurs from these cells. Later TBEV disseminate to the spleen, liver and bone marrow and, finally, to the CNS [9].

The entry of TBEV into the CNS can occur in several ways, the major route is the infection and replication of TBEV in brain microvascular endothelial cells (BMECs) and retrograde axonal transport [176]. It was shown that altered blood-brain barrier (BBB) permeability is not always a prerequisite to CNS infection [179]. Breakdown of the BBB in a BALB/c and C57BL/6 mouse model was observed at later stages of TBE infection when a high virus load was present in the brain [180]. In this study, the increased BBB permeability was associated with dramatic upregulation of proinflammatory cytokine/chemokine mRNA expression in the brain [180]. As the result of intensive virus replication neurons in the CNS display severe impairment. Acutely necrotic neurons and widespread inflammation can be observed throughout the CNS [181]. Different response of neurons and astrocytes was revealed using an in vitro model of TBEV infection in the human brain [182]. TBEV directly induced neuronal death in neurons and caused the activation of astrocytes as was evidenced by the increase in the expression of glial fibrillary acidic protein, a marker of astrocyte activation [183].

The inflammatory immune responses caused by TBEV were demonstrated to be site-specific and cytokines and chemokines associated with innate and Th1 adaptive immune responses were higher in cerebrospinal fluid (CSF), while mediators associated with Th17 and B-cell responses were higher in serum [184]. The overexpression of a high level of chemokines involved in the chemo-attraction of T cells was revealed in neurons and astrocytes, although astrocytes were stronger producers [182]. Out of chemokines, TBEV up-regulated RANTES production at both mRNA and protein levels in human brain-derived cell lines and primary progenitor-derived astrocytes [185]. The increased RANTES expression led to the subsequent activation of interferon regulatory factor pathway (IRF-3) [185]. The severity of the disease was associated with mediators of innate and Th1 adaptive immune responses [184].

7. Clinical Presentation of TBEV

The clinical presentation of TBE is determined by two main factors: the viral subtype and the host immune response. The incubation period of tick-borne encephalitis on average takes 8 days and it goes unnoticed in a third of patients [186]. The clinical outcome of TBEV infection in humans is determined by TBEV subtype [178]. Thus, the course of TBEV-Eu infections is mainly asymptomatic [187] and symptomatic cases caused by TBEV-Eu are mainly biphasic [188]. The level of viremia is unknown for asymptomatic cases. A non-specific influenza-like illness characterizes the first phase [188]. The most common symptoms of this stage include fever (99%), fatigue (63%), general malaise (62%), and headache and body pain (54%) [189]. The median duration of the first stage of illness is 5 days with a 7-day symptom-free interval to the second phase [189]. However, it should be noted that the documented length of various disease phases varies significantly across studies for TBEV-Eu. Leukopenia and thrombocytopenia were revealed in 70% of patients during this stage [18]. Also, 62.5% of patients had abnormal liver test results, elevated AST and ALT [190]. The second phase in 50% of adult patients presents as meningitis, about 40% as meningoencephalitis, and 10% as meningoencephalomyelitis [9]. During this phase increased WBC count, increased C-reactive protein (CRP) level, and a higher erythrocyte sedimentation rate (ESR) can be observed [9]. A review of the Polish TBE registry between 1993 and 2008 demonstrated that meningoencephalitis was predominant in patients >30 years old, while meningoencephalomyelitis prevalence increased and peaked at 50 years, suggesting that age is a risk factor for this disease phenotype [191]. During this stage, a

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spectrum of psychiatric symptoms from mild cognitive disorder to sleep disorder and overt psychosis were described [191]. Other neurological symptoms included chorea and cranial nerve palsies of the facial, ocular, and vestibular nerves [9]. The abortive form of TBE, manifested only by a febrile headache without meningeal involvement was reported in several studies [9,192].

