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Tick-borne encephalitis in Europe and Russia: Review of pathogenesis, clinical features, therapy, and vaccines

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ABSTRACT

Tick-borne encephalitis (TBE) is an illness caused by tick-borne encephalitis virus (TBEV) infection which is often limited to a febrile illness, but may lead to very aggressive downstream neurological manifestations. The disease is prevalent in forested areas of Europe and northeastern Asia, and is typically caused by infection involving one of three TBEV subtypes, namely the European (TBEV-Eu), the Siberian (TBEV-Sib), or the Far Eastern (TBEV-FE) subtypes. In addition to the three main TBEV subtypes, two other subtypes; i.e., the Baikalian (TBEV-Bkl) and the Himalayan subtype (TBEV-Him), have been described recently. In Europe, TBEV-Eu infection usually results in only mild TBE associated with a mortality rate of < 2%. TBEV-Sib infection also results in a generally mild TBE associated with a non-paralytic febrile form of encephalitis, although there is a tendency towards persistent TBE caused by chronic viral infection. TBE-FE infection is considered to induce the most severe forms of TBE. Importantly though, viral subtype is not the sole determinant of TBE severity; both mild and severe cases of TBE are in fact associated with infection by any of the subtypes. In keeping with this observation, the overall TBE mortality rate in Russia is ~2%, in spite of the fact that TBEV-Sib and TBEV-FE subtypes appear to be inducers of more severe TBE than TBEV-Eu. On the other hand, TBEV-Sib and TBEV-FE subtype infections in Russia are associated with essentially unique forms of TBE rarely seen elsewhere if at all, such as the hemorrhagic and chronic (progressive) forms of the disease. For post-exposure prophylaxis and TBE treatment in Russia and Kazakhstan, a specific anti-TBEV immunoglobulin is currently used with well-documented efficacy, but the use of specific TBEV immunoglobulins has been discontinued in Europe due to concerns regarding antibody-enhanced disease in naïve individuals. Therefore, new treatments are essential. This review summarizes available data on the pathogenesis and clinical features of TBE, plus different vaccine preparations available in Europe and Russia. In addition, new treatment possibilities, including small molecule drugs and experimental immunotherapies are reviewed. The authors caution that their descriptions of approved or experimental therapies should not be considered to be recommendations for patient care.

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1. Introduction

Tick-borne encephalitis (TBE) is the most important arboviral disease affecting the human central nervous system (CNS) in Europe and northeastern Asia. TBE is preventable by vaccination. Different vaccines are available in Europe and Russia, and one vaccine is also produced in China. Currently, there is no general, specific treatment available for TBE, but there are several ways to positively influence the disease severity in both acute and convalescent periods (as discussed further in this review). Here, we provide a comprehensive compilation and discussion of the data available on the pathogenesis and clinical presentation of TBE, as well as on the treatments and vaccines in use or in development in Europe and Russia. The data compiled in this review were obtained from searching PubMed, Web of Science and eLibrary, using keywords corresponding to the individual sections. We also include data from references that are not recorded in these databases, the majority of which are reports published in Russian-language journals and monographs. The authors caution that their descriptions of approved or experimental therapies should not be considered to be recommendations for patient care.

2. Background

2.1. Causative agent and routes of transmission

TBE is caused by tick-borne encephalitis virus (TBEV), a positive-sense, single-stranded RNA (+ssRNA) virus with a spherical enveloped virion approximately 50 nm in diameter (Füzik et al., 2018) (Fig. 1). TBEV is a member of the *Flaviviridae* family, genus *Flavivirus*. The viral genome is approximately 11 kb in length, and comprises a 5′-cap plus a single large open reading frame (ORF), that is flanked by 5′ and 3′ untranslated regions. The ORF codes for a single polyprotein that is co- and post-translationally cleaved by viral and cellular proteases into three structural (C, prM and E) and seven non-structural proteins (NS1, NS2A, NS2B, NS3, NS4A, NS4B and NS5) (Fig. 1). Replication of the virus occurs through the synthesis of negative (anti-sense) mRNA, which serves as the template for genomic + ssRNA production. Replication complexes are found localized in membrane structures within the endoplasmic reticulum (ER). Accordingly, assembled nucleocapsids acquire their lipid envelopes by budding into the ER lumen. Immature particles so formed pass through the Golgi complex and undergo maturation on passage through to the *trans*-Golgi. Maturation involves transformation from spiky immature into mature smooth viral particles. This process involves cleavage of prM and the reorganization of E proteins to form fusion-competent homodimers. Mature viral particles are then exported from the Golgi complex in cytoplasmic vesicles for their release from host cells by exocytosis (Fig. 2).

TBEV is typically able to infect humans starting from the bite of a TBEV-infected tick, primarily *Ixodes ricinus* in Europe and *Ixodes persulcatus* in Russia. In addition, approximately 1% of all TBE cases are thought to be caused by foodborne TBEV, although the numbers can differ greatly in different regions. In this case, patients are infected by consuming unpasteurized dairy (goat, sheep, and cow) milk and milk products containing TBEV (Kriz et al., 2009). This mode of transmission has been reported mostly in Eastern Europe and the Balkans; however, small outbreaks of foodborne TBE have also been reported in Central and Western Europe and Russia (Kohl et al., 1996; Gresikova et al., 1975; Holzmann et al., 2009; Caini et al., 2012; Hudopisk et al., 2013). Furthermore, a cluster of TBEV infections related to solid organ transplantation has recently been described in Poland (Lipowski et al., 2017).

TBE became notifiable at the EU level in 2012 and is now under the surveillance of the European Centre for Disease Prevention and Control (ECDC). Today, the disease is endemic in 27 European and in at least four Asian countries (Steffen, 2016). [Note: in this paper, “European” refers to countries to the west of the Russian Federation.] An increase in TBE morbidity has been observed in Europe, whereas a decrease in TBE incidence was noted in Russia compared to the late 1990s and the incidence is now at a constant level (Süss, 2008; Erber et al., 2018). However, we do note that there is a reporting problem with TBE cases, given that some countries report only clinical illness, while others (such as some Baltic countries) also report asymptomatic sero-converters.

2.2. Viral diversity and virulence variation in humans

Phylogenetic analysis has revealed three main subtypes of TBEV: European (TBEV-Eu), Siberian (TBEV-Sib), and Far Eastern (TBEV-FE) (Ecker et al., 1999). Two additional subtype lineages (“178–79” and “886–84 group”) have also been proposed as TBEV subtypes (Demina et al., 2010), although the strain 178-79 represents a single finding. On the other hand, the “886-84 group” (also named Baikalian TBEV subtype [TBEV-Bkl]) actually comprises 13 strains with the “886-84 group” as prototype. These strains were found in East Siberia near Lake Baikal and in Northern Mongolia (Kozlova et al., 2018). Finally, another new

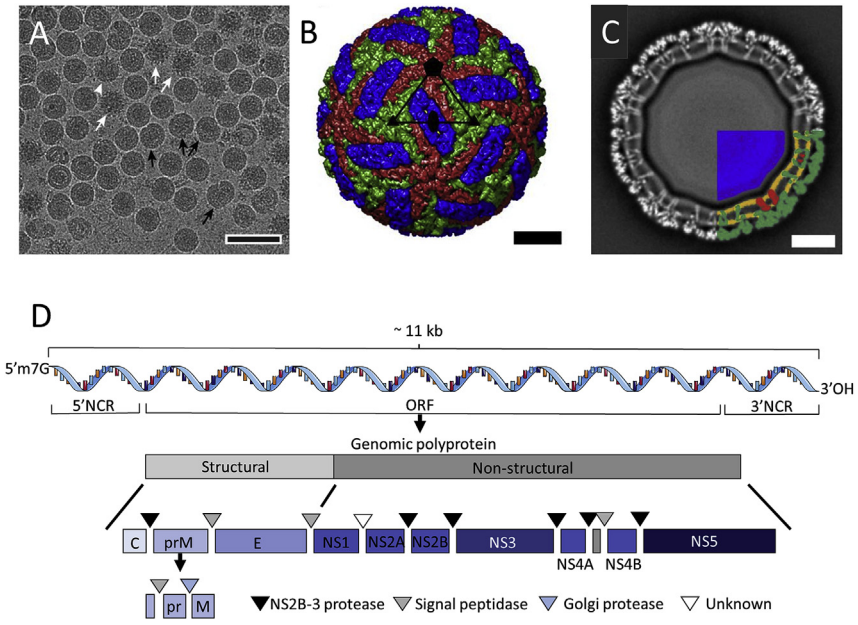

Fig. 1. Structure of a mature TBEV virion. (A) Cryo-electron microscopy image of TBEV virions. The sample contains mature, immature (white arrows), half-mature (white arrowheads), and damaged (black arrows) particles. Scale bar 100 nm. (B) Molecular surface of TBEV virion. The three E-protein subunits within each icosahedral asymmetric unit are shown in red, green, and blue. Scale bars 10 nm. (C) Central slice of TBEV electron-density map, perpendicular to the virus 5-fold axis. The virus membrane is deformed by the transmembrane helices of E-proteins and M-proteins. The lower right quadrant of the slice is color-coded as follows: nucleocapsid—blue; inner and outer membrane leaflets—orange; M-proteins—red; E-proteins—green. Scale bars 10 nm. (A–C) are reproduced from Füzik et al. (2018), under Creative Commons Attribution 4.0 International License, http://creativecommons.org/licenses/by/4.0/. (D) Schematic representation of TBEV genome organization and polyprotein-processing events. Figure created using Servier Medical Art available on www.servier.com.

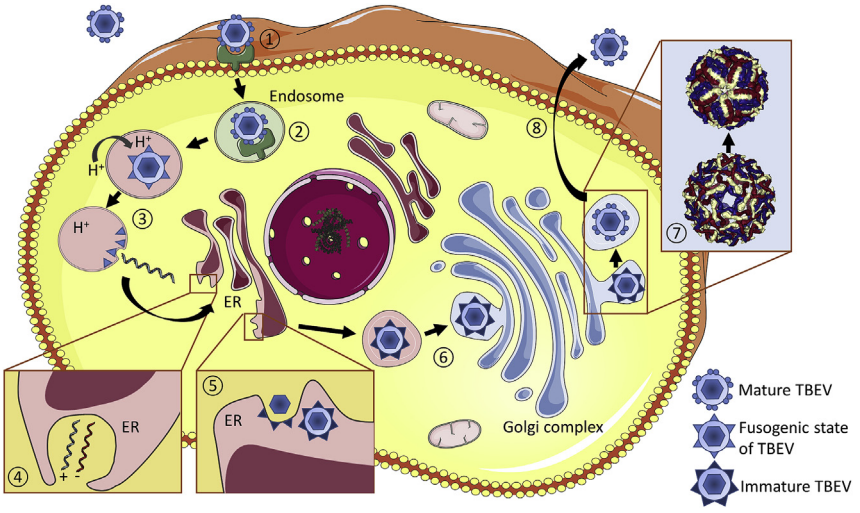

Fig. 2. Schematic illustration of the TBEV life cycle. (1) Infection begins with the binding of viral particles to specific cell-surface receptors, which have not yet been unequivocally identified. (2) Viral particles enter cells via endocytic pathway. (3) Low pH in the late endosome triggers conformational changes in the E proteins, leading to rearrangement of dimers to trimeric forms (fusogenic state) and the subsequent fusion of the viral envelope with endosomal membranes, which leads to virion uncoating. (4) Replication of the virus occurs through the synthesis of antisense (negative) RNA, which serves as the template for genome RNA production. Replication complexes are localized in membraneous structures within the endoplasmic reticulum (ER). (5) Assembled nucleocapsids acquire lipid envelopes by budding into the ER lumen. (6) Immature particles pass through the Golgi complex. (7) Maturation takes place in the *trans*-Golgi network, involving the cleavage of prM and the reorganization of E proteins into fusion-competent homodimers, leading to a change from spiky immature to smooth mature particles. Pseudoatomic structures of immature (PDB: 2OF6) and mature (PDB: 3J0B) flavivirus (West Nile virus) particles are shown. (8) Mature particles are transported in cytoplasmic vesicles and released into the extracellular space by exocytosis. Figure created using Servier Medical Art available on www.servier.com.

potential TBEV subtype (Himalayan [TBEV-Him]) was identified recently in wild rodent *Marmota himalayana* in the Qinghai-Tibet Plateau in China (Dai et al., 2018). The TBEV-Eu subtype is prevalent across Europe, including the European part of Russia, whereas the TBEV-Sib and TBEV-FE subtypes are present mainly in Asia. In some areas, two or all three main subtypes coexist (e.g., Baltic States, Siberia, Ukraine).

In Europe, TBEV-Eu infection usually results in a rather mild form of TBE with a mortality rate of < 2%. TBEV-Sib infection also results in a generally mild illness associated with a non-paralytic febrile form of encephalitis (Gritsun et al., 2003a), although there is a tendency towards persistent TBE caused by chronic viral infection. In contrast, TBEV-FE infection is thought to instigate the most severe forms of TBE and is associated with high fatality rates (Gritsun et al., 2003b). Indeed, in Russia, hemorrhagic forms of TBE have been reported that are not typically seen in Europe (Ternovoi et al., 2003). In addition, chronic (or progressive) forms of TBE have also been seen in Russia that are rarely seen if at all in Europe (Gritsun et al., 2003a, 2003b; Mickienė et al., 2002). Importantly though, viral subtype is not the sole determinant of TBE severity; both mild and severe cases of TBE are in fact associated with infection by any of the subtypes. So viral genotype or the apparent virulence of a particular TBEV subtype are not the sole determinants of disease severity. Other factors that are possibly involved include the infectious viral dose, the age, genotype, immune and nutritional state of an infected individual, plus his/her overall health status (Mickienė et al., 2014; Barkhash et al., 2010, 2012; 2013, 2016; 2018; Kaiser, 2012; Zajkowska et al., 2011).

3. Pathogenesis of TBE

For TBEV to cause disease after the tick bite, it must overcome a series of barriers that a vertebrate host employs in protection (Fig. 2). The first main barrier is the skin. However, since TBEV is transmitted by ticks, this barrier is immediately breached by injection of virus particles via the saliva during feeding. Tick saliva contains pharmacologically active molecules that modulate host defenses, such as pain and itch reflexes, hemostasis, inflammation, innate and adaptive immunity, plus wound healing, as reviewed in (Wikel, 2013). Accordingly, tick saliva components synergize with TBEV transmission between tick bites (Labuda et al., 1996) and so enhance TBEV infection and dissemination (Labuda et al., 1993). After such inoculation, the virus replicates locally in Langerhans cells and neutrophils of the skin. Migratory monocytes/macrophages produce infectious virus (Labuda et al., 1996), and these cells are likely to serve as vectors to transport virus particles to draining lymph nodes.

The second main barrier that the virus encounters is the immune response triggered by the virus infection itself. If the virus overcomes this second main barrier, it may spread and cause viremia. Infection is often cleared in this stage and seroconversion takes place without any obvious clinical signs (Prokopowicz et al., 1995). The third barrier that TBEV needs to cross is the blood brain barrier (BBB), which protects the CNS from toxic substances and pathogens. The BBB is composed of endothelial cells connected by tight junctions, astrocyte foot processes, and pericytes, all designed to prevent unrestricted entry of blood pool dispersed molecules into the brain. There are several different ways that virus particles could cross the BBB (Fig. 3):

- induction of BBB opening directly;
- infection of microvascular endothelial cells that make up the BBB frontline;
- direct axonal retrograde transport from infected peripheral neurons, spreading via neuromuscular junctions (NMJs) from muscles into somatic motor neurons in the spinal cord; and
- infection of olfactory neurons and spreading to the olfactory bulb.

There is also a so-called “Trojan horse” mechanism in which the virus is transported by infected immune cells that traffic to the CNS (Palus et al., 2017; Ruzek et al., 2013a, b).

Exactly how TBEV crosses the BBB is not clear, and it would seem most likely to be a combination of mechanisms. TBEV, Langat virus (LGTV), West Nile virus (WNV), and Japanese encephalitis virus (JEV) enter the CNS without disrupting the BBB (Li et al., 2015; Ruzek et al., 2011; Roe et al., 2012; Weber et al., 2014), since the permeability of the BBB is a consequence of cytokine release in response to viral replication within the brain (Roe et al., 2012). Therefore, TBEV neuroinvasion by direct infection of the microvascular endothelial cells seems rather probable. Although less than 5% of cells are infected in an *in vitro* BBB model, the infection is persistent thereby enabling the virus to cross the BBB, in high viral yield (Palus et al., 2017). LGTV infection probably makes use of the olfactory route of infection. After peripheral infection of mice, this virus was detected successfully first in the olfactory bulb before spreading to other brain regions (Kurhade et al., 2016). However, whether or not TBEV enters the brain via olfactory neurons or by another way is still not completely clear. It should be noted that most studies of this topic have been performed with *in vitro* or *in vivo* animal models, which may be rather poor models of the human situation.

