Monograph

Tick-Borne Encephalitis (TBE, FSME)
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Introduction

“In even though TBE was first described as early as 1931, this dangerous form of encephalitis has been underestimated for a long time.”

(C. Kunz, M D, co-inventor of the first Western-European TBE vaccine, Vienna)

In several European countries, tick-borne encephalitis (TBE) is one of the most common human infections of the central nervous system. The disease agent, i.e., the TBE virus (TBEV), is transmitted through tick bites. The virus persists in what are called natural foci, where it circulates among both vertebrate hosts (mainly rodents) and the arthropod host (tick). The disease occurs in Western and Central Europe, Scandinavia, in the countries that made up the former Soviet Union, and Asia, corresponding to the distribution of the ixodid tick reservoir. Most natural foci are well described, but new TBE areas could emerge and latent ones re-emerge. At least 10,000 cases of TBE are referred to hospitals each year. TBE has also become an international public health problem because of the increasing mobility of people traveling to risk areas. Today, the risk of infection is especially high for all people living in or visiting endemic areas who pursue leisure activities out in nature.

The TBE virus is only rarely found in Bulgaria, Greece, Italy, Norway, Romania, and Japan, with only sporadic cases reported so far. In several European countries, no TBE cases have occurred, among them Great Britain, Ireland, Iceland, Belgium, the Netherlands, Luxemburg, Spain, and Portugal.

The typical clinical picture of TBE is characterized by a biphasic course with non-specific influenza-like symptoms, followed by an asymptomatic interval and a second stage of the disease with at least four clinical manifestations of varying severity, i.e., meningitis, meningoencephalitis,
TBE virus is common in endemic foci in:

- Albania
- Austria
- Belarus
- Bosnia
- Croatia
- Czech Republic
- Denmark
- Estonia
- Finland
- France
- Germany
- Greece
- Hungary
- Italy
- Latvia
- Liechtenstein
- Lithuania
- Liechtenstein
- Norway
- Poland
- Romania
- Russia
- Serbia
- Slovakia
- Slovenia
- Sweden
- Switzerland
- Ukraine
2. Etiology

“The different subtypes of TBE virus in Europe and Asia are antigenically closely related - a prerequisite for the prevention of TBE with a single vaccine strain.”

(F.X. Heinz, PHD, Vienna)

2.1. The TBE virus

The TBE virus (TBEV), like the causative agents of yellow fever, Japanese encephalitis, and dengue fever, is a member of the flavivirus genus belonging to the flaviviridae family. Most flaviviruses are what are called arthropod-borne viruses, or arboviruses, because of their specific route of transmission by infected ticks (e.g., TBE virus, Louping ill virus) or mosquitoes (e.g., yellow fever virus, dengue viruses, West Nile virus, and Japanese encephalitis virus).

Flaviviruses are spherical, lipid-enveloped RNA viruses with a diameter of approximately 50nm (Figure 1). They contain only 3 different structural proteins, i.e., proteins C (capsid), protein M (membrane), and protein E (envelope) (Figure 2). Protein C is the only protein component of capsid, which encloses a positive-stranded RNA approximately 11,000 nucleotides in length. This RNA codes for the three structural proteins and a set of 7 non-structural proteins required for virus replication in the cell.

The proteins E and M are incorporated in the viral membrane. Glycoprotein E, the main component of the viral surface (Figure 2), is responsible for the formation of neutralizing antibodies and the induction of protective immunity. By isolating a soluble, crystallizable form of the TBE virus protein E, it was possible to elucidate its three-dimensional conformation using X-ray diffraction analysis.

Structural analysis (Figure 3) has shown that protein E, unlike the envelope proteins of many other lipid-enveloped viruses, does not form spi-
ke-like projections, but is aligned parallel to the viral surface (Figure 2).

Antigen analyses using monoclonal antibodies and comparisons of sequences of various virus isolates have shown that the TBE virus is fairly homogeneous in endemic areas of Europe (European subtype) and is not subject to significant antigenic variations under natural environmental conditions.10, 11)

Two further subtypes (Siberian and Far Eastern) have been identified, which predominately circulate in the Asian part of Russia, Northern Japan, and Northern China. These subtypes are closely related to the European subtype, having a 94-95% identity in their E-protein amino acid sequences. The European strains are mainly transmitted by Ixodes ricinus, whereas the Siberian and Far Eastern strains are transmitted mainly by I. persulcatus. Because of their close antigenic relationships, there is cross-protection between the different TBE virus subtypes.12) All subtypes are closely related both antigenically and phylogenetically.