In comparison with data, accumulated for the clinical presentation of TBEV-Eu, data on the detailed clinical picture of TBEV-Sib and TBEV-FE are very limited. It was shown, that similarly, with TBEV-Eu, the TBEV-Sib subtype also causes acute CNS inflammation, but from 1.0 to 1.7% of patients infected with this subtype develop a chronic course of the disease, with a fatality rate of 6.0 to 8.0% [193]. Chronic TBE has several forms and the hyperkinetic form is prevalent (53.6%), the amyotrophic form was observed in 41%, and Kojevnikoff's epilepsy was characteristic mainly for children and people under 35 years [194]. The most severe disease is caused by TBEV-FE subtype, characterized by a monophasic course and up to 20.0% fatality rate [12,193]. Post-encephalitis syndrome includes spinal nerve paralysis, dysphasia, ataxia and paresis [9] and has been correlated with increased age [9].

The clinic presentation of foodborne TBE (FB-TBE) was similar to those for the disease transmitted by ticks, and most symptomatic patients experience biphasic disease [195], as described above. Among patients with CNS involvement, most had meningitis or meningoencephalitis, and myelitis was a rare manifestation [9]. In comparison with TBE transmitted by ticks, the FB-TBE was characterized by a shorter incubation period (median 3.5 days) and lower rates of invasive disease (39%) [195].

8. Diagnostics of TBEV

As we describe above, results of complete blood count and biochemistry blood tests such as leukopenia, thrombocytopenia and liver function test in patients with TBE are non-specific during the first phase of the disease, therefore the diagnosis must be substantiated by microbiologic findings [9]. The specific diagnostic criteria were introduced by the European Centre for Disease Control (ECDC) [196].

8.1. Detection of Specific Immunoglobulins

According to ECDC, the TBE diagnosis can be confirmed in the case when two criteria are met: the patient has symptoms of CNS inflammation and at least one of the laboratory confirmation criteria. The criteria include: the presence of TBE-specific IgM and IgG antibodies in serum, and/or the presence of TBE-specific IgM or IgM and IgG antibodies in CSF [197], (Table 2). TBEV-specific IgM antibodies in CSF peak later than in serum; usually it is detectable from the second week [198]. The neurological symptoms may develop more rapidly and be present before IgM seroconversion occurs upon infection with TBEV-Sib [72]. The determination of IgG antibody levels is a method for confirming the presence of antibodies following infection or vaccination. Maximum IgG concentrations are detected in late convalescent-phase samples, peak within 3–7 weeks of symptom onset [198]. After TBEV infection, IgG have lifelong persistence, whereas IgM is typically detected up to 3 months, with persistence occasionally lasting up to 9 months [199]. In the study, evaluating the performance of five commercially available TBEV IgM and IgG ELISA kits, the overall sensitivity of the IgM TBEV ELISA kits was acceptable (94 -100 %), however low overall specificity was observed for the IgG TBEV ELISA kits (30-71%) [200]. Due to antigenic similarity, IgM antibodies may be cross-reactive, induced by other flaviviruses [200], reviewed in [201]. Thus, one of the first studies of cross-reactivity demonstrated that 9.5% of TBEV-vaccinated individuals had IgG antibodies cross-reactive to dengue virus (DENV) [202], cross-reactivity between West Nile virus (WNV) and TBEV also was shown [203]. Serum samples of patients with Japanese encephalitis virus (JEV) displayed cross-reactive antibodies to WNV, DENV, and TBEV in IgM and/or IgG ELISA [204]. The cross-reactivity also emphasizes the need for confirmatory testing by virus neutralization test (VNT), especially in patients from areas where several flaviviruses co-circulate [201]. In VNT assay, the neutralization titer is determined either based on the plaque reduction by a plaque reduction neutralization test (PRNT) or by using a microneutralization assay, based on the tissue culture infectious dose (TCID)

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[205]. VNT is considered the most specific serological test method [205], however, it has some disadvantages. The performance of VNT requires a BSL3 laboratory with appropriately trained personnel and therefore the test is expensive [206].