Once the virus has crossed the BBB in humans, it replicates in the

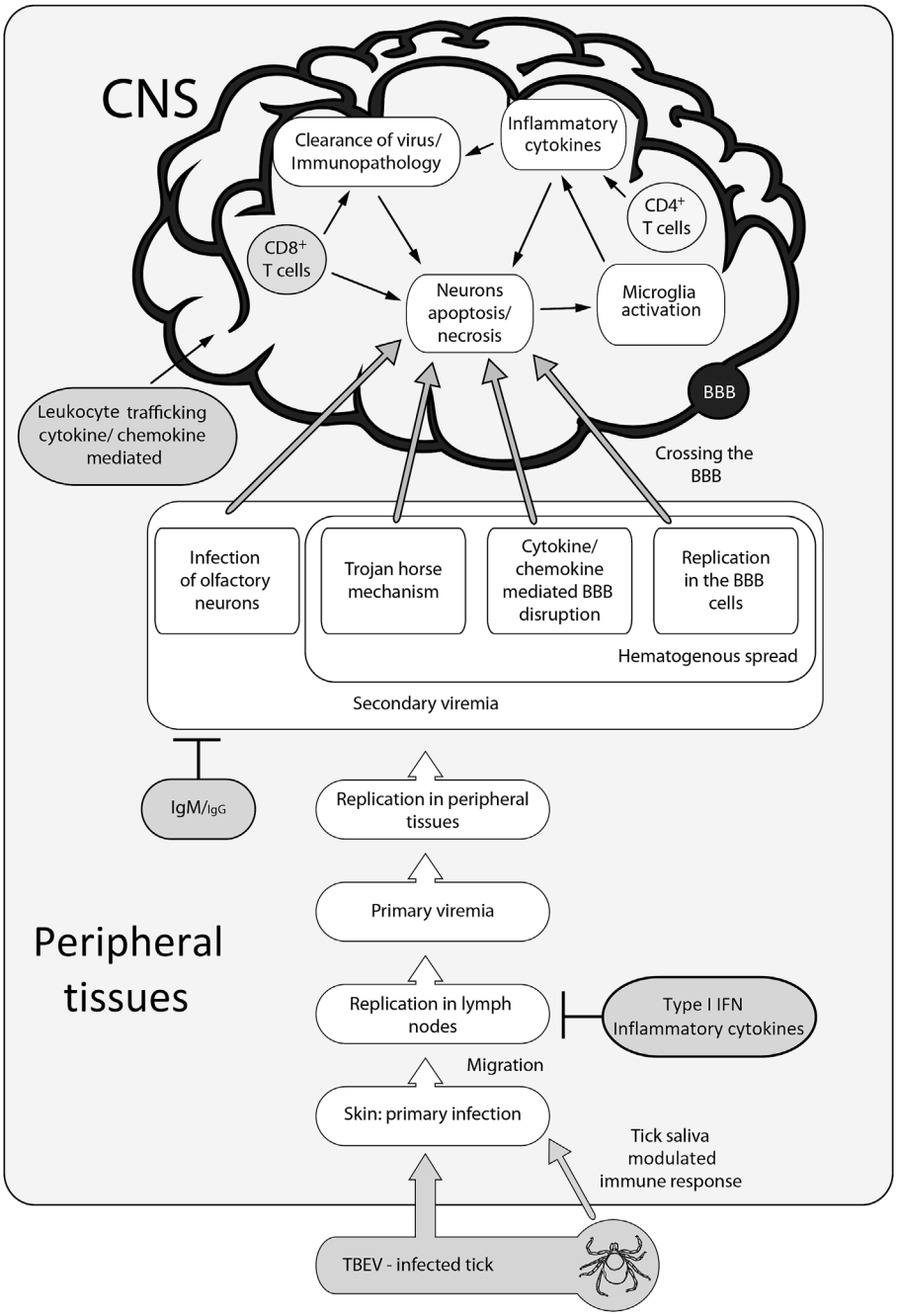

Fig. 3. Schematic of TBEV infection of the mammalian host. After a tick bite, TBEV replicates in subcutaneous tissues, and Langerhans cells transport virus particles to the draining lymph nodes. Viral replication in the nodes leads to spread into the bloodstream and induction of viremia. During primary viremia, the virus infects various peripheral organs and tissues; infection of these cells results in secondary viremia. At this time, the virus crosses the blood-brain barrier (several mechanisms have been proposed for viral transit – see text) and initiates infection in the brain. The biphasic nature of TBE reflects an initial spread of virus in peripheral tissues, eliciting a cytokine response, followed in some cases by viral penetration into the CNS and the establishment of a second neurological phase of the disease. BBB, blood-brain barrier; CNS, central nervous system. (Graphics by Patrik Kilian, adapted from Ruzek et al., 2013b).

large neurons of the anterior horns, medulla oblongata, pons, dentate nucleus, Purkinje cells, and striatum. Lymphocytic meningeal and perivascular infiltrates, plus microglial nodules, and neuronophagia are the predominant histological inflammatory reactions observed following TBEV infection of the brain (Fig. 4) (Gelpi et al., 2005, 2006).

3.1. Innate and adaptive immune responses against TBEV

The innate immune response is the first line of defense against any viral infection. This can be divided into an intrinsic intracellular response (e.g., mediated by type I interferon [IFN] responses) elicited by virus infection, and an innate extracellular response mediated by specialized immune cells (e.g., natural killer cells and antigen-presenting cells). Such an innate immune response is not specific to any one pathogen, but is rapid and necessary for downstream activation of pathogen-specific adaptive immune responses. Such adaptive immune responses combine antibody-associated humoral responses with cell-mediated responses involving T cells, and provide for long-term immune memory. Together these responses can clear TBEV infection.

3.2. Innate immune responses

3.2.1. Interferon responses

All nucleated cells can mount an innate immune response upon infection. This response is initiated by the recognition of pathogen-associated molecular patterns (PAMPs), which are conserved proteins or molecules specific to pathogens (Pichlmair and Reis e Sousa, 2007). These PAMPs include double-stranded RNA (dsRNA), which is a replication intermediate of RNA and DNA viruses (Weber et al., 2006), or 5′-triphosphate RNA which is a hallmark of most negative (anti-sense) ssRNA viruses (Habjan et al., 2008). The PAMPs are recognized in the cell by pattern recognition receptors (PRRs), which are classified

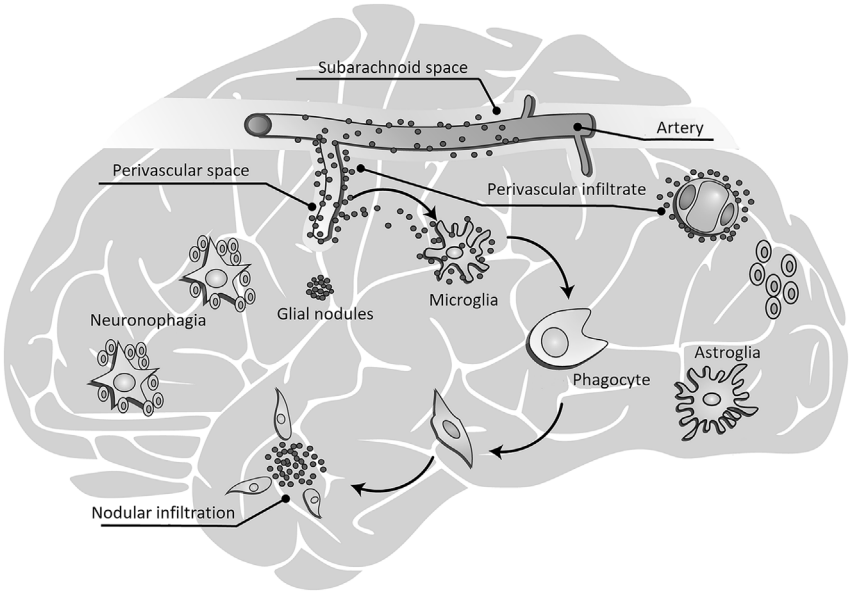

Fig. 4. Inflammatory histopathological changes in the TBEV-infected brain. Lymphocytic meningeal and perivascular infiltrates, microglial nodules, and neuronophagia are the predominant histological inflammatory reactions. (Graphics by Patrik Kilian, used with permission).

according to their intracellular localization, ligand specificity, and function. The most prominent PRRs that recognize RNA viruses are Toll-like receptors (TLRs) located in endosomes and the plasma membrane or the cytoplasmic retinoic-acid-inducible gene I (RIG-I)-like receptors (RLRs; RIG-I and melanoma differentiation-associated gene 5 [MDA5]) (Pichlmair and Reis e Sousa, 2007). Activated PRRs initiate a downstream signaling cascade that results in the activation of interferon regulatory factor 3 (IRF3) and the production of IFN.

IFN Type I (IFNα and β) and IFN type II (IFNγ) are the most well-studied interferons. Type I IFNs are expressed by most cells following viral infection, after which secreted IFNα and β bind to the IFNα receptor (IFNAR), a heterodimer of IFNAR1 and 2. IFN binding activates tyrosine kinases Jak1 and Tyk2, which then phosphorylate signal transducer and activator of transcription (STAT)-1 and STAT2 proteins, resulting in activation and translocation of the Interferon-stimulated gene factor 3 (ISGF3) into the nucleus. This results in the transcriptional activation of hundreds of IFN-stimulated genes (ISGs) encoding proteins that can either amplify IFN responses (e.g., PRRs and IRFs), modulate IFN responses (e.g., suppressor of cytokine signaling [SOCS]), or target the invading pathogen (e.g., antiviral effector proteins) (Schneider et al., 2014).

For TBEV, it is not clear which PRRs are dominant. For the RLRs, RIG-I is important (Miorin et al., 2012), but the involvement of MDA5 cannot be ruled out, as it has been shown to be important for other flaviviruses (Fredericksen et al., 2008; Loo et al., 2008). Upon RNA ligand binding to MDA5/RIG-I, a conformational change occurs that facilitates the association between PRRs and adaptor proteins such as IFNβ promoter stimulator 1 (IPS-1, also known as MAVS, VISA, or CARDIF). This interaction activates the transcription factors IFN regulatory factor 3 (IRF3), IFN regulatory factor 7 (IRF7), and NF-κB. IRF3 and IRF7 become phosphorylated and form homodimers and heterodimers, which translocate into the nucleus to activate the transcription of IFN. After TBEV infection, IPS1 is crucial for IFNβ upregulation both *in vitro* and *in vivo* (Kurhade et al., 2016; Overby et al., 2010). As mouse embryonic fibroblasts (MEFs) lacking IPS1 are more susceptible to TBEV and are unable to induce IFNβ transcription (Overby et al., 2010), mice deficient in IPS1 succumb to LGTV and TBEV infection earlier, with lower systemic IFNα levels and higher viral loads (Kurhade et al., 2016) resulting in earlier neuroinvasion. In the CNS, IPS1 expression appears important for controlling viral spread and replication (Kurhade et al., 2016; Zegenhagen et al., 2016a, 2016b), indicating a very important role for RLRs in the type I IFN response in TBEV infection. Upregulation of IFNβ after TBEV infection has also been shown to be highly dependent on IRF3 expression (Overby et al., 2010). IRF3 dimerizes and translocates into the nucleus upon TBEV infection, but this occurs quite late in infection, resulting in late IFNβ production (Overby et al., 2010; Miorin et al., 2012). The reason for this is that the TBEV replication complexes and dsRNA produced by the virus during replication are hidden away from cellular PRRs in vesicular structures, making them inaccessible early in infection (Overby et al., 2010; Overby and Weber, 2011).

Very little is known about the importance of TLRs in TBEV infection. TLR3 is present in different types of glial cells in the CNS, and its expression is upregulated during inflammation. Several studies of TLR3 polymorphisms have concluded that functional TLR3 is a risk factor for severe TBE (Mickiene et al., 2014; Kindberg et al., 2011); however, the underlying mechanism behind is not clear. Since TBE is at least partly immunologically driven, it is possible that an impaired TLR3 response attenuates immunopathological reponses and thus a more severe disease (Kindberg et al., 2011). Only TLR7 has been investigated in the context of LGTV infection in a mouse model. TLR7-deficient mice have higher viral loads in the CNS and lower levels of pro-inflammatory cytokines after LGTV infection. Although primary neurons have not been found to exhibit different infection rates, the TLR7-deficient neurons had higher levels of IFNβ (Baker et al., 2013), indicating that TLR7 may be important for regulating neuroinflammation.

After secretion, IFN binds to the IFNAR, a key receptor molecule in the IFN type I responses. In its absence, cells are unable to upregulate ISGs. For many viruses, mice deficient in the IFNAR have been shown to be highly sensitive to viral infections (Muller et al., 1994). For instance, Weber et al. have shown that LGTV and TBEV replicate uncontrollably and that mice lacking the IFNAR die very quickly (Weber et al., 2014). The IFNAR is important in controlling and limiting LGTV replication in all cell types, including hematopoietic, stroma, and neuroectodermal cells, plus cells in the periphery. Astrocytes within the brain are resistant to TBEV replication due to their ability to mount a fast IFN type I response. IFNs secreted from astrocytes can prevent infection of neurons and astrocytes already 3 and 6 h post infection, respectively (Lindqvist et al., 2016). On the other hand, IFNAR-deficient astrocytes are sensitive to infection. As this response is so strong and important, natural selection has favored the evolution of viruses that are able to block IFN signaling. LGTV and TBEV do this by expressing the NS5

protein, which interferes with the phosphorylation of Jak1 and Tyk2 and subsequent STAT1/2 phosphorylation (Best et al., 2005; Werme et al., 2008). In addition, NS5 has been shown to block the transportation and maturation of the IFNAR1 subunit to the plasma membrane (Lubick et al., 2015), ensuring a reduced antiviral response within infected cells.

The antiviral effector proteins responsible for the strong antiviral effect of IFNs are the ISGs, that can target most steps of the viral life cycle, therefore there is some functional redundancy between the different proteins (Schneider et al., 2014; Schoggins and Rice, 2011). For TBEV, two critical antiviral proteins have been identified thus far: the murine tripartite motif 79α (TRIM79α) protein and the virus inhibitory protein, endoplasmic reticulum-associated, interferon-inducible (viperin) protein (Taylor et al., 2011; Upadhyay et al., 2014; Vonderstein et al., 2017). TRIM79α directly targets viral NS5 for lysosomal degradation and seems to be specific for TBEV and LGTV, since mosquito-borne flaviviruses are not affected (Taylor et al., 2011). On the other hand, viperin appears to be a broad-spectrum antiviral protein that inhibits many different viruses from different families, including DNA viruses (Chin and Cresswell, 2001), negative (anti-sense) ssRNA viruses (Wang et al., 2007), retroviruses (Nasr et al., 2012), and positive (sense) ssRNA viruses (Helbig et al., 2011; Szretter et al., 2011; Teng et al., 2012; Upadhyay et al., 2014). Viperin seems to target TBEV in two different ways. First, it inhibits positive-sense ssRNA replication by interacting with and degrading the viral NS3 protein via the proteasome (Upadhyay et al., 2014; Panayiotou et al., 2018). Second, it targets viral assembly by interacting with the cellular protein Golgi Brefeldin A resistant guanine nucleotide exchange factor 1 (GBF1), a key protein in the cellular secretory pathway. The interaction of GBF1 with viperin induces capsid particle release from cells (Vonderstein et al., 2017).

3.2.2. NK and antigen-presenting cells

Another branch of the innate immune system includes natural killer (NK) and antigen-presenting cells. NK cells are large granular cells that limit viral infection by killing infected cells during early stages of infection. The direct killing of infected cells is primarily mediated by perforin and granzyme release, as well as the production of several pro-inflammatory cytokines, including IFNγ and tumour necrosis factor α (TNFα) (Jost and Altfeld, 2013). The role of NK cells in TBEV infection is largely unknown. One study demonstrated a decrease in perforin and granzyme B expression in activated NK cells from TBE patients, indicating that cytotoxic granules are released early in NK cell activation, possibly contributing to the pathogenesis of infection (Blom et al., 2016). Furthermore, low pathogenic TBEV strains were shown to activate NK cells post *ex vivo* infection of whole blood cells, whereas highly pathogenic TBEVs were shown to inhibit NK activation, which may be one way that the virus suppresses the innate immune system (Krylova et al., 2015). Tick saliva may also contribute to suppressing NK cell activity, since salivary gland extracts from ticks have been shown to decrease NK cell activity *in vitro* (Kubes et al., 1994).

NK cells do not seem to be the only cells affected by tick saliva, since saliva from *I. ricinus* inhibits dendritic cell (DC) maturation. Treatment of TBEV-infected DCs with tick saliva was found to increase the proportion of virus-infected cells and decrease the virus–induced expression of TNFα and Interleukin-6 (IL-6) (Fialova et al., 2010). Immature DCs are among the first cells to recognize infection and may be among the first infected after a tick bite. Immature DCs migrate to the lymphoid tissue and undergo maturation and antigen presentation to activate naïve T cells in order to shape the adaptive immune response. DCs bridge the innate and adaptive immune responses, partly by the production of IFN type I, inducing co-stimulatory molecules CD40, CD80, and CD86, MHC class I and MHC II, and cytokine Interleukin-12 (IL-12) in addition to ISG effector proteins (Steinman and Hemmi, 2006). One study has shown that the infection of DCs with LGTV and TBEV *in vitro* inhibits DC maturation and selective inhibition of IL-12 secretion, reducing T cell proliferation (Robertson et al., 2014). These findings indicate that the interplay between TBEV and the immune system is a balancing act, and successful establishment of viral infection requires reduced and altered activation on many levels. Notably, TBEV strains differ regarding the characteristics of their interactions with DCs in terms of the replication in these cells, virus dose triggering IFNα production, and the impact on DC maturation (Shevtsova et al., 2017).

3.3. Adaptive immune response

3.3.1. Humoral immunity

Immunity elicited by natural infection with TBEV is known to confer lifelong protection against TBE due to the long-lasting presence of virus-neutralizing antibodies (Holzmann, 2003; Remoli et al., 2015). In TBE patients, TBEV-specific IgM and IgG can be found in serum and cerebrospinal fluid (CSF). However, the intensity and duration of antibody production in serum and CSF do not correlate with disease severity (Günther et al., 1997). At the time of the first CNS symptoms, TBEV-specific IgM, and often IgG, is present in serum; CSF TBEV-specific IgM starts to increase between day 0 and day 6, reaching peak concentration approximately 14 days after the onset of CNS symptoms (Holzmann, 2003). However, large variations in the kinetics of the antibody response are seen in individual patients (Günther et al., 1997). TBEV-specific IgM persists for 6–7 weeks post-infection. In some rare cases IgMs can be detected for several months, or even years, even if there are no persisting neurological symptoms (Krylova et al., 2015). IgG levels increase only moderately during the CNS phase of the infection, peaking in both serum and CSF approximately 6 weeks after the onset of the first neurological symptoms (Holzmann, 2003; Günther et al., 1997; Dörrbecker et al., 2010); however, their presence in serum is long-lasting, or even lifelong, conferring immunological protection to the host.