Human immunoglobulins consist of two heavy and two light chains kappa (κ) or lambda (λ), bound by disulfide bridges. The light chains are produced in excess and those light chains which did not bind with heavy chains are released into the blood as free light chains (FLCs) [197]. The comparative study of FLCs in serum and CSF of patients with TBE before and after the treatment revealed, that pre-treatment concentrations of λ FLCs in the sera of patients with TBE were significantly higher than post-treatment levels [207]. On the other hand, the concentration of λ FLCs in the CSF was lower in pre-treatment samples than in post-treatment. Probably, these differences reflect the intrathecal synthesis of immunoglobulins and increased permeability of BBB in patients with TBE [207].

In case of questionable results of ELISA the alternative method, immunofluorescence assays (IFA) offers a good alternative. The main advantage of IFA is the possibility of simultaneous measurement of eight different flaviviruses. This method allows the comparison of the fluorescence intensity for each flavivirus and the detection of the virus causing the strongest antibody response [205]. Also, luciferase immunoprecipitation system (LIPS) antibody detection assay for several flavivirus antigens, allowing the sensitive detection of specific antibodies without the need to express large amounts of antigens was developed [208]. LIPS utilizes genetically encoded recombinant luciferase antigen fusion proteins in an immunoglobulin capture format and provides antibody measurement with high diagnostic sensitivity and specificity [209]. The use of this method decreases the time and effort needed to produce highly purified antigens as well as the labour-intensive assay optimisation steps needed for standard ELISA [210]. Thus, LIPS was used for the assessment of TBEV-specific serum antibodies in a cohort of thirty early tick-borne encephalitis (TBE) patients [211]. The study's results indicated that T-cell responses early after diagnosis of TBE using LIPS correlated with severe acute illness, including the development of paresis (meningoencephalomyelitis). Different viral antigens were tested in a modified LIPS assay for identification candidates allowing differentiation between TBEV and West Nile virus (WNV) in dogs. The study demonstrated that the NS1 protein is a suitable antigen to distinguish between TBEV- and WNV-specific antibodies [210].

8.2. PCR-Based Methods

Since the complete genome sequence of the TBEV became available [212,213] several polymerase chain reaction (PCR) based assays have been developed to detect TBE virus in both clinical and environmental samples [214–216]. Among these PCR assays, nested reverse transcriptase PCR (n RT-PCR) is characterized by its high specificity and sensitivity [217]. However, due to its low throughput screening capabilities and high risk of contamination, real-time PCR methods have become much more widely used [218]. To identify TBEV and its subtypes in the samples, various parts of the viral genome have been used for PCR primer design [219,220] however, direct sequencing methods remain the primary option to identify TBEV subtypes [218,221]. The major limitation of PCR-based techniques is that, in most cases, they fail to detect TBE viral RNA after the onset of neurological symptoms of tick-born encephalitis [222]. Despite some limitations of PCR-based assays, the key advantage over other tests is their ability to detect viral RNA in blood and serum samples at the early stage of infection, before antibodies appear in the samples [223]. PCR-based techniques can also be used to identify the TBE virus in infected tissues postmortem as an alternative to much more expensive and time-consuming electron microscopy-based tests [224,225].

8.3. Biomarkers

Some biomarkers support the diagnosis of TBE, used for differential diagnosis of TBE with other infectious diseases and assessment of the severity of TBE.

Thus, matrix metalloproteinases (MMPs), a family of enzymes responsible for the degradation of extracellular matrix proteins were investigated as potential TBE biomarkers. Out of 8 different matrix metalloproteinases (MMPs), only MMP-9 showed significantly increased CSF and serum

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levels in TBE patients [226]. MMP-9 is capable of degrading collagen IV, a major component of the basement membrane of the cerebral endothelium, promoting the migration of cells across the BBB [227]. Higher serum MMP-9 levels were observed in patients with encephalitis than in patients with meningitis [228]. It was suggested, that the positive effect of corticoids on TBE may be explained at least in part by the down-regulation of MMP-9 activity [229].

The importance of serum procalcitonin (PCT) and CRP levels in differential diagnostic of TBE and bacterial infections was demonstrated [230]. TBEV did not cause elevation of these indicators, while elevated serum concentration of CRP and PCT were characteristic of bacterial infection and, in particular, acute human granulocytic anaplasmosis (HGA) [230] (Table 2).

The effect of TBE on cytokines and growth factors in the serum of patients with acute TBE was assessed [231]. The contribution of chemokines to the pathogenesis of TBE has been evaluated in several studies and reviewed in detail in [197]. Many studies showed significant differences in the concentrations of various chemokines, including CCL2, CXCL5, CXCL10, CXCL11, CXCL12, CXCL13, macrophage migration inhibitory factor (MIF), CCL7 in the CSF and CXCL10, CXCL13 in the serum of TBE patients, usually in comparison with patients diagnosed with other inflammatory CNS diseases (reviewed in [232]), therefore, in this review, we will not discuss the use of chemokines as biomarkers.

TBEV elicited increased serum levels of the pro-inflammatory cytokines interleukin (IL): IL-6, IL-8, IL-10 and IL-12 [231,233]. The opposite trend was revealed in CSF, where concentrations of IL-6, IL-10 and IL-9 were lower in TBEV patients, but the difference was statistically significant for IL-9 only [233].

IL-6 exhibits a neuroprotective role in CNS by promoting the differentiation of oligodendrocytes, and regeneration of peripheral nerves [232]. It was suggested that the level of IL-6 reflects the severity of the disease and has prognostic importance for permanent sequelae [207]. IL-8 maintains neuroimmune homeostasis, recruiting neutrophils and T cells into the CNS in response to inflammation or injury and amplifying BBB permeability [226]. IL-9 is a cytokine controlling pathogenic inflammation mediated by Th17 cells. IL-10 is known to limit inflammation of the brain, its expression increases during the major diseases in the CNS and promotes the survival of neurons and glial cells in the brain by blocking the effects of proapoptotic cytokines [234]. IL-12 is a critical part of the immune response to viral infections since it activates natural killer cells and T lymphocytes and is involved in the enhancement of the cytotoxic activity of natural killer cells and $CD8^+$ T cells [235].

Concentrations of IL-5, IFN-γ and IL-22 were higher in the CSF of the TBEV patients compared with control [232,236]. High concentrations of IL-5, produced by activated Th2 cells suggest the contribution of Th2 responses to the pathogenesis of TBE [232]. It was suggested, that elevated CSF/serum IL-5 index indicates increased permeability of the BBB [197]. IL-22 is cytokine, downregulating inflammatory immune responses, thus promoting the repair and regeneration of epithelial cells [237]. IFN-γ is a pro-inflammatory cytokine, capable of interfering with viral replication, in CNS it has an anti-proliferative function, and activates macrophages and microglia stimulating the production of nitric oxide [238].

Another cytokine, which can be used for differential diagnostics of TBE and neuroborreliosis (NB) is the high mobility group box 1 protein (HMGB-1) protein. It is alarmin, endogenous protein promoting the immune response to an infection via activation of toll-like receptors [239,240]. The concentration of HMGB-1 in the serum of patients with NB was significantly higher than in the control group, while in the serum of patients with TBE, it was not statistically different during the first phase of the disease [241]. The HMGB-1 concentration was significantly higher in the CSF of patients with both NB and TBE than in the control [241]. These findings indicate the potential use of HMGB1 as a biomarker for differential diagnosis of TBE and NB. A similar study was performed for toll-like receptor TLR-2 [242], stimulating the production of cytokines [243]. It was suggested that the innate immune response of the CNS involves direct activation of TLR signaling [244]. The serum and CSF TLR-2 concentration in both NB and TBE patients during the second phase of the disease was

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significantly higher than in the control, indicating that TLR-2 can be a biomarker of both TBE and NB [242].