The antibody response to TBE is targeted primarily against the E and NS1 proteins of TBEV and is critically important in controlling and clearing the infection. Both TBEV-neutralizing antibodies (mainly against E) and in part non-neutralizing antibodies (against NS1 or prM) can prevent development of disease post viral infection (Gould et al., 1986; Schlesinger et al., 1985; Iacono-Connors et al., 1996; Kreil et al., 1998a). Passive administration of human or mouse monoclonal or polyclonal TBEV-specific antibodies (against E protein) can protect mice against an otherwise highly lethal challenge with TBEV (Kreil and Eibl, 1997; Elsterova et al., 2017). However, although TBEV-neutralizing antibodies provide protection against the disease, they do not prevent localized infections in the host (Kreil et al., 1998b), even though rapidly cleared. Interestingly, infectious TBEV can be recovered from infected mice, which were passively protected by TBEV-specific antibodies, indicating that short-term, low-level virus replication occurs in passively protected mice. These challenged animals develop an antibody response, which is predominantly specific for NS1, which is a sign of active virus replication (Kreil et al., 1998a). Similarly, an anti-NS1 antibody response is observed in mice vaccinated with whole-killed TBEV vaccine and challenged with a lethal dose of TBEV (Kreil et al., 1998b). In this regard, TBEV-specific antibodies are not necessarily associated with sterilizing immunity (i.e., extensive neutralization of the virus inoculum), but antiviral defense mechanisms other than antibodies are also involved (Kreil et al., 1998a,b; Chambers and Diamond, 2003). However, it should also be noted that some E-specific monoclonal neutralizing antibodies do protect *in vivo* when administered passively whilst others do not necessarily provide any protection. Different strains of the virus may react differently in these tests. Thus a single monoclonal antibody might (i) neutralize the virus *in vitro* and provide protection *in vivo*, or (ii) neutralize the virus *in vitro* but fail to protect against the disease/death *in vivo*, or (iii) provide protection *in vivo* but fail neutralize the virus *in vitro* depending on the particular flavivirus or strain of flavivirus concerned (Iacono-Connors et al., 1996; Gould and Buckley, 1989; Gould et al., 1986).

Most neutralizing antibodies recognize the viral E protein, and a subset of neutralizing epitopes are also found on the prM protein (Chambers and Diamond, 2003). There are several possible mechanisms by which antibodies can neutralize the virus, such as direct neutralization of receptor binding, post-binding/pre-fusion neutralization inside endosomes, and Fc receptor-mediated clearance by cells of the reticuloendothelial system (Chambers and Diamond, 2003; Marasco and Sui, 2007). A recent study investigated the molecular mechanisms underlying TBEV neutralization by IgG monoclonal antibody 19/1786. The antibody blocked the low-pH-triggered structural changes in E protein, and reorganization of this protein from dimer to trimer as required for the fusion between viral and endosomal membranes during virus entry. This resulted in a delay or actual prevention of viral nucleocapsid penetration of target-cell cytoplasms (Füzik et al., 2018).

Non-neutralizing, yet protective, antibodies that target the NS1 protein are also known (Timofeev et al., 1998; Kreil et al., 1998a). Such anti-NS1 antibodies are thought to mediate the lysis of TBEV-infected cells via the presentation of NS1 on cell surfaces leading to cell death by complement or antibody-dependent cell-mediated cytotoxicity (Chambers and Diamond, 2003; Kurane et al., 1984). Otherwise, antibodies bound to TBEV particles can mediate the attachment and endocytosis of these complexes by Fcγ receptor-bearing cells, such as monocytes, macrophages or DCs, causing subsequent antibody-dependent enhancement (ADE) of infection (Haslwanter et al., 2017; Phillpotts et al., 1985; Kopecký et al., 1991). However, the same antibodies that enhance TBEV replication in mouse peritoneal macrophages *in vitro* were found protective against lethal TBEV infection in mice (Kreil and Eibl, 1997). Neither sublethal TBEV challenge nor suboptimal dilutions of the immunoglobulins, even if applied together, have provided any indication of antibody-enhanced disease occurring *in vivo* (Kreil and Eibl, 1997). Therefore, the antibody-mediated enhancement of infectivity during TBE lacks clear *in vivo* proof. However, the situation does remain somewhat controversial since *in vivo* studies on Langat virus, louping ill virus as well as yellow fever virus and JEV all demonstrate antibody-enhanced disease (Webb et al., 1968; Gould and Buckley, 1989).

3.3.2. Cellular immunity

Research on animal models as well as in human patients indicates that both humoral and cellular immunity are usually required to clear TBEV infection from a vertebrate host. Infection in the CNS leads to the recruitment of T cells, therefore infected neurons are potential targets for cytotoxic T cells. Studies in mice have revealed that the number and activation level of T cells in the brain has no impact on the outcome of infection, but differences were found between recovering and dying mice in terms of the accumulation of specific T cell clones in brain tissue (Fujii et al., 2011). By contrast, only a poor topographic correlation was reported between inflammatory changes in post-mortem human brains (consisting primarily of T cells and macrophages/microglia) and the distribution of viral antigen (Gelpi et al., 2005, 2006). As early as the 1970's and 1980's under certain conditions, immune responses were found activated in parallel with virus-mediated damage of host tissue (reviewed in Ruzek et al., 2010). Consistent with these observations, pharmacological immunosuppression was shown to prolong the mean survival time of infected mice for 5 days (Semenov et al., 1981; Vince and Grcevic, 1981). Furthermore, adoptive transfer of sensitized splenocytes to immunosuppressed mice significantly decreased the mean survival time of infected animals (Semenov et al., 1981). However, this immunopathological effect was only observed when splenocytes were introduced to mice at later time points post-infection. If the splenocytes were adoptively transferred on the day of infection, the mean survival time increased, suggesting a protective role of immune responses early stage peripheral infection, even though immunopathology is still generated post CNS infection (Semenov et al., 1981). There again, immunosuppression of mice with sublethal X-ray irradiation appears to reduce the development of cellular immune infiltrations to the CNS following TBEV inoculation thereby significantly delaying the onset of disease symptoms compared to the situation with non-irradiated TBEV-infected mice (Vince et al., 1972). Similarly, recent data indicate that SCID or CD8 knockout mice infected with TBEV have longer mean survival times compared to TBEV-infected immunocompetent controls, though infection is ultimately fatal in all groups (Ruzek et al., 2009).

Mechanistically speaking, adoptive transfer of $CD8^+$ T-cells into TBEV-infected SCID mice was found to decrease the mean survival time, suggesting that $CD8^+$ T cells contribute to immunopathological reactions in the infected brain. However, if the mice were infected with a low-pathogenic strain, $CD8^+$ T cells appeared instead to contribute to increased survival (Ruzek et al., 2009). These data support the notion that T cells have both protective and immunopathological roles, although the division between these two roles is unclear. The virulence/pathogenicity of a particular strain, the infectious dose, the immunological status of the host, and even the host genotype may influence the pathogenesis of the disease and determine whether or not T cell responses are protective or pathological during TBE. Nevertheless, in mild TBE cases, the immune response appears substantially protective. Indeed, $CD8^+$ T cell-mediated cross-protection has been demonstrated between different flaviviruses (Wen et al., 2017). Therefore, T-cell mediated cross-immunity might also arise amongst strains of TBEV and such interactions might have relevance to vaccine performance against different strains (for instance comparing European versus Russian viruses and vaccines, and also vaccination efficacy in those parts of Europe where the Asian and European TBEV strains overlap geographically).

Little is known about the role of $CD4^+$ T cells during TBE, though experimental models indicate a requirement for such cells in protection against acute flavivirus infections (Chambers and Diamond, 2003). $CD4^+$ T cells are thought to control viral infections through several mechanisms, such as the priming of neutralizing antibody production and sustaining $CD8^+$ T cell responses (Aberle et al., 2015), the production of inflammatory and antiviral cytokines, direct cytotoxic effects on infected cells through Fas-Fas ligand or perforin-dependent pathways, and in promoting immune memory responses (Sitati and Diamond, 2006). Adoptive transfer of $CD4^+$ T cells into TBEV-infected SCID mice prevents the development of lethal TBE, though the mechanism is not yet clear; it is probably based on $CD4^+$-mediated secretion of IFN-γ and other pro-inflammatory cytokines and/or the stimulation of macrophage-like cells (Ruzek et al., 2009).

4. TBE in humans

Clinical case definitions and criteria for diagnosis of TBE in Europe are presented in Table 1. Details of methods used in TBE diagnosis are outside the scope of this article, but are reviewed by Ergunay et al. (2016). The incubation period of TBE post-infection ranges from 2 to 28 days, most commonly between 7 and 14 days. Shorter lead time of 3–4 days to clinical symptoms is seen in the case of foodborne infections (Zajkowska and Czupryna, 2013; Kaiser, 2012; Hudopisk et al., 2013). TBEV infections and resulting TBE are categorized with a first viremic phase, which can progress to a second (neurological) phase (Smorodintsev and Dubov, 1986). The virus spreads systemically during the first phase, producing fever and other symptoms, such as headache, fatigue, myalgia, anorexia, nausea, and/or vomitting. In some patients, there is no virus invasion of the CNS and the disease terminates after the first phase (monophasic disease). In others, virus does penetrate the CNS, and there is a second phase of illness, with neurologic signs and symptoms (biphasic TBE). In the first phase, TBEV can be detected in blood samples by RT-PCR (Saksida et al., 2018), while patients during the neurological phase are diagnosed serologically (Table 1, Ergunay et al., 2016).

TBE is typically an acute disease and progression may even terminate after the first phase and go no further. This clinical pattern is

Table 1
Clinical case definitions of TBE/criteria for the diagnosis of TBE in Europe (Taba et al., 2017). The table combines diagnostic criteria for confirmed and probable cases based on EU decisions. A case is defined by the presence of clinical signs, epidemiological links, pleocytosis ($> 5 \times 10^6$ cells/l), and recent TBEV infection, as demonstrated by the presence of specific serum IgM and IgG. Probable cases are defined as patients (i) meeting the clinical criteria, having pleocytosis and detectable TBEV-specific IgM in a single serum sample, or (ii) meeting the clinical criteria, with an epidemiological link, and having pleocytosis. CNS, central nervous system; CSF, cerebrospinal fluid; Ig, immunoglobulin.

	Confirmed TBE	Probable TBE	
Clinical criteria	Symptoms of CNS inflammation: meningitis, meningoencephalitis, or encephalomyelitis	Symptoms of CNS inflammation: meningitis, meningoencephalitis, or encephalomyelitis	Symptoms of CNS inflammation: meningitis, meningoencephalitis, or encephalomyelitis
Epidemiological link	Yes	Yes	No
CSF findings	Pleocytosis $> 5 \times 10^6$ cells/l	Pleocytosis $> 5 \times 10^6$ cells/l	Pleocytosis $> 5 \times 10^6$ cells/l
Microbiological/ serological criteria	TBE-specific IgM *and* IgG antibodies[a] in serum; *or* TBE-specific IgM antibodies in CSF; *or* seroconversion or 4-fold increase in TBE-specific IgG antibodies in paired serum samples; *or* detection of TBE viral nucleic acid in a clinical specimen	No	TBE-specific IgM antibodies in a single serum sample

[a] The antibodies used in the ELISA methods are cross-reactive with other flaviviruses. In patients immunized against TBE, intrathecal synthesis of TBEV-specific antibodies in the CSF should be shown.

termed 'abortive'. This abortive form of TBE may be asymptomatic or manifest in a mild febrile illness including headache, fever, fatigue, myalgia, anorexia, nausea, and vomiting. There is no progression to any form of encephalitis (Bogovic et al., 2010). The term monophasic is used to describe TBE which terminates after the first phase but manifests itself in a mild febrile illness during disease progression.

At least one-third of TBE patients develop full second phase neurological symptoms. TBE cases with neurological symptoms are reported mandatorily in the majority of endemic countries (ECDC technical report 2012). Second (neurological) phase TBE can be further classified into meningeal and focal forms (i.e., TBE with brain damage leading to paresis and/or paralysis). These focal forms may be differentiated as meningoencephalitis, meningoencephalomyelitis, and encephaloradiculitis based on the leading, most functionally significant syndrome observed (Smorodintsev and Dubov, 1986; Ammosov, 2006; Lobzin et al., 2015). In some TBE patients, TBEV can persist active in the CNS for an extended time, and the infectious process continues unabated. In this case, TBE becomes a chronic (progressive) disease (Pogodina et al., 1986; Smorodintsev and Dubov, 1986; Lobzin et al., 2015).

Epidemiological studies and epidemiological benchmarking data have certain limitations with TBE. The frequency of asymptomatic TBEV infections has been estimated as between 70 and 98% of total infections on the basis of published data (Bogovic and Strle, 2015). In one highly endemic region of Sweden, 88 of 745 subjects had TBE antibodies, and of those 88 seroconvertants, only 23 (26%) had a substantive history consistent with TBE-induced CNS disease (Gustafson et al., 1993). However, overall the fatality rate in Europe is certainly < 2% (Kaiser, 2012; Lindquist and Vapalahti, 2008; Borde and Zajkowska, 2017). Indeed, the annual TBE epidemiological report for 2015 published in 2018 by the ECDC indicated a fatality rate of only about 0.2% (five deaths among 1908 confirmed TBE cases). These probably represent the most reliable current data on fatality rates and epidemiology, despite variations in TBE definitions in different European countries. The number of asymptomatic TBEV-Sib and TBEV-FE infections has similarly been estimated as between 70 and 95% of total infections (Gritsun et al., 2003b), although up to 50% of infections in the Far East resulted in some kind of monophasic TBE (Leonova et al., 2013).

4.1. Asymptomatic infection, febrile form of TBE

Seroprevalence studies from highly-endemic regions indicate that a significant proportion of TBEV infections remain asymptomatic (Gustafson et al., 1992; Gustafson et al., 1993; Bogovic and Strle, 2015; Leonova et al., 1996). As noted above, the number of asymptomatic TBEV infections has been estimated as between 70 and 98% of total infections (Kaiser, 2008; Gustafson et al., 1992; Bogovic and Strle, 2015). However, a serological survey conducted in the Czech Republic, in a highly endemic TBEV focus, revealed a ratio of 6.07:9.64 manifest TBE cases to asymptomatic seroconvertants, i.e. suggesting that approx. 40 % of TBEV infections resulted in some form of illness (Lunácková et al., 2003).

The first phase lasts for 2–4 days (range 1–8 days) and manifests as a mild febrile illness including headache, fever, fatigue, myalgia, anorexia, nausea, and vomiting. In this case, a patient's body temperature quickly reaches 38–39 °C and fever lasts from a few hours to several days. (Bogovic and Strle, 2015). The first phase is followed by clinical amelioration or an interval without any symptoms for up to 1 week (range 1–21 days). Up to 46% of patients with the first clinical phase of TBE may go on to experience a second phase of TBE and develop long-term sequelae (Bogovic and Strle, 2015).

4.2. Neurological forms of TBE

The asymptomatic period between the first and second (neurological) phase lasts for an average of 8 (range 1–20) days. The second (neurological) phase of TBE begins with increased body temperature, 1–2 °C higher than peak temperatures in the first phase, frequently exceeding 40 °C (i.e., fever resolves after the first phase, but then returns at the beginning of the second phase of the disease). The clinical course of acute, second-phase TBE can be classified as mild, moderate, or severe. The disease involves the CNS, with meningitis or focal forms: meningoencephalitis, meningoencephalomyelitis or encephaloradiculitis, characterized by lesions in the CNS. Specific areas of the brain can be affected by virus replication and/or neuroinflammation, resulting in movement disorders (Zajkowska et al., 2013; Lenhard et al., 2016). In Russia, data on the relative frequency of different forms of TBE differ significantly between regions. In all regions, except the Far East, meningoencephalitis is registered less frequently than the meningeal form. Apparently, these data are very dependent on the level of registration of mild forms of the disease, which in turn is a function of available diagnostics, access to medical care (when patients live far from medical centres) and the general health of the population.

4.2.1. Meningitis

Meningitis is associated with headache, nausea, vomiting, vertigo, eye pain, photophobia and nuchal rigidity. Approximately 10% of patients without meningeal signs show pleocytosis in the CSF. Patients feel weak and sluggish, have stiff neck muscles and Kernig and Brudzinsky signs are observed. A moderate increase in lymphocyte count and increased protein concentrations in the CSF are detected. Intracranial pressure is increased. CSF changes that occur during the acute period of the disease may persist long-term, even during recovery.

Fever typically lasts 7–14 days. In pediatric TBE patients, fever without neurological symptoms is the chief complaint (Kaiser, 2012; Zajkowska and Czupryna, 2013; Bogovic and Strle, 2015).