The granulocyte-macrophage colony-stimulating factor (GM-CSF) and monocyte chemoattractant protein-1 (MCP-1/CCL2) decreased in the serum of patients with TBE and this finding requires further investigation [231]. GM-CSF is the principal microglial growth factor; its expression is upregulated in the injured or diseased CNS [245]. MCP-1 is a key chemokines that regulate the migration and infiltration of monocytes/macrophages [246].

Serum concentrations of hepatocyte growth factor (HGF) and vascular endothelial growth factor (VEGF) were increased in TBE patients in comparison to control [231]. Since HGF is a mitogen and a morphogen [247], increased serum HGF levels may reflect a response to virus-mediated brain tissue damage to the development of encephalitis by increasing the permeability of peripheral and CNS vasculature [248]. The VEGF level in TBE patients allows to estimate the severity of BBB injury. Investigation of vaccine breakthrough (VBT) revealed that VBT TBE patients were characterized by significantly higher VEGF in CSF, [249]reflecting higher vascular permeability, associated with a more severe disease course [249].

The levels of neurotransmitters such as serotonin, dopamine, and noradrenaline were significantly lower in the serum of TBE patients than in the control group [231–233]. Interestingly, the paralytic form of TBE was characterized by lower levels of serum serotonin than the nonparalytic form and serum serotonin level was proposed as a predictive indicator for the development of severe TBE forms [233]. The lower levels of monoamine neurotransmitters detected in sera from TBE patients may be associated with neuropsychological complications [231]. A new approach based on the characterization of the serum metabolome and lipidome of adult TBEV patients was applied in the study performed using liquid chromatography-tandem mass spectrometry [250]. The results of this study demonstrated that phospholipid levels were significantly increased in the serum of TBE patients, while triacylglycerols (TAGs) significantly decreased [250]. Since lipid profile is routinely determined in hospitalized patients, these indicators can be used as additional biomarkers of TBE diagnostics. Amino acids, including D-glutamine, pyroglutamic acid, and L-cystine decreased in the plasma of patients with TBE [250]. These findings can indicate cellular demand for these metabolites.

Table 2. Biomarkers of TBE.

Biomarker	Material	Direction of changes	Stage of the disease	Application	References
IgM	Serum CSF	Increase	Second phase	Conformation of the diagnosis	[198,199]
IgG	Serum CSF	Increase	Second phase	Conformation of the diagnosis	[198]
λ FLCs	Serum	Increase	Second phase	Indicates the rate of intrathecal synthesis of immunoglobulins	[207,251]
	CSF	Decrease in pretreatment Increase in post-treatment		A decrease indicates increased permeability of the BBB Post-treatment increase can be used for monitoring response to therapy	
PCT	Serum	Reference range	First phase	Differential diagnostics with bacterial infections	[230]
CRP	Serum	Reference range or increased (up to 16 mg/l)	First phase	Differential diagnostics with bacterial infections	[230]

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MMP-9	Serum	Increase	Second phase	The increase indicates BBB damage	[226,228]
	CSF	Increase	Second phase		
IL-5	Serum	Decrease	Second phase	Increase correlates with increased permeability of BBB	[197,231,232,236].
	CSF	Increase			
IL-6	Serum	Increase	Second phase	The degree of increase correlates with the severity of the disease and permanent sequelae	[231,232]
	CSF	Decrease concentration, higher content than in serum			
IL-8	Serum	Increase	Second phase	BBB dysfunction	[226,231]
IL-9	CSF	Decrease	Second phase	Decrease associated with the development of neuroinflammation	[232,252]
IL-10	Serum	Increase	Second phase	A low level indicates complications	[231,233]
	CSF	Decrease			
IL-12	Serum	Increase	Second phase	The increase indicates enhancement of immunopathology	[231]
IL-22	CSF	Increase	Second phase	Additional marker for TBE diagnostics	[232].
IFN-γ	CSF	Increase	Second phase	Increase correlates with strength of immune response	[232].
HMGB-1	Serum	Reference range or increase	First phase	Differential diagnostic of TBE and NB	[241]
	CSF	Increase			
TLR-2	Serum	Increase	Second phase	Additional marker for TBE diagnostics	[242]
	CSF	Increase			
GM-CSF	Serum	Decrease	Second phase	Decrease associated with the development of neuroinflammation	[231]
MCP-1	Serum	Decrease	Second phase	Prognostic marker for the development of CNS complications	[227,253].
HGF	Serum	Increase	Second phase	Virus-mediated brain tissue damage	[231]
VEGF	Serum	Increase	Second phase	Degree of BBB injury	[231,249]
	CSF				
Serotonin	Serum	Increase	Second phase	Development of severe TBE forms	[201,203]
Dopamine	Serum	Increase	Second phase	Development of severe TBE forms	[231]
Noradrenaline	Serum	Increase	Second phase	Development of severe TBE forms	[231]
Phospholipids	Serum	Increase	First phase	Additional marker for TBE diagnostics	[250].

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TAGs	Serum	Decrease	First phase	Additional marker for TBE diagnostics	[250].
Acylcarnitine	Serum	Increase	First phase	Additional marker for TBE diagnostics	[250].
D-glutamine	Serum	Decrease	First phase	Additional marker for TBE diagnostics	[250].
Pyroglutamic acid	Serum	Decrease	First phase	Additional marker for TBE diagnostics	[250].
L-cystine	Serum	Decrease	First phase	Additional marker for TBE diagnostics	[250].

9. Prevention and Treatment

Prevention of TBEV infection involves the reduction of tick population by application of eco-friendly tick control treatments, including the application of the entomopathogenic fungi, and biological acaricides [254], use of personal protection measures such as using repellents; wearing long sleeves cloth [43] as well as joint multisectoral effort in the milk production industry, involving processing, transport, and consumption including the pasteurisation of milk [255]. Active immunization is the most important protective measure against infection with TBEV and essential for individuals exposed to endemic areas professionally or recreationally [43,256]. All licensed vaccines against TBEV are based on inactivated whole viruses, containing various TBEV-Eu or TBEV-FE strains (reviewed in [257]). These vaccines can be grouped as European (based on 2 Austrian and German TBEV-Eu isolates), Russian (based on Russian TBEV-FE isolates) and Chinese vaccines (based on Chinese TBEV-FE isolate). All vaccines are highly immunogenic with high seroconversion rates ranging from 86–100% (reviewed in [256]). Even though the broad availability of European vaccines, vaccine coverage in European TBE-endemic countries is relatively low in the range of 0-33%, except Austria, Latvia and Åland Island (vaccination rate exceeds 50%) [258]. In Russia vaccination is obligatory only in the endemic territories, where vaccination coverage reaching 88%, however, in other regions, less than 10% of the population is vaccinated [258]. Vaccination rates for TBE in China are not available, but according to estimates, vaccine uptake is limited [259].

The TBEV vaccines available for the moment have some disadvantages, the main disadvantage is reduced immunogenicity, vaccination failures and breakthrough infections, occurring mainly in people older than 50 years (reviewed in [256]). Therefore, novel TBEV vaccine approaches aiming at the induction of humoral and cellular immunity are continuously developed (reviewed in [256]).