4.2.2. Meningoencephalitis

Meningoencephalitis is observed in about 50% of adult TBEV-infected individuals with neurological symptoms. This form of TBE is severe and more often lethal compared to meningitis. Patients feel weak, sluggish, and sleepy, and complain of severe headache, nausea, and vomiting. Stiff neck muscles and Kernig and Brudzinsky signs are observed. Patients may have delusions, hallucinations, psychomotor agitation with loss of orientation in place and time, and epileptic seizures. The altered mental state can range from somnolence to coma. Disorientation, excitation, seizures and confusion may also be observed, as well as hyperkinesia of the limbs and facial muscles. Cranial nerve involvement with paresis of the facial and ocular nerves, cerebellar ataxia, and autonomic disturbances are frequently diagnosed. Spinal nerve paralysis has been documented in about 4% of neurologic TBE patients. Severe myalgia of the extremities sometimes precedes paresis. Involvement of the cranial nerve nuclei and spinal cord motor neurons results in flaccid paralysis of the neck and upper extremity muscles (Mickienė et al., 2002).

With *diffuse meningoencephalitis*, cerebral disorders, such as consciousness disorders and epileptic seizures, are typical. Scattered focal lesions in the brain manifest as pseudobulbar disorders and cardiovascular system dysfunction. Fibrillation (twitching) of facial limb muscles, hand tremor, suppression of deep reflexes, and decreased muscle tone are also observed. In the case of a favorable outcome, consciousness becomes clear in 2 weeks (Lenhard et al., 2016; Lobzin et al., 2015). With *focal meningoencephalitis*, clinical presentation is determined by the location of damage to the brain. Using MRI, one of the two cerebral hemispheres shows damage with spasmodic paresis of the right or left extremities, and paresis of the facial and IX cranial nerve (glossopharyngeal nerve) may develop on the same side. When the process is localized in the left hemisphere, speech problems occur. If white matter is damaged in the brain stem, so-called alternating syndrome develops, which manifests as cranial nerve paresis on the side of the inflammatory focus and limb paresis on the opposite side of the body. Among the affected cranial nerves are the III, IV, V, and VI pairs, and somewhat more often cranial nerve VII, IX, X, XI, and XII pairs, resulting in paresis of the soft palate, slurred speech, aphonia, inability to swallow, tachycardia, and dyspnea. CSF tests performed in the acute period reveal lymphocytosis and increased protein content. Therefore, when it comes to the severe encephalitic form of the disease, the focal CNS lesions are revealed in addition to cerebral and toxic syndrome manifestations (Lobzin et al., 2015).

4.2.3. Meningoencephalomyelitis

Patients with meningoencephalomyelitis (polio-like) may experience paresis of the arms, back, and legs, symmetrically affecting the musculature of the neck, shoulder girdle, upper limbs, and sometimes the intercostal muscles and diaphragm. The upper extremities are affected more often than the lower extremities. A characteristic of such patients is “floppy head” or “dropped head” syndrome, in which the patient cannot hold their head in a vertical position, so their head hangs passively (Panov, 1956). Involvement of the medulla oblongata and central parts of the brainstem indicate a poor prognosis. Cranial nerve involvement is associated mainly with ocular, facial, and pharyngeal motor dysfunctions. Occasionally, TBE can be linked to autonomic dysfunction, including reduced heart rate variability and tachycardia. Flaccid paralysis with mono-, para-, or tetraparesis develops in 5–10% of second (neurological) phase TBE patients. Furthermore, respiratory muscle paralysis may develop, resulting in respiratory failure, making respiratory support essential; a risk of sudden respiratory and circulatory failure is sometimes present (Kaiser, 2012; Lindquist and Vapalahti, 2008). Motor disorders gradually develop in patients over the course of 7–12 days, and atrophy of the affected muscles develops by the end of week 2–3 of the disease.

4.2.4. Encephaloradiculitis or the polyradiculoneuritic form

The polyradiculoneuritic form of TBE is relatively rare (up to 3% of clinical TBE reported in Russia; however, not all physicians classify polyradiculoneuritis as a separate form of TBE). In addition to general transient febrile and meningeal symptoms, patients develop signs of damage to the roots and peripheral nerves, which manifests as paresthesia in the form of the “crawling ants” sensation, tingling in various areas of the skin, pain along the nerve trunks, Lasègue's sign (the straight leg raise), Wasserman symptoms (a condition caused by irritation of the femoral nerve, which runs along the upper-outer thigh), and polyneurial type sensitivity disorders (“gloves” and “socks” type) in distal segments of the extremities. Flaccid paralysis usually begins with the legs and spreads to the musculature of the trunk and hands. The process may begin with the muscles of the shoulder girdle, affecting neck muscles.

4.2.5. Chronic (progressive) disease

Many patients with neurologic forms of TBE resolve their acute illness, but are left with chronic sequelae of infection. In contrast, some patients show evidence of a continuing disease, which is described as chronic (progressive) TBE. The chronic form is reported in Russia, where it represents 1–3% of cases, but virtually no cases of this form have been seen in Europe. Russian clinicians divide chronic TBE into persistent, relapsing, and progressive forms of the disease. In patients with chronic infection, focal CNS lesions are observed during later periods of the disease, weeks or even months after the body temperature drops to normal levels during a period of convalescence (Pogodina et al., 1986; Smorodintsev and Dubov, 1986; Lobzin et al., 2015). Chronic infection can occur in a latent form and manifest after several months or years under certain circumstances (hypothermia, physical or psychological trauma, overwhelming physical labor, alcohol intoxication, abortion, labour or even physiotherapy) or may manifest as a continuously progressive form with anincrease in focal CNS lesions, leading to patient death (Shapoval, 1976). An early sign of the disease is headache, which increases in intensity as the disease progresses. CSF tests continue to show signs of inflammation, and blood tests reveal moderate increases in the erythrocyte sedimentation rates (ESR) and mild leukocytosis, usually with a shift towards absolute or relative lymphocytosis. The duration of the disease course ranges from 1 to 20 years or more. In 17% of cases, chronic forms result in death between 9 and 20 years post infection (Umansky, 1977).

Our understanding of chronic TBE is based on long-term persistence of TBEV in patients who showed clear symptoms of disease for several years, decades, or their entire life. This includes patients with a clinical diagnosis of hyperkinetic syndrome, Kozhevnikov epilepsy, amyotrophic lateral sclerosis, epidemic encephalitis, arachnoencephalitis, syringomyelia, and progressive polyencephalomyelitis, among others (Umansky, 1977; Ammosov, 2006; Lobzin et al., 2015). In some chronic and focal forms of TBE, a form of epilepsy develops, known as Kozhevnikov epilepsy, which was first described by A. Kozhevnikov in 1894, half a century before the discovery of TBEV (Lobzin et al., 2015). Kozhevnikov epilepsy typically begins with local convulsive twitching of the muscles of the paretic limbs, usually the hand muscles. Occasionally, the local muscle twitching can be multi-focal, affecting the muscles of the hand, face, and feet. Seizures are characterized by asynchrony and irregularity. The second sign of Kozhevnikov epilepsy is generalized convulsive seizures, which, as a rule, are rare. After a seizure episode, the patient's paresis may worsen. On the other hand, hyperkinesis may decrease (Shapoval, 1976). After the discovery of TBEV, researchers suggested that patients with Kozhevnikov epilepsy syndrome have long-term persistence of TBEV in the CNS (Chumakov et al., 1944). This assumption was later confirmed in experiments using fluorescent antibodies and isolating the virus from lesions in laboratory

animals (Frolova et al., 1982). It is also interesting to note that the postmortal brain sample of Professor M. P. Chumakov, who underwent a severe form of TBE in 1937 and died in 1993, was positive for TBEV RNA (Pogodina, 2009).

Chronic forms of TBE are described following infection by TBEV-FE and -Sib, although it is believed that the Sib subtype produces chronic disease more often (Pogodina, 2005). There is a whole set of strains isolated from the blood or CSF of patients with chronic TBE, for example, strains Aina and Zausaev. Comparison of these strains with those isolated from patients with acute TBE did not show unambiguous differences (Gritsun et al., 2003a; Pogodina et al., 2004a,b; Sobolev et al., 2010).

4.2.6. Hemorrhagic form

In the last few years, sporadic cases of hemorrhagic TBE have been reported in the Asian part of Russia. A hemorrhagic syndrome during TBE was documented for the first time in the Novosibirsk Oblast of Siberia in 1999, when eight fatal cases were observed (Ternovoi et al., 2003). The latent period was 5–26 days (average 12.8 days). Disease onset included typical clinical symptoms of TBE, such as fever, myalgia, and malaise, then was followed by severe viral encephalitis accompanied by loss of consciousness, paresis, and paralysis. Hemorrhagic signs developed as massive gastrointestinal bleeding and local hemorrhages on the mucosa and skin. The first sign of the hemorrhagic syndrome was the presence of erythrocytes in the urine on day 7 of the infection, which is not usual from TBEV infection. Common CNS manifestations occurred 3 days later. Despite intensive treatment, patients died 2–3 days after the massive hemorrhagic syndrome developed. The average time of death was 16 days after disease onset. Importantly, the presence of TBEV was confirmed by sequencing in six brain samples from the patients.

4.3. Post-encephalitic syndrome

TBE may cause persistent sequelae with significant consequences for daily activities and the quality of life. Studies suggest that 40–50% patients with TBE develop a post-encephalitic syndrome (Misić Majerus et al., 2009; Haglund and Günther, 2003; Bogovič et al., 2018). The most frequently reported signs are neuropsychiatric disorders, such as apathy, irritability, memory and concentration dysfunction, and altered sleep patterns. Sensory disturbances and persistent flaccid paresis or paralysis have been documented (Fig. 5), but which clinical details, if any at all, of the post-encephalitic syndrome are TBE-specific is still matter of debate (Schmolck et al., 2005). It should also be noted that risk factors for severe forms of the disease may not be identical with risk factors for the development of post-encephalitic syndrome.

4.4. Predisposition and risk factors

All age groups are at risk of infection with TBEV from an epidemiological perspective. Age, neurological signs at onset, and a low early IgM response in the CSF are risk factors for severe forms of TBE. A disease that progresses from a febrile syndrome to CNS manifestations without an intervening asymptomatic period, or a biphasic course with a prompt febrile onset and a short asymptomatic interval (rapid progression to the second neurological phase) have been associated with severe forms of TBE. Comorbidities and immunomodulating therapies are associated with severe clinical forms of TBE. Fatal outcomes after TBEV infection are reported in solid organ transplant recipients (kidney) and in patients with longstanding immunosuppressive therapy in the context of rheumatoid arthritis (Zajkowska et al., 2011; Lipowski et al., 2017). The potential role of genetic background in TBE is currently being studied. Most of the analyzed factors are part of the innate immune response to TBEV of the mammalian host. Select genetic predispositions to TBE or severe forms of TBE are polymorphisms in genes encoding C−C chemokine receptor type 5 (CCR5), TLR3, 2′-5′-oligoadenylate synthetase 2 (OAS2), 2′-5′-oligoadenylate synthetase 3 (OAS3), interleukin-28 (IL-28), interleukin-10 (IL-10), matrix metalloproteinase-9 (MMP-9), and CD209 (DC-SIGN) (Mickienė et al., 2014; Barkhash et al., 2010, 2012, 2013, 2016, 2018). Also, virological factors, such as dose and virulence of particular TBEV strain, may be important for the severity and long-term sequelae in TBE (Ruzek et al., 2008).

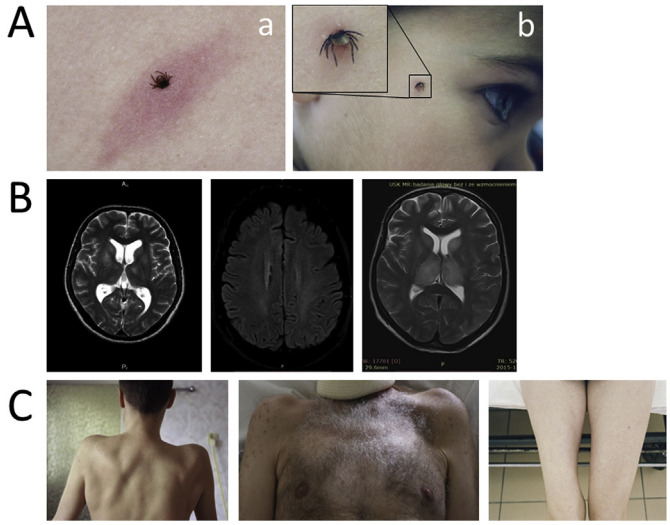

Fig. 5. TBE in humans. (A) Tick attachment. In most cases, TBEV is transmitted to humans via the bite of a TBEV-infected tick, mainly *Ixodes ricinus* in Europe and *Ixodes persulcatus* in Russia. (a) Tick bite with nonspecific skin reaction. Nonspecific reactions around the site of tick bite are common and usually disappear quickly, without any clinical significance. (b) Tick bite without any skin reaction. (B) The brain is the main target for TBEV in humans. MRI findings are usually normal in TBE patients, but MRI signal abnormalities can be seen in severe TBE cases. Examples of MRI lesions are shown. (C) Inflammation can affect the spinal cord and nerve roots. Examples of muscle atrophy as sequelae of radiculomyelitis are shown. All photographs belong to the authors.

4.5. Laboratory and clinical analyses

Leukocyte counts are low in the CSF of TBE patients with neurologic disease (median 60/μl, range 5–1200/μl) compared to other forms of viral or aseptic meningitis. This laboratory syndrome is very similar to the white blood cell findings in other flaviviral infections such as West Nile virus (WNV) or dengue virus (DENV) infection. Initially, there is a predominance of polymorphonuclear cells (granulocytes) in the CSF, but the immune response switches within a few days towards an increased lymphocytic cell count. Albumin is moderately increased in the CSF, and patients with TBE exhibit only moderate markers of inflammation in serum samples. At the time of hospital admission, TBE-specific IgM and IgG antibodies are usually present in serum and in CSF samples. Prior to the development of neurological signs and symptoms when serology is negative, RT-PCR can be used to detect viral RNA in blood/serum. RT-PCR can be, therefore, used as complementary method in TBE diagnostics (Veje et al., 2018; Saksida et al., 2005, 2018) However, during the first, febrile stage of the illness, specific tests are rarely performed.

4.5.1. Neuroimaging

Cranial and spinal magnetic resonance imaging (MRI) is the imaging standard for the evaluation of patients with any type of encephalitis, including TBE. However, only about 18% of neurologic TBE patients presenting with meningitis and encephalomeningitis have abnormalities in cranial MRI scans. These radiological findings are mainly located in the thalamus, cerebellum, brainstem, and nucleus caudatus

(Lenhard et al., 2016); (Bender et al., 2005) (Fig. 5). Cranial computed tomography (CCT) is usually negative and not recommended for the diagnosis of encephalitic brain lesions (Taba et al., 2017).

4.5.2. EEG

In acute CNS inflammation, the EEG shows pathological patterns. EEG may be of prognostic value regarding long-term sequelae or fatal outcomes when there is a persistence of pathological patterns or new irregularities (Juhász and Szirmai, 1993).

4.6. Prognosis and long-term sequelae

The fatality rate from infection with TBEV-Eu is < 2%. TBEV-FE strains are believed to cause a more severe form of the disease with high fatality rates (up to 20%). In lethal cases, death occurs within 5–10 days from the onset of neurological symptoms in the context of diffuse brain oedema and bulbar involvement (Kaiser, 2011). Up to 46% of patients experiencing the second (neurological) phase of TBE develop long-term sequelae (Bogovic and Strle, 2015) resulting in a high burden of disability. Recovery from acute TBE depends on the form of infection, as well as its severity. For febrile and meningeal forms, the outcome is mostly favorable, whereas adverse outcomes are recorded more often in polio-like and polyradiculoneuritis forms. The recovery period after the focal form of acute TBE is long, up to 2 years. Atrophic paralysis of the muscles is often partially restored, whereas sequelae related to the CNS damage persist for 1–2 years, and sometimes for life (Ammosov, 2006; Lobzin et al., 2015).

4.7. Pediatric aspects of TBE

Pediatric TBE cases account for an estimated 6–20% of all ECDC reported cases in European countries (ECDC, 2012). In Europe, the incidence of TBE in the age group < 4 years is about ~0.2 cases/100,000 population and in the age group 5–14 years about 0.3 cases/100,000 population (ECDC, 2012). Children typically present non-specific symptoms such as elevated temperature, headache, fatigue, and exhaustion. Toddlers are not able to fully verbalize symptoms, which may delay times to diagnosis. Fully 5–30% of TBEV-infected children develop a second phase of the disease after exhibiting non-specific febrile syndrome (Sundin, 2017). The disease reappears with febrile temperatures and clinical signs suggestive of meningitis or meningoencephalitis. Impaired consciousness (from mild apathy and drowsiness to coma), convulsions, ataxia, tremors, cranial nerve palsies, or hemiparesis are rare in pediatric patients. Clinical signs of white matter and brainstem involvement is also extremely rare in children (Zuccoli et al., 2015). The course of the encephalitic form of TBE in children, though less frequent than in adults, is more severe and often requires specialized intensive care.

Overall, the course of the disease is usually milder in children than in adults. However, even a mild course of the disease may result in long-term sequelae. It is hypothesized that a developing CNS is more susceptible to long-term deficits than an adult CNS. Neuropsychiatric disorders, such as attention and concentration deficits, are persistent in 2% of pediatric TBE patients (Krbkova et al., 2015; Steffen, 2019).

5. Management of TBE

Given that there is no specific treatment, supportive and symptomatic therapy are the mainstay of TBE management. The clinical course of the disease (neurological phase) has three partially overlapping domains that require specific approaches: the early stages of the neurological phase of the disease, in which management is focused on differential diagnosis and empirical treatment of other conditions/co-infections; the in-hospital phase focused on symptom relief, supportive management and managing co-morbidities, preferably in neurointensive care for more severe manifestations of the disease; and the post-acute phase in which recovery and neurorehabilitation are facilitated after the hospital stay and discharge.