The treatment of TBE focuses on symptomatic and supportive measures since no specific antiviral therapy is available. The development of specific therapeutic agents and strategies for the treatment of TBE is performed in two main directions: immunotherapy and screening of small-molecule antivirals. Specific and nonspecific immunoglobulins, recombinant anti-TBEV immunoglobulins and vaccines are used for the therapy (reviewed in [258]). Among small-molecule antiviral analogues of nucleosides and nucleotides are the most numerous. Several approaches used for the design of such compounds included nucleobase substitution (introduction of side chains into different positions), nucleobase modification by the use of different heterocycles; sugar substitution and modification of furanose ring (reviewed in [260]). Chemically modified nucleosides act via DNA or RNA chain termination [261]. The first synthesized nucleoside with anti-TBEV activity was ribavirin (Figure 5A), a triazole nucleoside with anticancer and antiviral properties [262]. Ribavirin was shown to impair TBEV replication and markedly inhibited TBEV propagation, leading to a dose-dependent reduction in TBEV titers and the viral RNA levels [263]. A well-studied nucleoside-based inhibitor of TBEV is 7-deaza-2′-C-methyladenosine (7-deaza-2´-CMA, Figure 5B), originally developed for the treatment of HCV. It was shown to increase the survival rate and reduce the severity of neurological signs of TBE [264]. Differential activity of several nucleotide analogues against TBEV was tested on human cell lines [265]. The study revealed that galidesivir (Figure 5C) uniformly inhibited the TBEV in all human cell lines. Galidesivir is a nucleoside analogue that targets the RNA-dependent RNA polymerase of TBEV [266]. Cellular kinases should phosphorylate it to a

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triphosphate (BCX4430-TP) and then incorporate it into the viral RNA, causing premature chain termination [267].

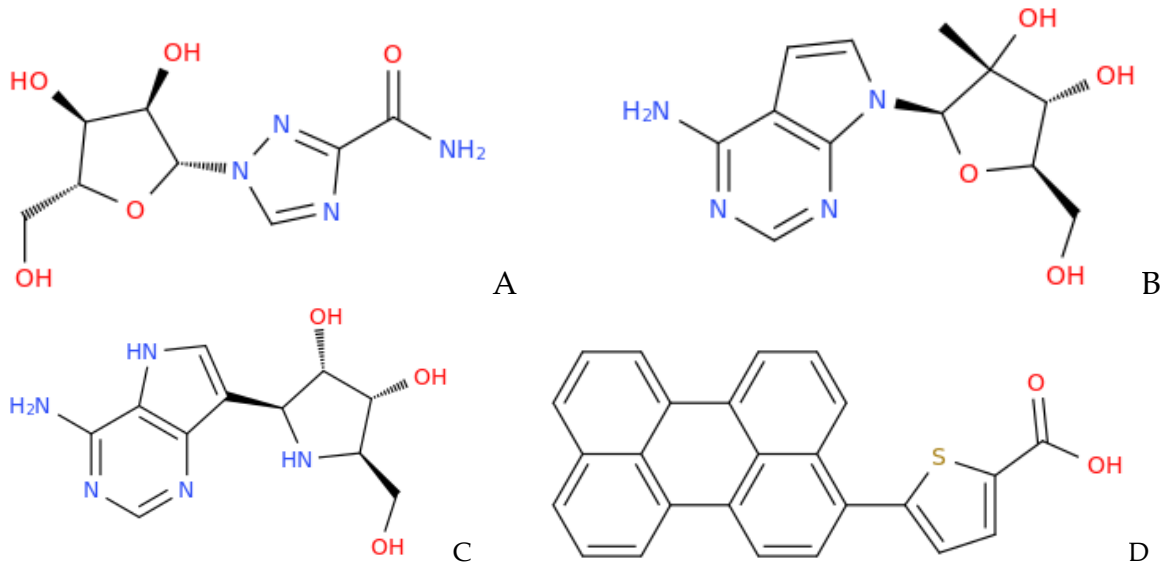

Figure 5. Structures of some of the main compounds investigated as anti-TBEV drugs: (A) ribavirin; (B) 7-deaza-2′-C-methyladenosine; (C) galidesivir; (D) 5-(perylen-3-yl)-2-thiophenecarboxylic acid.

The pronounced activity of rigid amphipathic fusion inhibitors (RAFIs) preventing membrane fusion of enveloped viruses was discovered [268]. Among these compounds 5-(perylen-3-yl)-2-thiophenecarboxylic acid (Figure 5D) showed the highest TBEV antiviral activity with a 50% effective concentration of 1.6 nM [269]. It is to be assumed that at least some compounds discussed above will be subjected to a clinical examination soon.