5.1. Management while determining diagnosis

During the initial diagnostic work-up of a patient with febrile headache and neurological symptoms of varying severity (usually seen in patients who are awaiting the results of TBE blood serology and tests of CSF), other etiologies with available effective treatment regimes must be actively investigated and treated empirically until disease origins are otherwise proven. This includes the administration of acyclovir, especially in cases of patients with hemiparesis, aphasia, and confusion, where brain imaging suggests the possibility of herpetic encephalitis (Solomon et al., 2012). Bacterial infections with non-purulent inflammation in the CSF also need to be considered, including Lyme neuroborreliosis, leptospirosis, listeriosis, syphilis, and tuberculosis (Studahl et al., 2013). However, a thorough discussion of the non-infective causes of aseptic meningitis/encephalitis is beyond the scope of this review.

In non-endemic regions of TBE, this diagnostically uncertain phase may be prolonged, since the medical teams concerned may not fully appreciate the importance of prior travel to endemic areas, and/or serological testing for TBEV is not readily available. After a TBE diagnosis is confirmed, potential co-infections must be considered, especially of *Borrelia* spp., but also other tick-borne zoonotic agents, including *Babesia* and *Anaplasma phagocytophyllum* (Moniuszko et al., 2014; Moutailler et al., 2016; Lotric-Furlan et al., 2005). There have been rare individual cases of other coinfections that clinicians need to be more fully aware of, including *Rickettsiae* (TIBO-LA), *Franciscella tularensis,* and *Coxiella burnetii* (Suess et al., 2004). In addition, a fatal case of TBE and *Listeria monocytogenes* coinfection has also been reported (Zajkowska et al., 2008, 2011).

In Russia, there is a defined course of action after a tick bite (Sanitary rules SP 3.1.3.2352–08). The following scheme is used: (1) the potential patient brings tick/ticks to a laboratory of the Russian Federal Service for Surveillance on Consumer Rights Protection and Human Well-being (Rospotrebnadzor); (2) the ticks are examined by PCR for the presence of up to four potential infectious agents (TBEV, *Borrelia burgdorferi* sensu lato [except for *B. myamotoi*], *Ehrlichia* and *Anaplasma phagocytophyllum*; (3) if the tick is positive for TBEV RNA, a specific immunoglobulin is administered (no later than 96 h after removal of the tick). To patients from any territory of Russia, if bacteria are found in the tick, then appropriate antibiotics are administered, whereas if the tick is not available for PCR, then antibiotics are administered plus immunoglobulin if the potential patient was in a TBE-endemic area; (4) the patient is hospitalized if first clinical symptoms of TBE emerge after the tick bite. In some regions of Russia, patients use jodantipyrin for emergency prevention after a tick bite (see section 6.3.1 for details).

5.2. In-hospital management

5.2.1. Acute neurologic phase

There are several leading and specific manifestations that need to be controlled during the acute neurological phase of TBE (Kaiser, 1999; Chmelík et al., 1999), including headache, electrolyte disturbance, cognitive impairment/delirium, signs of intracranial hypertension, and palsies of the cranial nerves and limbs. Signs of the most severe form of TBE include bulbar syndrome with difficulty in swallowing and impaired clearance of airway secretions. Concurrent and preceding health conditions must also be managed, especially those with poorer outcomes, such as cardiovasular and cerebrovascular impairment associated with older age, and diabetes mellitus (Lenhard et al., 2016).

5.2.2. Management of pain and fever

Paracetamol and non-steroidal anti-inflammatory drugs, including

metamizol, are the mainstay of pain and fever management in viral meningoencephalitis. Other physical measures, such as cooling blankets or the infusion of cooled intravenous fluids, can be employed to reduce body temperature effectively. Opioid analgesia should be avoided if possible, as it may increase intracranial pressure, deepen the loss of consciousness, and decompensate for subclinical respiratory depression.

5.2.3. Nausea and vomiting

Nausea and vomiting are mainly a manifestation of meningitis or meningoencephalitis. These symptoms may be moderated by 5-HT3 receptor antagonists (setrons). Another useful group is that of dopamine receptor antagonists, such as domperidone, olanzapine, haloperidol, chlorpromazine, and prochlorperazine (keeping in mind the risk of extrapyramidal side effects and over-sedation). Metoclopramide should not be used for longer than 5 days. Another option in refractory nausea is the administration of mirtazapine or corticosteroids.

5.2.4. Ataxia and risk of falls

Ataxia and poor balance are common signs and symptoms of TBE. There is an increased risk of falls, especially in elderly patients with TBE. This needs to be considered during nursing care.

5.2.5. Electrolyte balance

Electrolyte imbalance is seen uniformly in patients with severe TBE, but even patients with milder disease should be monitored closely. Ongoing fever with perspiration, vomiting, and/or nausea, loss of appetite, and possible low hypoactive delirium or cognitive impairment and/or confusion may exacerbate dehydration and electrolyte disturbances. On the other hand, excessive hydration may deteriorate brain oedema. Furthermore, thalamic lesions may cause the development of the syndrome of inappropriate antidiuretic hormone secretion (SIADH) (Czupryna et al., 2014).

5.2.6. Neurointensive specialized unit

In severe cases, patients should be managed in an intensive care unit or, preferably a neurointensive unit under the care of a multidisciplinary team with experience in the management of CNS infections (Suarez et al., 2004). Timely and proactive symptom management not only improves patient experience, but prevents loss of muscle mass and strength, plus the development of healthcare-associated complications, including aspiration pneumonia, urinary tract infection, or delirium (Kelesidis et al., 2014; Sarpong et al., 2017).

5.2.7. Intracranial hypertension

TBEV causes both direct neuronal damage and an inflammatory response resulting in brain oedema. Intracranial pressure (ICP) and/or cerebral perfusion pressure monitoring should help in decision-making regarding the means of lowering ICP, including mechanical ventilation, deepened analgo-sedation, and therapeutic hypothermia (Venkatesan and Geocadin, 2014; Taba et al., 2017). Continuous osmotherapy with mannitol or hypertonic saline should not be employed, as it increases fatality rates; however, hyperosmotic boluses may be considered for a short period of 1–2 days at most (Taba et al., 2017). Decompressive craniotomy has been reported for the treatment of other flaviviral diseases, but not for TBE, though it might be considered if other measures fail (Kofler et al., 2016).

5.2.8. Brain stem involvement

The main signs of damage to the brainstem and surrounding structures include singultus (hiccups), dysarthria, weak swallowing, and respiratory depression. Persistent singultus should be closely monitored for the risk of developing of respiratory insufficiency. Drugs used to moderate singultus include older antipsychotics, such as haloperidol, and metoclopramide or dexamethasone.

5.2.9. Difficulty swallowing

When the brain stem is affected in TBE, bulbar palsy may develop as a result of the impairment of cranial nerves IX, X, XI and XII lower motor neurons. This may lead to a swallowing dysfunction, in some cases with normal findings on brainstem MRI. Checking the ability to swallow must be a daily routine in the nursing and medical care of patients with encephalitic forms of TBE, and warning signs of poor swallowing and/or dysarthria must be actively sought. Adequate measures for managing bulbar syndrome range from thickened fluids or nasogastric tube feeding and nil by mouth to insertion of a balloon-cuffed tracheostomy (Lenhard et al., 2016).

5.2.10. Respiratory insufficiency and difficulty coughing

Brain stem damage may also be associated with respiratory depression and an inability to maintain airway patency due to poor cough and mucus build-up. Deterioration may develop very rapidly after a prolonged period of borderline respiratory compensation, especially in previously fit and well people. Poor clearance of respiratory secretions and/or repeated micro-aspirations may contribute to this problem and result in hospital-acquired/aspiration pneumonia. Early intubation and/or cuffed tracheostomy may prevent the development of more extensive lung damage (Gaieski et al., 2017). In Russia before the 1980s, pneumonia was the cause of about 50% of fatal outcomes in TBE patients.

5.2.11. Seizures

Unlike TBEV-Sib and TBEV-FE, TBEV-Eu infection is rarely associated with seizures. Thus, a different etiology should be investigated (Kaiser, 2012). In the case of seizures, treatment usually begins with intravenous benzodiazepines, followed by phenytoin, valproate, levetiracetam, ketamine to deepen anesthesia in refractory cases, and propofol or barbiturates if intracranial pressure monitoring is in place (Michael and Solomon, 2012). In cases of prolonged unresponsiveness, EEG monitoring is advisable to identify non-convulsive status epilepticus (Brophy et al., 2012; Claassen et al., 2013). Primary prophylaxis of seizures in TBE is not recommended (Pandey et al., 2014).

5.2.12. Use of corticosteroids

The role of corticosteroids in the management of TBE is disputed. Their anti-oedematous effect on CNS infection has been known for a long time (Cantu and Ojemann, 1967). An anti-oedematous dosage (i.v. hydrocortisone 5–10 mg/kg/day) resulted in faster resolution of fever and the moderation of headache, nausea, and other symptoms (Duniewicz et al., 1974). However, later studies have suggested that continued dexamethasone administration can lead to poorer long-term outcomes, although these were observational studies in which there is a tendency for patients to be administered steroids more readily in cases of severe disease (Mickiene et al., 2002). Therefore, corticosteroids should not be used routinely in anti-oedema treatment, but might be administered by experienced clinicians in selected cases (Wengse et al., 2017). Treatment is most likely to be beneficial for patients in the early stages of developing neurological deficits, increasing somnolence or sopor, severe headache, intense vomiting and singultus (Pancewicz et al., 2015). However, in patients with acute encephalitis due to JEV infection, no statistically significant benefit on the outcome of the disease was observed following high-dose dexamethasone administration (Hoke et al., 1992).

5.3. Post-acute phase and neurorehabilitation

More than 90% of lost disability-adjusted life years for TBE are due to long-term disability in survivors. Moderate long-term neurological disability contributes the most to the disease burden in endemic countries (Šmit and Postma, 2015). Neurorehabilitation is a key element in returning patients to normal life. Historical studies have suggested that a neurological deficit lasting one year will not greatly

improve afterwards (Duniewicz et al., 1975). Apart from permanent palsies in approximately 5% of patients, roughly one-third to one-half report postencephalitic syndrome as a subtle consequence of TBE. This may disturb the quality of life for months to years, including tremor, persistent headache (especially during stress), poor concentration/memory loss, hypersensitivity to light and noise, depressive moods and increased anxiety, pseudoneurasthenia, and social role dysfunction (Haglund et al., 1996; Chmelík et al., 2004). The time from hospital discharge to a full return to work or school may range from 2 to 4 months in mild cases of TBE, up to one year in cases with post-encephalitic syndrome. Adjustments in school or work may be required for those with permanent neurological deficits. Given recent developments in neuroscience, one may expect a more effective and expanded window of opportunity for recovery and return to normal life.

5.3.1. Neurorehabilitation

Patients with acquired brain injury depend on neurorehabilitation to be able to return to activities of daily living. Plasticity of the nerve tissue in the brain is suggested to facilitate such a transition (Kolb and Muhammad, 2014). Interdisciplinary coordination of rehabilitation is more effective for recovery than a spontaneous return to daily living (Formisano et al., 2017), and rehabilitation has also been shown to improve quality of life (Fortune et al., 2015). However, which type of neurorehabilitation is the most beneficial in post-encephalitis acquired brain injury is not known, although the concept of setting performance goals and associated social interactions during a given rehabilitation process may have beneficial effects on quality of life and a return to pre-morbid performance status (Rogan et al., 2013). The universal timing and extent of neurorehabilitation after TBE is not known and should be individualized. The key to successful rehabilitation appears to be the rationing of activity and sufficient rest.

5.3.2. Social and community support

The first weeks after discharge from the hospital require, apart from family involvement in supportive care, a significant input from the community and adequate mental and physical stimulation to help with convalescence. Further phases focus on re-learning the skills of daily activities. In mild cases, a phased return to work with pre-negotiated time-outs may be beneficial. Adjustment to new situations in cases of long-term neurological deficit may last months to years for both the patient and their families.

5.3.3. Psychological and psychiatric support

Facing real life following a convalescence period may be associated with increased anxiety and/or depressive mood (Rogan et al., 2013). Apart from pharmacotherapy, training in coping strategies reduces the level of distress perceived by the patient (Brands et al., 2014). In general, children are thought to have a milder disease course; however, “soft” signs have been reported, including learning difficulties and poor concentration (Rostasy, 2012). Therefore, a coordination between learning processes and adjustments at school are desirable.

6. Current and experimental antiviral therapy

No specific antivirals are approved for the treatment of TBE in Europe (Studahl et al., 2013; Taba et al., 2017), and patient care is mainly symptomatic and supportive, including intensive care interventions in severe cases. Therefore, specific therapeutic agents and strategies are required for the treatment of unvaccinated patients and vaccinated individuals with postvaccine complications and breakthrough TBE. Immunotherapy or use of specific antivirals represent possible approaches.

6.1. Immunotherapy

Specific anti-TBEV immunoglobulins, nonspecific immunoglobulins, or recombinant anti-TBEV immunoglobulins are used or tested for prophylaxis or treatment. Vaccines can also be used in a therapeutic context as well.

6.1.1. Specific anti-TBEV immunoglobulin

In Russia and Kazakhstan, specific immunoglobulins produced from the plasma of donors are currently used for post-exposure prophylaxis and treatment (Pen'evskaia and Rudakov, 2010). This preparation is able to prevent or decrease the severity of clinical symptoms (Lashkevitch and Karganova, 2007). Analysis of the results of cohort studies has established that a timely single administration of a specific immunoglobulin (0.05 ml/kg body weight) ensures protection in 79% of cases on average. For post-exposure prophylaxis, it is necessary to use immunoglobulins with an anti-hemagglutination titre of at least 1:80. (Pen'evskaia and Rudakov, 2010). However, in Europe, the anti-TBE immunoglobulin Encegam (FSME-Bulin) was previously administered for post-exposure prophylaxis and treatment, but is no longer used. Encegam demonstrated therapeutic effects, but concerns regarding antibody-enhanced disease led to its suspension (Kluger et al., 1995; Arras et al., 1996; Waldvogel et al., 1996). Notably, no clinical cases of aggravated disease have been described after correct and timely administration of anti-TBE immunoglobulins (Bröker and Kollaritsch, 2008). Importantly, antibody-enhanced course of TBE has not been observed in *in vivo* experiments in mice after pre- and post-exposure administration of specific anti-TBEV antibodies (Kreil and Eibl, 1997; Baykov et al., 2014; Huisman et al., 2009). Nevertheless, some researchers speculate that immunoglobulin therapy may be responsible for the relatively high incidence of chronic forms of TBE in Russia, compared to Europe; however, no data are currently available to support this concern. On the other hand, antibody-enhanced disease has been observed in mouse studies with Langat virus and louping ill virus, close relatives to TBEV. Furthermore, observations of similar effects in mice following administration of of JEV does suggest that concerns about antibody-enhanced disease during flavivirus encephalitis are not unfounded (Webb et al., 1968; Gould and Buckley, 1989). More research needs to be done with TBEV to clarify this important issue.

6.1.2. Nonspecific immunoglobulin

One possible immunotherapy approach is the administration of high doses of intravenous immunoglobulin (IVIG). The preparation is approved for clinical use (Rhoades et al., 2000) in patients with various diseases, including flavivirus encephalitides (reviewed in Ruzek et al., 2013a; Elsterova et al., 2017). Its effectiveness is due to the inclusion of a broad repertoire of neutralizing antibodies against various pathogens and its immunomodulatory activity (Boros et al., 2005). The use of IVIG has been reported in the treatment of a patient with severe TBE, who received IVIG for 5 days at a dose of 400 mg/kg body weight/day (Kleiter et al., 2007). After treatment, some symptoms improved, but not the neurological symptoms. However, no data were available on the presence of TBEV-specific antibodies in this batch of IVIG. More recently, only IVIG preparations containing neutralizing anti-TBEV antibodies were shown to prevent infection *in vitro* and TBEV-infected mice (Elsterova et al., 2017).

6.1.3. Recombinant antibodies

The administration of recombinant antibodies, including chimeric and humanized antibodies, could be another possible approach for immunotherapy going forward. Such engineered antibodies have some advantages over immunoglobulin preparations from human blood, including production in blood-free biotechnological conditions and standardization of the ratio of protein concentration to neutralizing activity in each prepared batch. An engineered chimeric anti-TBEV antibody has been demonstrated to be significantly more effective than commercial anti-TBEV serum immunoglobulin in an animal model post-exposure and does not elicit antibody-enhanced disease in a lethal mouse model (Baykov et al., 2014). Further investigations should

confirm the applicability of this antibody for specific therapy, and the prospect that this antibody could enhance the anti-TBEV activity of IVIG preparations that do not contain any directly TBEV-specific antibodies.

6.1.4. Therapeutic vaccination

There have only been a few cases in which inactivated vaccine has been administered for treatment. In one case, the TBEV-Sofjin vaccine was administered to a patient with chronic TBE (Pogodina et al., 1986), who had been infected with TBEV-Sib and developed chronic disease 4 years after the onset of illness. The patient received a complete vaccination course with three consequent doses at the end of the fourth year of the disease, which led to an increase in the anti-hemagglutination titers of specific antibodies. The anti-hemagglutination activity in the patient's serum decreased, and a three-dose course of immunization was repeated a year after the first therapeutic vaccination. After that, the hemagglutination titre in the serum dropped (Pogodina et al., 1986). The reader should note that patients usually have high levels of TBEV-specific antibodies, which can interact with the vaccine antigens, thus the effect of therapeutic vaccination remains unclear. In other cases, inactivated vaccine was used for therapeutic immunization, supplemented with glucocorticoids (Umanskyi et al., 1981), so that the observed improvements in symptoms might have been caused by the hormones and other non-specific therapeutic agents. Importantly, elimination of virus has not been recorded in patients with chronic TBE (Pogodina et al., 1986).

6.2. Small molecule antivirals

As for other flaviviruses, no schemes for the specific treatment with small molecule antivirals have been recognized or introduced widely. For a detailed discussion of flavivirus biology and drug targets see the review (Boldescu et al., 2017). Target-based drug design is also restrained by the limited availability of enzymatic assays for the main non-structural enzymes of TBEV, and the paucity of structural protein binding assays.

6.2.1. Screening small molecules for anti-TBEV activity

Currently, the most accessible strategy for the measurement of potential small molecule activity is that of a primary assay, which at least provides robust experimental data and establishes potential mechanisms of action (MoAs) for hit compounds. The most important technical limitations of such a strategy are the requirement for a BSL3 containment laboratory, and the fact that only low-throughput cellular assays are available, denying opportunities for the mass screening of thousands of compounds in a short time frame. These limitations dictate that compounds for testing should undergo some form of pre-selection, to limit the number in evaluation as potential anti-TBEV agents.

Two main strategies have been used for compound pre-selection. In the first, Osolodkin et al. developed a structure-based virtual screening procedure (Osolodkin et al., 2013), accessing a homology model of the E protein β-n-octyl-D-glucoside binding site, which was further supported by molecular dynamics simulation data (Dueva et al., 2014). In the second, a ligand-based strategy was devised relying on drug or hit repurposing and an exploration of compounds such as nucleoside analogues (Jordheim et al., 2013).

6.2.2. Non-nucleoside compounds

In this and the following sections, numbers in bold refer to molecules in Fig. 6. 1,4-Dihydropyridine and 1,3,5-thiadiazine derivatives **1** and **2** were identified using the structure-based virtual screening procedure described above (Osolodkin et al., 2013), and show activity against the Absettarov strain of TBEV at low micromolar concentrations. The same docking-based approach was also employed in structure-activity relationship studies of tetrahydroquinazoline N-oxides **3** (Sedenkova et al., 2015) and several other yet to be disclosed compound classes. Compounds identified using this approach were studied in 'time-of-addition' assays; the results suggested inhibition of virus reproduction through virion binding. Poliovirus (a non-enveloped virus) was not inhibited, suggesting a MoA involving a specific interaction with the viral envelope (Sedenkova et al., 2015). Strain selectivity profiling revealed a wide range of activity of tetrahydroquinazoline N-oxides against various TBEV strains (Dueva, 2016). Several selenorganic compounds also showed TBEV reproduction inhibition at micromolar concentration levels (Orlov et al., 2018).

6.2.3. Nucleoside analogues

Several series of nucleoside analogues have been assessed against TBEV (Eyer et al., 2015, 2016, 2017a, 2017b; Lo et al., 2016; Orlov et al., 2017; Kozlovskaya et al., 2018). Nucleoside analogues form the backbone of therapy for many serious diseases induced by medically important DNA or RNA viruses (De Clercq, 2011), and they have promising potential for the treatment of TBE (Eyer et al., 2015, 2016, 2017a, 2017b). The general MoA for most nucleoside inhibitors is their interaction with the viral polymerase, resulting in premature termination of nucleic acid synthesis (De Clercq and Neyts, 2009); however, other MoAs have been considered, including inhibition of the viral helicase/NTPase, inhibition of enzymes responsible for intracellular nucleoside/nucleotide biosynthesis (Leyssen et al., 2005), increased mutagenesis in viral genomes, resulting in "error catastrophe" (Crotty et al., 2001), and immunomodulation (Hultgren et al., 1998).

Well-studied nucleoside-based TBEV inhibitors include the 2′-*C*-methyl-substituted analogues originally developed as therapeutics for chronic hepatitis C (Carroll et al., 2003, 2011; Eldrup et al., 2004; Migliaccio et al., 2003; Olsen et al., 2004). They suppress TBEV replication (Hypr and Neudorfl strains) in both porcine stable kidney cells (PS) and human neuroblastoma cells (UKF-NB4) at low micromolar concentrations with favorable cytotoxicity profiles (Eyer et al., 2015, 2016). One of these molecules, 7-deaza-2′-*C*-methyladenosine **4** (7DCMA), substantially improves disease outcomes, with increased survival, and reduces signs of neuroinfection and viral titres in the brains of BALB/c mice infected with a lethal dose of TBEV Hypr (Eyer et al., 2017b). However, *in vitro* treatment of TBEV-infected PS cells with 7DCMA results in the rapid evolution of resistance to 2′-*C*-methylated nucleoside inhibitors, associated with a signature mutation (S603T) within the active site of the viral RdRp. The biological properties of this resistant variant are manifested as a loss of replication efficacy in cell culture and markedly reduced virulence for mice (Eyer et al., 2017b).

Introduction of the ethynyl moiety to the C2′ position of nucleoside **4** provided 7-deaza-2′-*C*-ethynyladenosine **5** (NITD008), initially synthesized for DENV inhibition (Chen et al., 2010, 2015; Latour et al., 2010; Yin et al., 2009), exhibiting nanomolar or low micromolar anti-TBEV activity in various cell-based screening systems (Lo et al., 2016). Another important family of nucleoside inhibitors are the 4′-azido-substituted analogues of cytidine, particularly 4′-azidocytidine **6** (RO-1479) and its arabino counterpart 4′-azido-aracytidine **7** (RO-9187) (Eyer et al., 2016). The anti-TBEV efficacy of both is cell-type dependent, as they exhibit antiviral activity only in PS cells, not in UKF-NB4 neuroblastoma cells. The ester prodrug of 4′-azidocytidine, balapiravir, is completely inactive against TBEV *in vitro*, probably because of its poor intracellular uptake or insufficient kinase phosphorylation in the tested cell lines (Eyer et al., 2016).

The adenosine analogue BCX4430 **8** also exhibits a low micromolar level of anti-TBEV activity (Eyer et al., 2017a), which is important, given that this compound is representative of the imino-*C*-nucleosides that have entered Phase I clinical trials for treatment of Ebola virus infection (De Clercq, 2016; Taylor et al., 2016; Warren et al., 2014). Another interesting compound is the 1′-*C*-cyano-substituted nucleoside prodrug GS-5734, that has micromolar activity against TBEV Hypr strain, but also exhibits pronounced toxicity (reported SI value of 4.8), indicating a limited therapeutic potential in TBEV infection (Lo et al.,

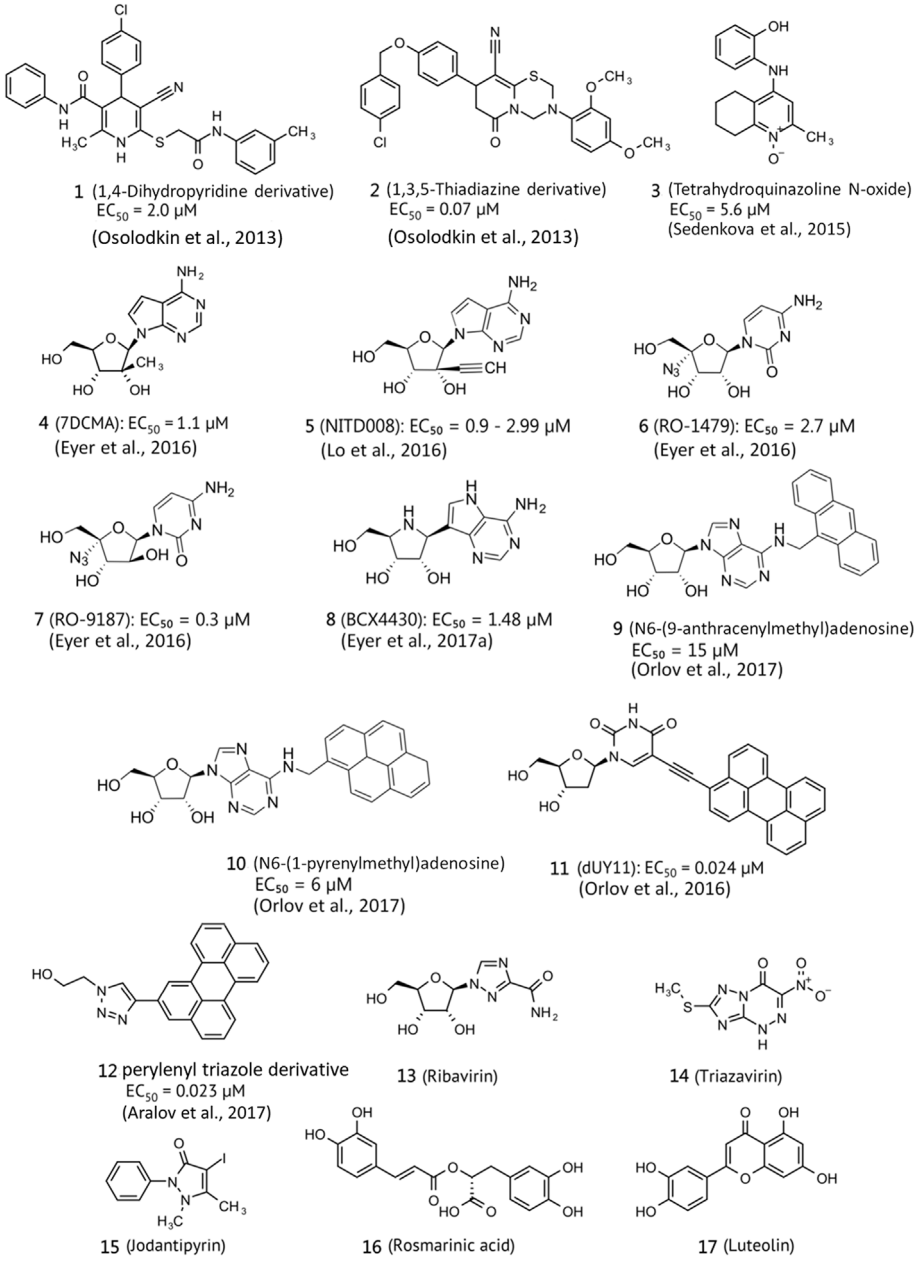

Fig. 6. Examples of small-molecule compounds tested for anti-TBEV activity. No specific drugs are approved for TBE therapy, but several molecules exhibit anti-TBEV activity *in vitro* and/or in animal models. They represent either potential TBEV antivirals or promising lead candidates for further development.

2017). In addition, several N^6-alkyl/aryl-substituted nucleosides, such as N^6-(9-anthranylmethyl)adenosine **9** and N^6-(1-pyrenylmethyl)adenosine **10** (Orlov et al., 2017), have shown micromolar level inhibition of the TBEV Absettarov strain *in vitro*. Many other nucleoside analogues have been evaluated *in vitro*, but most of the tested ribose/heterobase substitutions resulted in complete abrogation of anti-TBEV effects. Such modifications include methylation of the O2′, O3′, or C3′ positions, as well as deoxy-modification of the C3′position (Eyer et al., 2016; Orlov et al., 2017). Similarly, nucleosides possessing the 2′-α-fluoro-2′-β-*C*-methyl substitution (PSI-6206, its prodrug sofosbuvir and mericitabine) have no anti-TBEV activity (Eyer et al., 2016). In contrast, heterobase-modified analogues of 2′-*C*-methyladenosine (e.g., tubercidin, sangivamycin, and toyocamycin) are highly cytotoxic, so that their antiviral effect could not be assessed (Eyer et al., 2016).

A specific group of nucleoside derivatives, the so-called rigid amphipathic fusion inhibitors (RAFIs) **11** and **12**, were initially described as nucleoside analogues bearing a perylene moiety (Orlov et al., 2016; Aralov et al., 2017; Proskurin et al., 2018). These compounds inhibit the reproduction of various enveloped viruses in a rather non-specific manner, attributed to mechanical or photochemical impairment of the function of the viral membrane (Colpitts et al., 2013; Vigant et al., 2014; Speerstra et al., 2018; Hakobyan et al., 2018). RAFIs exhibit the highest potency among all compounds tested against TBEV in plaque assays, up to nanomolar levels, but many are poorly soluble. More soluble analogues show higher anti-TBEV potency (Proskurin et al., 2018). The nucleoside moiety seems to be non-essential for antiviral activity (Aralov et al., 2017), whereas the substitution of perylenyl with a long alkyl chain reduces anti-TBEV activity back to micromolar concentrations (Kozlovskaya et al., 2018). Thus, viral titre is reduced by RAFIs with pronounced efficiency, and total virus elimination can be achieved for virus doses up to 10^5 PFU (Orlov et al., 2016). RAFIs are supposed to have low cytotoxicity, due to the presence of membrane repair machinery in cells.

Ribavirin **13** is a broad-spectrum antiviral commonly used in the

treatment of several viral diseases and is often the first choice in the *in vitro* search for reproduction inhibitors of poorly studied viruses; at least 36 virus species from 17 genera have been tested for sensitivity to ribavirin (Nikitina et al., 2019). Several attempts have been made to study the anti-TBEV efficiency of ribavirin, but mixed results have been obtained. Eyer et al. (2015, 2016) and Rogova et al. (2008) did not observe any sufficient antiviral effect, whereas Krylova and Leonova (2016) and Loginova et al. (2014) found that ribavirin was active, and used it as a positive control in their studies of other antivirals. In the latter studies, however, ribavirin concentrations were as high as 127–2047 and 400 μM, respectively; such high concentrations in *in vitro* studies are a sign of low therapeutic efficiency. Triazavirin **14** was initially suggested as an anti-influenza drug (Karpenko et al., 2010) and was approved for influenza therapy in Russia, based on a small phase III trial (Sologub et al., 2017). It demonstrated anti-TBEV activity comparable to ribavirin *in vitro* (Loginova et al., 2014), and antiviral effect of triazavirin was also observed in TBEV-infected mice, when dose of 400 mg/kg was used (Loginova et al., 2015). The clinical relevance of such high doses is not clear. The mechanism of action of triazavirin has not been clearly established.

Taken together, nucleoside analogues represent promising potential drugs for TBE. In particular, 7-deaza-2′-*C*-methyladenosine demonstrates high antiviral effects in mice. However, research needs to continue on the development and testing of nucleoside analogue inhibitors active against TBEV (Eyer et al., 2018).

6.3. Interferon and interferon inducers

6.3.1. Interferon inducers

Interferon inducers are compounds developed principally in Russia to increase interferon levels and, thus, non-specifically protect humans against viral infections. Administration of these compounds usually does not cause undesired side effects; however, their therapeutical efficacy remains questionable (Penievskaya, 2010). This class of compounds includes tilorone, cycloferon (meglumine acridonacetate), ridostin (sodium ribonucleate), sodium polyprenilphosphate, and jodantipyrin **15**. The latter was initially described as a radiologic imaging agent and is apparently the most studied and widely used; its interferon-inducing properties were described in (Khudoley et al., 2008). However, the significance of jodantipyrin use data in pre-2010 studies of TBE was heavily criticized by Penievskaya (2010), because most publications describing the efficacy of this drug were affiliated with or sponsored by the manufacturer. More recent studies presented by the manufacturer have reported the clinical efficacy of jodantipyrin using a prophylactic scheme of treatment starting a couple of weeks before expected exposure to the virus (Lepekhin et al., 2012; Doroshenko et al., 2013; Lepekhin et al., 2016). *In vitro* TBEV titre reduction by 3 lg $TCID_{50}$ was observed at a jodantipyrin concentration of 3.2 mM (1000 μg/ml) (Krylova and Leonova, 2016).

6.3.2. Interferon preparations

A recombinant interferon preparation formulated into a liposomal carrier for oral administration, marketed as Reaferon-ES-Lipint, was studied in combination with specific immunoglobulins (Reaferon-ES-Lipint was administered perorally; immunoglobulins intrathecally). Available data from manufacturer-sponsored studies demonstrated an improved clinical outcome in different forms of TBE (Salabay et al., 2012; Vorobeva et al., 2012). The administration of this interferon without immunoglobulins also improved prognosis, but was less effective than the interferon-immunoglobulin combination.

6.4. Natural extracts

Natural extracts have been assessed for anti-TBEV activity. The most studied are luromarin (*Zostera asiatica* extract containing rosmarinic acid (95%) and luteolin (5%)) and tinrostim (peptide extract from *Berryteuthis magister* optical ganglia, containing 1–12.5 kDa peptides (84%) and free amino acids (16%, mostly Asp, Glu, and Lys)). Luromarin contains two main components, well-known as anti-flavivirals: rosmarinic acid **16**, which has been shown to be effective against JEV in mice (Swarup et al., 2007), and luteolin **17**, which inhibits reproduction of JEV in cell culture (Fan et al., 2016). The difference in potency between luromarin and its main components was not statistically significant (Kryilova et al., 2009; Krylova et al., 2010, 2011a). Combinations of luromarin with ribavirin or cycloferon were found to effect improved survival rates in mice compared to rates observed with individual preparations (Krylova et al., 2011b). As oxidative stress is observed during TBE (reactive oxygen species contribute to antiviral defence but also cause pathology to the host) (Łuczaj et al., 2016; Kovalskii et al., 2013), the use of antioxidants, such as rosmarinic acid **16** and luteolin **17**, may be a viable therapeutic strategy.

Alternatively, the peptide mixture tinrostim inhibits TBEV reproduction and positively modulates ribavirin efficiency (Krylova and Leonova, 2016), although this has not been characterized properly, and a precise MoA cannot be defined. The current hypothesis is that the peptides mediate immune system modulation, and/or may interact non-specifically with viral particles to prevent cell entry and interactions with E-protein trimers (Schmidt et al., 2010; Chew et al., 2017).