10. Conclusions

The scientific progress in the study of TBEV has been enormous since the 1930s when TBE was first described. In this review, we summarized the current knowledge on the structure and the life cycle of the virus, TBEV circulation in nature, epidemiology, pathogenesis, clinical symptoms, diagnostic methods and new approaches to TBE treatment. The revision of the current knowledge allowed us to identify several TBE-related issues which require further investigation and improvement. The first issue is the limited information on TBE epidemiology in many countries outside the EU. Thus, in the Caucasus region, despite extensive research, comprehensive data on TBEV circulation remains sparse. Limited reports suggest isolated cases of TBE in Kabardino-Balkaria, Dagestan, and Stavropol Krai, with a notable number of cases in Georgia linked to tick bites and consumption of raw dairy products. Although Armenia and Azerbaijan have not reported TBE cases, new endemic foci have been identified, indicating potential areas of concern. In Turkey, while TBEV genomic RNA was not detected in ticks, serological evidence suggests exposure in livestock and a possible, though not confirmed, human risk. This highlights the need for further epidemiological studies and surveillance in the Caucasus region to better understand TBEV distribution and risks. The creation of a global database containing data on the burden of TBE in different countries, distribution of different TBEV subtypes, available vaccines and natural foci would significantly contribute to extending the knowledge of global TBE epidemiology.

The maturation process of TBEV as well as the TBEV life cycle require detailed investigation in ticks. It is also necessary to develop quick and highly sensitive TBEV diagnosis techniques as well as reveal biomarkers for differential diagnostics of TBE and other viral infections of CNS. More data on the clinical presentation of TBEV-Sib and TBEV-FE and clarification of the length of various disease phases caused by TBEV-Eu will contribute to a prompter diagnosis of the disease. Preventive measures against TBEV infection via substances of human origin should be developed. The clinical examination of different potential candidate drugs for the treatment of TBEV as well as clinical

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protocols combining sequential antiviral and anti-inflammatory therapy are also required. Finally, it is crucial to emphasize that preventing TBEV effectively relies on minimizing tick exposure through protective measures and vaccination. Meanwhile, treatment strategies remain focused on managing symptoms due to the absence of specific antiviral therapies, which are highly desirable and expected to change shortly thanks to advancements in antiviral research and vaccine development. Recent advancements in the study of oxidative processes and xenobiotic metabolism in plants [270], innovations in computational drug discovery [271], and progress in marine-derived therapeutic research [272,273] highlight the expanding role of natural product-based approaches in modern medicine. These developments offer promising new avenues for the discovery of novel treatments, which could contribute to the development of more effective therapies for TBEV and other viral infections.

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Abbreviations

BBB—the blood-brain barrier.
BMECs—brain microvascular endothelial cells
CNS—central nervous system.
CRP—C-reactive protein.
CSF—cerebrospinal fluid.
ECDC—European Centre for Disease Control
ELISA—enzyme-linked immunosorbent assay
ER—endoplasmic reticulum
ESR—erythrocyte sedimentation rate
GM-CSF—granulocyte macrophage colony stimulating factor
HGA—acute human granulocytic anaplasmosis
HGF—hepatocyte growth factor
HMGB-1—high mobility group box 1 protein
IFA—immunofluorescence assays
IL—interleukin
IRF-3—interferon regulatory factor pathway
MCP-1/CCL2—monocyte chemoattractant protein-1
MMP-9—matrix metalloproteinase-9
MMPs—matrix metalloproteinases
NB—neuroborreliosis
n RT-PCR—nested reverse transcriptase PCR
PCT—procalcitonin
PCR—polymerase chain reaction
PRNT—plaque reduction neutralization test
prM—precursor M protein
RAFIs—rigid amphipathic fusion inhibitors
TAGs—triacylglycerols
TBEV—tick-borne encephalitis virus
TBE—tick-borne encephalitis
TCID—tissue culture infectious dose
VBT—vaccine breakthrough
VEGF—vascular endothelial growth factor

VNT—virus neutralization test

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