Plant-derived carbohydrate mixtures also demonstrate anti-TBEV activity *in vitro* and in mice. Cellular glycosaminoglycans significantly bind TBEV (Mandl et al., 2001; Kroschewski et al., 2003; Kozlovskaya et al., 2010) and play a role as low-affinity binders to receptors. Anionic carbohydrates are considered to be a viable class of anti-flaviviral compounds (Hidari et al., 2013). Fucoidans derived from brown seaweeds are sulphated fucans, typically containing galactose and mannose residues along with fucose, providing protective effects in mice and inhibiting TBEV reproduction *in vitro* (Makarenkova et al., 2009, 2012). A hexose polysaccharide derived from potato (*Solanum tuberosum*) shoots is marketed as a broad-spectrum antiviral drug in Russia under the trade name Panavir (Lepekhin et al., 2007; Litvin et al., 2009). However, the quality of the clinical studies leading to the approval for clinical use of this preparation in Russia was questioned by Penievskaya (2010). The MoA of panavir is claimed to be immunomodulation, with polysaccharide nanoparticles presumably mimicking virions (Stovbun et al., 2012), although non-specific binding with virions cannot be excluded.

6.5. Other treatments

Arbidol, also known as umifenovir, is a broad-spectrum antiviral compound licensed in Russia and China for the prophylaxis and treatment of human influenza A and B infections, plus post-influenza complications (Blaising et al., 2014). It is active against numerous DNA/RNA and enveloped/non-enveloped viruses (Blaising et al., 2014). Recently, it was shown that arbidol possesses micromolar antiviral effects against TBEV and other flaviviruses (Haviernik et al., 2018), but no animal or human studies investigating the efficacy of arbidol against TBEV have been done so far.

Anaferon is another marketed preparation for TBE treatment in Russia (Tarasov et al., 2016; Pavlova et al., 2009; Skripchenko et al., 2015; Skripchenko et al., 2007). It is claimed to contain “ultra-low doses” of polyclonal rabbit antibodies to IFNγ, so this is an essentially homeopathic remedy prepared by sequential dilutions (Don et al., 2017; The PLOS ONE Editors, 2018). Consequently, the anti-TBEV effect of this preparation, if any, is unclear. Cinical data are represented by a single open-label study, in which Anaferon or immunoglobulin were used for treatment of patients after a tick bite (Skripchenko et al., 2007). The quality of the Anaferon studies has been generally criticized (Penievskaya, 2010; Dueva and Panchin, 2017), pointing out a number of issues, including non-transparency of sample preparation, undisclosed conflicts of interests, unacceptable study design, biased cohort assignment, and poor statistical analyses. This criticism led to retraction

Table 2
Characteristics of TBE vaccines licensed in Europe and Russia. All are produced in primary chicken embryonic cells (PCECs), with aluminium hydroxide as an adjuvant.

	Strain	Amount of antigen
FSME-IMMUN® (Pfizer)	Neudoerfl (TBEV-Eu)	2.4 µg (adults)/1.2 µg (children)
Encepur® (GSK)	K23 (TBEV-Eu)	1.5 µg (adults)/0.75 µg (children)
TBE Moscow (FSBSI "Chumakov FSC R&D IBP RAS")	Sofjin (TBEV-FE)	1.0 ± 0.5 µg/ml (dose 0.5 ml for children from 3 years old and adults)
Tick-E-Vac/Klesch-E-Vac (FSBSI "Chumakov FSC R&D IBP RAS")	Sofjin (TBEV-FE)	1.0 ± 0.5 µg/ml (dose 0.25 ml for children 1–13 years old; 0.5 ml for adults)
EnceVir® (Microgen)	205 (TBEV-FE)	2.0–2.5 µg

of a published study claiming the antiviral activity of this preparation (The PLOS ONE Editors, 2018).

7. TBEV vaccines in Europe

European vaccines have been used for more than 30 years and have been highly effective in preventing TBE (Barrett et al., 2003). The first European vaccine, FSME-IMMUN® (Pfizer, USA), was first approved for people living and working in highly endemic areas in 1976. The vaccine is prepared from seed virus, the Neudoerfl strain of the European subtype, isolated from ticks (Barrett et al., 2003). The second vaccine, Encepur® (GlaxoSmithKline), was registered in 1991 in Germany and is based on the Karlsruhe (K23) strain (Harabacz et al., 1992; Girgsdies and Rosenkranz, 1996). The vaccines can be used interchangeably (Table 2).

Over the last few decades, there have been changes in the manufacturing processes of both vaccines, which consist of formaldehyde-inactivated whole virus purified by ultracentrifugation, with the antigen adsorbed to aluminum hydroxide. The production of FSME-IMMUN® was originally based on a master seed virus passaged in mouse brain, with the actual working seeds subsequently propagated in primary chicken embryo fibroblast cells (PCECs). In the late 1990s, the virus master cell bank was modified by passaging the seed virus through chicken embryo cells instead of mouse brain cells. The antigen content in the current version of the vaccine is now specified for a narrower range than the historic vaccine (Zent and Broker, 2005). Encepur® is prepared similarly, but the master and working seeds of the K23 strain have always been prepared from PCECs. Sucrose is used as a stabilizer in Encepur®, whereas FSME-IMMUN® uses human serum albumin; neither contains polygeline or thiomersal (Barrett et al., 2003; Zent and Broker, 2005).

Both vaccines have adult and pediatric formulations, namely FSME-IMMUN®/Encepur® and FSME-IMMUN® (Junior)/Encepur-K®. The age-specific formulations were initiated due to the frequency and degree of fever, which is age-dependent and most common in preschool-aged children. Therefore, additional dose-finding studies have been performed in children (Girgsdies and Rosenkranz, 1996), and the antigen content of the pediatric vaccines was reduced to half the antigen dose, compared with the adult vaccines. The antigen content per dose of FSME-IMMUN® is currently 2.4 µg for adults and 1.2 µg for children aged 1–15 years old; for Encepur®, it is 1.5 µg for adults and 0.75 µg for children aged 1–11 years old (Barrett et al., 2003; Pavlova et al., 2003a; Zent and Broker, 2005).

Both vaccines are generally considered safe, though mild to moderate adverse effects occur in 16–25% of individuals, compared to 13% in placebo groups. Frequently reported events include mild local transient redness or pain at the site of injection, and fever, headache, muscle and joint pain and fatigue (Loew-Baselli et al., 2006; Demicheli et al., 2009). Such adverse effects were common in children prior to the introduction of pediatric vaccines, but since the reduction in antigen content, they have been reported much less frequently (Girgsdies and Rosenkranz, 1996; Barrett et al., 2003).

7.1. Vaccine immunogenicity

Data from clinical studies and post-marketing surveillance show that FSME-IMMUN® and Encepur® are safe, efficacious and interchangeable (Zavadska et al., 2013; Zent and Broker, 2005; Demicheli et al., 2009). Both are highly immunogenic, with seroconversion rates reaching 92%–100% after complete vaccination. Several studies have been performed to determine the cross-protection of European TBE vaccines, which were shown to offer protection against TBEV-FE and TBEV-Sib (Hayasaka et al., 2001; Leonova and Pavlenko, 2009; Orlinger et al., 2011; Domnich et al., 2014). Additional studies involving sera from donors following TBEV vaccination or infection and experiments in laboratory animals found a cross-protection against OHFV, Kyasanur virus (KFV) and Alkhumra/Alkuhrma virus, but the neutralization of Powassan virus (POWV) was minimal (Chidumayo et al., 2014; McAuley et al., 2017). However, the strain selected was an isolate from a human in Canada, while all the other viruses were from Europe/Asia. Canadian POWV isolates may provide different results in neutralization and *in vivo* protection experiments, since they have been evolving in very different environments for many years.

The presence of circulating TBEV antibodies is used to assess the immune response to the vaccine and estimate necessary booster intervals. The methods most commonly used to determine the antibody concentration are ELISA, virus neutralization or the hemagglutination-inhibition assay (HI) (Holzmann et al., 1996). Differences in detected antibody levels can be a consequence of different tests used; the commercially available ELISA tests, in particular, can produce significantly different results, due to the strain used for antigen production (Jilkova et al., 2009). Neutralization tests produce the most reliable results and are the best surrogate marker of protection against TBEV (Vene et al., 2007; Stiasny et al., 2009).

Several studies have been published on the immunogenicity of Encepur® and FSME-IMMUN® following primary immunization (Ehrlich et al., 2003; Zent et al., 2003; Loew-Baselli et al., 2006; Schoendorf et al., 2007; Schondorf et al., 2007; Wittermann et al., 2009b; Heinz et al., 2007). Various schedules have been proposed for both vaccines. Standard and rapid vaccination schemes are available. Rapid schedule is used in summer months to reduce the time interval between first and second application for rapid protection. Both approaches lead to similar protection efficiency in terms of antibody levels after the third dose. However, rapid schedule elicits lower immune response than the conventional schedule after the second dose, and antibodies decline more rapidly after the rapid immunization (Schondorf et al., 2007; Amicizia et al., 2013). The standard schedule recommends the administration of the first two doses 1–3 months apart and the third dose 5–12 month (FSME-IMMUN®) or 9–12 months (Encepur®) later (Fig. 7). Under the rapid schedule, FSME-IMMUN® is given on days 0 and 14, and the third dose after 5–12 months, and for Encepur® on days 0, 7, and 21 and a fourth dose 12–18 months later. With both vaccines, the seroconversion rate determined by ELISA, HI, or NT has been found to be 92–100%, and similarly high levels of immunogenicity have also been achieved with the rapid immunization schedule (Heinz et al., 2007; Wittermann et al., 2009a, 2009b; Pöllabauer et al., 2010; Loew-Baselli et al., 2011). Similar results were obtained for both standard and accelerated schemes in children with both FSME-IMMUN® (Junior) and Encepur-K®,

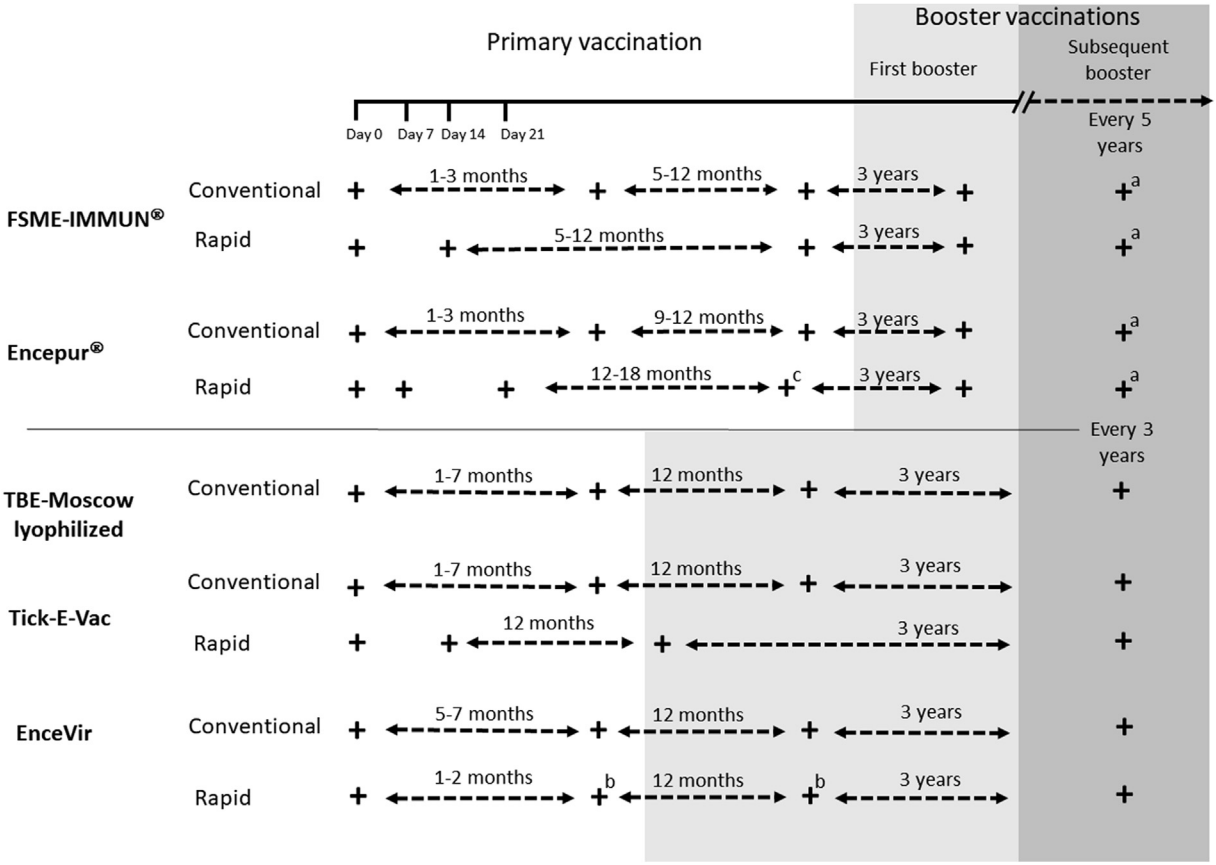

Fig. 7. Conventional (standard) and rapid vaccination schedules. Two vaccines are available in Europe:®FSME-IMMUN and®Encepur. The standard schedule calls for administration of the first two doses 1–3 months apart and the third dose 5–12 months (FSME-IMMUN) or 9–12 (Encepur). The rapid schedule is recommended for FSME-IMMUN on days 0 and 14, and the third dose after 5–12 months, and for ENCEPUR on days 0, 7, and 21 and a fourth dose 12–18 months later. Conventional schemes of the Russian vaccines TBE-Moscow and Tick-E-Vac are administered 1–7 months apart, first booster after 12 months with subsequent boosters every 3 years. During rapid schedule for Tick-E-Vac two doses are 14 days apart with first booster in 12 months and the following boosters every 3 years. Conventional vaccination scheme with EnceVir consists of second dose administered 5–7 months after the first dose, a first booster after 12 months and the following boosters every 3 years. In the case of the rapid schedule, the second dose is administered 1-2 months after the first dose, the first booster after 12 months and following boosters every 3 years. Vaccinations are marked with +. First booster is indicated with a light grey background, subsequent boosters with dark grey background. a = Booster intervals should be every 3 years for the elderly. b = Double dose of total 1 ml c = Considered as the first booster.

after receiving all three primary doses (Wittermann et al., 2009b; Pöllabauer et al., 2010).

Several studies have shown that the antibody response to vaccination is generally lower in the elderly population than in young adults, and the rate of antibody decline is faster in those over 60 years of age (Hainz et al., 2005; Weinberger et al., 2010; Paulke-Korinek et al., 2013). Data on immunogenicity induced by TBE vaccines in immunosuppressed patients are scarce. A study in Sweden of treated rheumatoid arthritis patients showed that the standard vaccination scheme does not produce a satisfactory antibody response, and the immune response was significantly different from age-matched healthy controls. An additional dose of vaccine is recommended (Hertzell et al., 2016). With both vaccines, the manufacturers recommend a booster 3 years after primary vaccination, followed by boosters every 5 years, or every 3 years in the elderly. Longitudinal studies have shown that geometric mean titres (GMTs) of neutralizing antibodies decline at a slower rate following at least one booster, compared to primary vaccination (Rendi-Wagner et al., 2004, 2006; 2007; Loew-Baselli et al., 2009; Paulke-Korinek et al., 2009; Plentz et al., 2009; Beran et al., 2014; Wittermann et al., 2015). Immunity after at least one booster vaccination lasts more than 5 years. Several studies have reported that, even 10 years after receiving primary vaccination followed by a booster, 77–84% of adult recipients remain seropositive (Paulke-Korinek et al., 2013; Konior et al., 2017).

Studies performed to date have described similar rates of antibody decline in all age groups. Nevertheless, the antibody decline is greater in those over 60, because they achieve lower antibody titres after booster vaccinations, especially if primary vaccination occus after the age of 60 (Hainz et al., 2005;; Weinberger et al., 2010; Galgani et al., 2017; Konior et al., 2017). Irregular vaccination schedules may lead to temporarily inadequate protection, but it can be re-established quickly through the administration of a single catch-up dose of either vaccine, regardless of age, number of previous vaccinations or interval since last vaccination (Askling et al., 2012; Schosser et al., 2014; Aerssens et al., 2016).

7.2. Vaccine effectiveness, safety, and coverage in EU countries

The incidence of TBE has decreased substantially in endemic regions of Europe where vaccination programs have been implemented successfully. Prior to vaccination, Austria had the highest recorded morbidity for TBE in Europe, but vaccination coverage has been steadily increasing since the 1970s, when the first vaccine was developed. Almost 88% of the Austrian population has now received at least one dose, and 58% maintain a regular vaccination schedule. Field studies have shown that the overall effectiveness in regularly vaccinated individuals is almost 99% and, according to available data, vaccination prevented approximately 2800 cases in Austria between 2000 and 2006 (Kunz, 2003; Heinz et al., 2007).

Vaccination rates in other TBE-endemic European countries are still

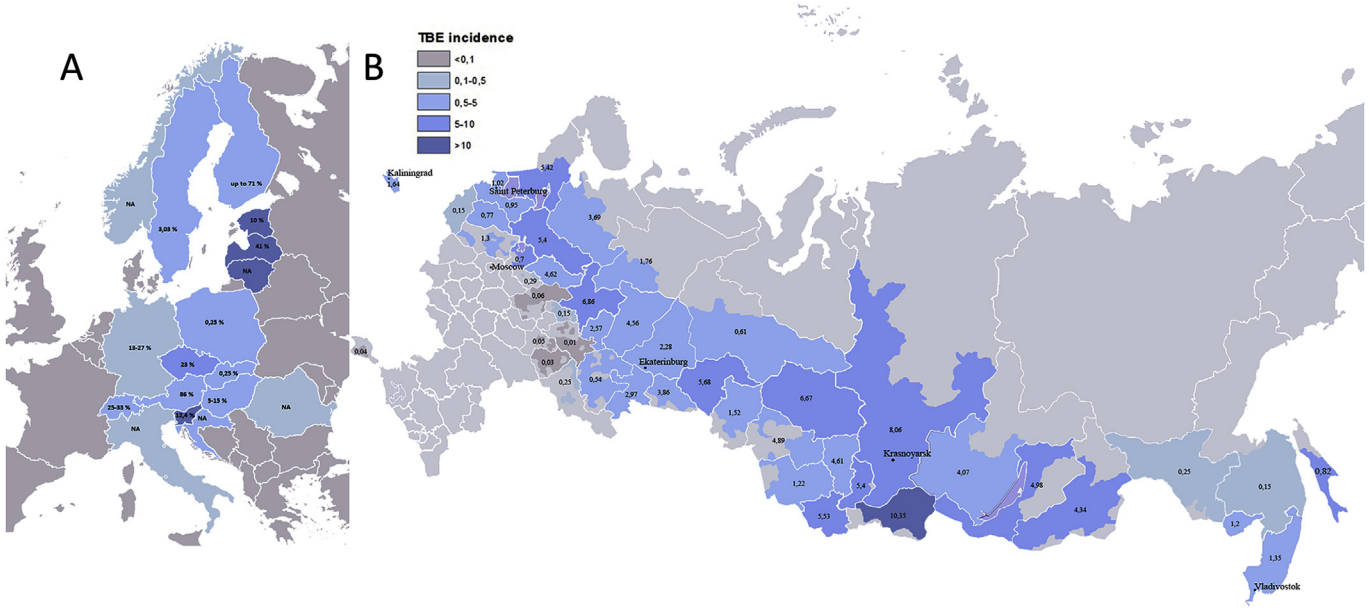

Fig. 8. TBE incidence in endemic countries in Europe (A) and in Russia (B). Endemic areas are wide-spread across the southern part of the non-tropical forest belt of Eurasia, from far eastern Russia to western Europe. The maps were prepared based on data originating from local public health authorities. Black numbers in (A) indicate TBE vaccination rates in Europe. NA, no data available on vaccination rates in (A). Black numbers in (B) indicate TBE incidence rates in Russia.

relatively low, with little or no effect on disease incidence (Fig. 8A). The only country other than Austria in which the vaccination rate exceeds 50% is Latvia, where the rate in children in highly endemic areas is 77%. In this case, TBE has been part of the national vaccination scheme since 2007, and a reduction of 12.5% in cases has occurred in children in highly endemic areas. By 2010, the vaccination rate for the whole population of Latvia was 41% (Zavadska et al., 2013). Åland Island in Finland also has high vaccination coverage (71%). In other endemic European countries, vaccination rates are between 0 and 33% (Czech Republic 23%, Germany 13–27%, Estonia 10%, Hungary 5–15%, Lithuania low, Poland 0.34%, Slovakia 0.25% in adults and 0.4% in children, Slovenia 12.4%, Sweden 11%, and Switzerland 25–33%) (Zavadska et al., 2013; Kunze, 2015). Both vaccines are available in most European countries, apart from Bulgaria, where none is registered, and Romania, where only the German vaccine is available. Apart from Latvia, TBE vaccination is not a part of a national vaccination program in European countries, but it is highly recommended in high-risk areas and advised for high-risk groups such as forestry workers, farmers and military personnel (Zavadska et al., 2013).

Vaccine breakthroughs are rare, but there have been several confirmed cases of TBE which developed despite vaccination. Twenty-five cases of TBE after vaccination were reported in Austria in the years 2002–2008, 27 in Sweden in the years 2000–2008, and 39 in Slovenia in the past 15 years, which is 1.7% of all laboratory-confirmed cases. Of these 91 cases, 54 received complete vaccination and 37 received with only 1–2 doses, or received irregular vaccination (Stiasny et al., 2009; Andersson et al., 2010; Lotric-Furlan et al., 2017). Approximately 70% of these patients are more than 50 years old, and acute illness in patients with breakthrough TBE is more severe than in unvaccinated patients who develop the disease. The mechanism of vaccine breakthrough has not been studied to date, therefore any hypothesis is premature. Generally, diagnosing vaccine failure can be confusing because the development of specific IgM is delayed, and initially undetectable, but there is an increase in TBEV-specific IgG in the serum (Stiasny et al., 2009; Andersson et al., 2010; Grgic-Vitek et al., 2010; Lotric-Furlan et al., 2017).

8. TBE vaccines in Russia

8.1. History of vaccine production

In 1937–1939 three expeditions to the Far East of USSR were organized, where many cases of severe CNS damage were recorded with a high mortality rate, and TBEV was discovered (Silber, 1939). During the first expedition in 1937 M. P. Chumakov, V. D. Solovyov and A. A. Shubladze suffered TBE and remained disabled for life. Following the first expedition, the first vaccine was prepared and it underwent clinical trials in 1938. In that year, Dr. N. V. Kagan and her technician N. Y. Utkina died during vaccine preparation, and in 1939 parasitologist B. I. Pomerantsev died after multiple tick bites.

The vaccine was prepared as a formaldehyde-inactivated 1% mouse brain suspension from the brains of mice intracerebrally infected with the Sofjin strain of TBEV-FE that had been isolated from the brain of a patient in Primorskiy Kray, Russia, in 1937 (Kagan, 1939; Smorodintseff et al., 1941). The first human trials were conducted in 1939. Among 925 volunteers who received two subcutaneous doses of the vaccine, only two suffered from mild forms of TBE after a subsequent tick bite, while in the control group of 1185 individuals, 27 cases were recorded, 7 with a fatal outcome. Beginning in 1958, a vaccine variant of formaldehyde-inactivated 2.5% mouse brain suspension was used in different regions of the USSR. It was effective, but a major problem was the high level of allergic reactions among vaccinated individuals (Smorodintsev and Doubov, 1986).

In the 1960s, studies were begun on the development of inactivated vaccines using virus grown in various cell lines. Since 1962, several versions, based on the Sofjin strain, were developed and released. The first was a formaldehyde-inactivated antigen of the Sofjin strain adsorbed on aluminum hydroxide (Chumakov et al., 1963a, 1963b, 1965a,b). Vaccine was prepared from the culture supernatant of PCECs infected with brain suspensions from TBEV-inoculated suckling mice. After virus inactivation with formaldehyde (200 μg/ml), the preparation was purified by separation, followed by clarification and sterile filtration. Human albumin (1 mg/ml) was used as a preservative. The vaccine was administered subcutaneously at a dose volume of 1 ml for recipients aged 7 years and older and 0.5 ml for those 4–6 years of age. As it had low immunogenicity, the primary course consisted of four

injections, with annual revaccinations for the next 3 years. Several clinical trial campaigns with different vaccine preparations were carried out from 1960 to 1975. These were the first carefully performed field trials to provide evidence of efficacy with this low-concentration vaccine (Lvov et al., 1963). The vaccine was widely used in the 1970s-1980s throughout the USSR, but ultimately required too many injections and did not provide the level of protection needed (Smorodintsev and Doubov, 1986). At the same time, a highly virulent TBEV strain 205 was used for the preparation and use of a non-concentrated, non-purified inactivated vaccine (Chumakov et al., 1990, 1991), but a high rate of post-vaccine adverse reactions led to its discontinuation.

It was concluded that the best solution was to use a concentrated inactivated, purified vaccine, or to make use of a live vaccine. Several attempts were made to prepare a live vaccine from Langat virus (Price et al., 1970; Il'enko et al., 1968, 1989; Mayer et al., 1975; Doubov et al., 1969, 1971), or from louping ill virus, which is closely related to TBEV (Andzhaparidze and Stepanova, 1970), and from various TBEV strains (Erofeev et al., 1976; Mayer and Rajcani, 1967). The most elaborate randomized double-blind clinical trials with the Langat virus involved 649,479 persons (Doubov et al., 1969; 1971). They were performed in comparison with inactivated, purified vaccine in two regions (Perm and Sverdlovsk) involving 10 administrative districts, that included 684 settlements. In total 35 post-vaccination cases were recorded, after which live vaccine development was terminated. Nevertheless, the Doubov vaccination trials demonstrated the efficacy of such a vaccine not only with subcutaneous administration, but also per oral administration, and no cases of chronic infections in vaccinated individuals were reported (Shapoval et al., 1989).

An inactivated TBE vaccine based on the Sofjin strain was developed in the 1980s (El'bert et al., 1980, 1984, 1985) and has been produced as a commercial preparation since 1982. This vaccine was a lyophilized purified concentrated suspension of formaldehyde-inactivated virus obtained by reproduction in PCECs, and was intended for the prophylactic vaccination of adults (> 18 years of age), and also for vaccination of blood donors to obtain specific immunoglobulins. Initially, a combination of two methods was used to purify the preparation: filtration and flow ultracentrifugation in a sucrose gradient. The efficiency of purification was later increased by using ultrafiltration and chromatography. Vaccination was performed with two subcutaneous injections of 0.5 ml of vaccine at 1–7-month intervals. Clinical trials demonstrated a high level of immunogenicity and a low level of reactogenicity (Popov et al., 1985). In 1989, a new technology for vaccine purification with protamine sulfate was introduced (El'bert et al., 1989, 1990). To date, over 25 million doses of this highly effective concentrated vaccine have been used for prophylactic vaccination against TBE in Russia and countries of the former Soviet Union.

8.2. Currently produced Russian vaccines

Three vaccines are produced in the Russian Federation. “TBE vaccine Moscow” and “Tick-E-Vac” (“Klesch-E-Vac”) are both produced by the Chumakov FSC R&D IBP RAS in Moscow. “EnceVir®” vaccine is produced by Microgen (a branch of the FSUC “SIC “Microgen” of the MoH of Russia ”SIC “Virion”, Tomsk) (Table 2). The vaccines produced in Moscow are based on the Sofjin strain (Vorovitch et al., 2015) and EnceVir® on strain 205 (Safronov et al., 1991; Krasilnikov et al., 2004) of the Far Eastern subtype.

"TBE vaccine Moscow" is tissue cultured, purified, concentrated, inactivated, and lyophilized. It has been in use since 1982, and was approved for pediatric use it 2002. This vaccine is intended for the vaccination of children from 3 years of age to adults (dose 0.5 ml). During its development, the optimal containment of antigen was determined (1 ± 0.5 μg/ml for the Sofjin strain). The vaccine is sold in solution, together with an aluminum hydroxide gel (0.6–1.0 mg/ml in the final suspension).

“Tick-E-Vac” is the second preparation of a cultured, purified, concentrated, inactivated, adsorbed vaccine based on the Sofjin strain, which was released in 2012. It is available in two versions: a 0.25 ml dose for children from 1 to 16 years of age and a 0.5 ml dose for individuals 16 and older (Vorovitch et al., 2012).

“EnceVir®” is a tissue cultured, purified, concentrated, inactivated, adsorbed suspension based on strain 205, which has been produced since 2001 (Krasil'nikov et al., 2004). It is also available in two versions: as EnceVir Neo® for children from 3 to 17 years of age (dose 0.25 ml; 0.3–1.5 μg TBEV antigen) and as EnceVir® for individuals of 18 years and older (dose 0.5 ml).

The vaccination schemes are similar for all three vaccines. The primary course includes two intramuscular injections. Vaccines can be used according to a standard schedule with an interval of 1–7 months, plus an emergency schedule with an interval of just 14 days. The course of two vaccinations provide a full protective effect, and the recipient can visit endemic territories just 2 weeks after a second vaccination. The first revaccination should be done 1 year after the second immunization with subsequent revaccinations every 3 years. Like the European vaccines, the Russian vaccines belong to the third generation of TBE vaccines. Manufacturing technologies are practically identical between the two manufacturers due to the technology transfer from the FSBSI "Chumakov FSC R&D IBP RAS" in Moscow to Microgen in Tomsk. PCECs are used as the cell substrate for amplification. Virus-containing cell supernatant is inactivated by formaldehyde, clarified from cell debris and tissue fragments by filtration, concentrated by centrifugation, then further fractionated by gel filtration to obtain a specific fraction. The final preparation is stabilized with human albumin, sucrose, gelatoze (only in the lyophilized TBE vaccine Moscow), protamine sulfate (up to 5 mg per dose), and buffer salts. The manufacturing process was in accordance with the national control regulations. Quality controls include safety testing to prove complete inactivation of the virus, and immunogenicity testing using BALB/c mice for immunization followed by challenge with the Absettarov strain of the European subtype to determine the immunogenicity coefficient in comparison to standard samples and the minimal immunization dose (MID_{50}). Russian vaccines do not contain antibiotics or other preservatives. The protein content (including viral antigen) in TBE vaccine Moscow and EnceVir® is 12 ± 8 μg per dose.

8.3. Clinical trials

Each vaccine version from each manufacturer has passed through clinical trials. Trials of the formerly used preparations showed low reactogenicity and immunogenicity (Vorob'eva et al., 1983; Elbert et al., 1989; Pavlova et al., 1999, 2003a; Gorbunov et al., 2002a, 2002b; Vorovitch et al., 2017). Clinical trials of the lyophylized version of the vaccine TBE Moscow were conducted in the 1980–90s. In 2001–2002, blinded controlled trials were conducted with the EvceVir® TBE vaccine Moscow (lyophilized) in 400 adults (Gorbunov et al., 2002a, 2002b) and 325 children aged 3–18 (Pavlova et al., 2003b). According to standard and rapid schedules for both vaccines, these studies showed adult seroconversion rates of 100% and of > 96% in children. In 2011, randomized blind comparative trials of Tick-E-Vac and EnceVir® vaccines were conducted with adults 17–60 years old (Vorovitch et al., 2017; Maikova et al., 2019). Studies involving children and adolescents age 1–16 were conducted with Tick-E-Vac and FSME-IMMUN® (Ankudinova et al., 2014; Maikova et al., 2016). Seroconversion rates after two immunizations in both adults and children were 100% for both vaccines using the standard vaccination scheme, and 95% after rapid vaccination.

8.4. Vaccine safety and coverage

The immunogenicity of Russian vaccines against a wide range of TBEV strains has been shown in *in vitro* studies of sera from immunized mice (Khotlubeĭ et al., 1982; Chernokhaeva et al., 2016), in studies of

protective efficacy in mice (Afonina et al., 2014; Chernokhaeva et al., 2016), and in vaccine recipients (Lvov et al., 1963; Vorob'eva et al., 1996; Surova et al., 2002; Leonova and Pavlenko, 2009, 2010; Morozova et al., 2014; Maikova et al., 2016). The introduction of widespread vaccination has resulted in a significant decrease in the incidence of TBE (Borodina et al., 2004; Loshko et al., 2004). This impact on disease incidence was reported in a region with > 80% vaccination coverage, where the subtype of the vaccine strain differed from the locally circulating strain(s) (Pogodina et al., 2006; Romanenko et al., 2006, 2007).

Overall in Russia, vaccination coverage differs significantly between regions. Vaccination of adolescents (at school) and of high-risk groups is obligatory in the endemic territories as prescribed by the Rospotrebnadzor regulations, funded from the regional budget. The list of endemic territories is updated annually. In some endemic areas, vaccination coverage is high, for example, in the Sverdlovsk region vaccination coverage is 88% (Romanenko et al., 2006, 2007) and in the Altaisky Krai more than 50% (www.rospotrebnadzot.ru), but in other endemic regions, less than 10% of the population is vaccinated. The reason for these differences is that vaccination is carried out in endemic districts, but the level of vaccine coverage is calculated for the entire regions as a whole. In non-endemic areas, vaccination is optional, and, therefore vaccination effects are hard to assess.

9. Cross-protection against other flaviviruses

With a growing abundance of ticks and an increasing area of distribution, the population threatened by tick-borne infections, including flaviviral infections, has increased. Based on high genome conservation (Grard et al., 2007) and significant cross-reactivity among tick-borne flaviviruses (Clarke, 1964; Casals and Webster, 1944; Calisher et al., 1989; Pervikov et al., 1975), attempts have been made to use approved TBE vaccines for prophylaxis against other flaviviral infections. Two million doses of a TBEV-FE inactivated vaccine were administered during a KFD outbreak in India, but without a desired effect when KFD has been reported also in the vaccinated individuals (Aniker and Work, 1962; Shah et al., 1962). Live-attenuated candidate vaccines have demonstrated some protection against OHFV (Smorodintsev and Doubov, 1986) and Kyasanur forest disease virus (KFDV) (Erofeev et al., 1976) in mice and nonhuman primates. Modern concentrated TBE vaccines also demonstrated high protection from OHFV in mice (Chernokhaeva et al., 2016; Chidumayo et al., 2014).

Live, attenuated vaccines may be more likely than inactivated vaccines to cause antibody-enhanced replication during subsequent infection by the virus, because the epitopes are likely to be modified during the inactivation process, as seen for other viruses (Fergusson et al., 1993). In experiments with monkeys challenged with OHFV, it was shown that double immunization with an inactivated TBE vaccine protected animals against the hemorrhagic syndrome, but did not prevent virus invasion of the CNS (Pripuzova et al., 2013). The vaccine could be used for further studies as a surrogate vaccine against other tick-borne infections. Inactivated TBE vaccines have also been studied in mice challenged with POWV. Little protection was observed, but there were no signs of ADE (Chernokhaeva et al., 2016).

10. Recommendations for future TBE research

Future research should focus on the development and application of practical and affordable disease control approaches, including cheaper and more effective vaccines conferring long-lasting protection, together with effective therapies, such as small-molecule antivirals. The possible role of specific immunoglobulins in ADE reactions or the development of chronic forms of TBE requires further investigation. Detailed knowledge of TBEV biology and mechanisms of pathogenesis, including virus-host interactions at the molecular and cellular levels, are prerequisites for successful future research.

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