2.2. Virus transmission

2.2.1. Transmission through ticks

Ticks are the chief carriers (vectors) and reservoir hosts of the TBE virus in nature. The lack of digestive enzymes in the tick gut favors the survival of ingested microorganisms and may explain why ticks transmit a greater variety of pathogens than any other group of arthropods.13) Their ability to feed on the blood of a variety of host animals and to adapt to domestic animal species, as well as their long life cycle make them ideal vectors for a variety of pathogens (rickettsiae, spirochetes, other bacteria, fungi, protozoans, nematodes, viruses), among them the TBE virus.

The TBE virus can be transmitted to man or other hosts by larvae, nymphs, or adult ticks (Figure 4).

2.2.2. Other routes of transmission

Infection by the alimentary route resulting from ingestion of raw milk has been reported in Slovakia, Poland, and other Eastern European countries. Recently, the family outbreaks of TBE in Lithuania have reappeared. It is reported that in the year 2000 4% of TBE patients were infected via unboiled milk.14) Also, in Slovakia, goats and sheep play an important role in alimentary TBE infections.15) Since 1974, more than 50 cases of TBE have occurred in Slovakia after the...
patients had eaten cheese made from raw sheep milk or drunk home produced raw goat or sheep milk.15)

Laboratory infections have likewise been reported.16) Although not observed so far, man-to-man transmission is also a theoretical possibility, e.g., through blood transfusion from a viremic to a healthy person.17)

2.3. TBE natural foci

A natural focus, as defined by Pawlowsky, is a "region of distinct geographic features and ecological settings where by way of evolution a certain interrelation ship between the species has developed, i.e. by the pathogen (microorganism) on the one hand and its carrier (vector) on the other. The latter transmits the pathogen from a vertebrate host, acting as the donor of infection, to another - recipient - host under environmental conditions that are either conducive or adverse to further circulation of the agent in such biozoonoses".18)

The continental distribution of TBE in Europe is statistically associated with a specific pattern of the seasonal dynamics of Ixodes ricinus, and a particular characteristic of the seasonal land surface temperature profile.19) The development of a TBE natural focus also depends on the coincidence of other factors (Table 1).

Circulation of the TBE virus also depends on the population density of ticks and their hosts. Virus prevalence in the tick population within TBE foci is determined by the duration of viremia in hosts, because the virus is mostly ingested by ticks while engorging on a viremic host. Virus circulation in nature is also influenced by the percentage of immune hosts in a particular region.

The properties of the biotope also play a role in the development of TBE foci. In Austria, more than 90% of all natural foci are within the 7°C annual isotherm. Rare isolated natural foci have been observed up to a height of 1,300 meters above sea level.21)

Climate is another determinant of tick-borne disease dynamics. Even if the major discontinuities in TBE incidence cannot be explained satisfactorily by the recorded temperature increases, the seasonal shifts in reported cases of TBE in Central and North-Eastern Europe suggest that TBE virus transmission dynamics have changed - perhaps as a result of warmer temperatures.20) Although the dependence of TBE on temperature is not a direct one and various factors could be involved, an impact of climate warming on the vertical disease distribution in Central Europe is evident.22)

Tick activity also depends on soil humidity and relative humidity. The critical water equilibrium for I. ricinus is at 92% relative humidity. Without blood feeding, individual ticks can survive at a higher relative humidity for several months, but they soon perish at levels below 92% relative humidity.23)

2.4. The vector - the ixodid tick

Throughout the world, 850 tick species have been described. Eight members of the family of hard ticks have become notorious as carriers of disease agents in our climate. Ixodes ricinus, the common castor-bean tick, is the most important and most common tick species in Europe (Figure 4) and, thus, mainly responsible for the spread of TBE virus (Western subtype) in Europe. The
Far-Eastern subtype of the TBE virus is found mainly beyond the Ural mountains; its primary vector is *Ixodes persulcatus*.

The scientific name of *I. ricinus* is derived from the replete tick's close resemblance to a ricinus seed or castor bean. A fasting adult female is 3-4 mm in size, while male ticks are about 2.5 mm long. The body, which is variously covered with hairs as well as warts and rings, is vastly extensible in the female and often takes on a light grey color after blood feeding. The female can take in up to 100-200 times its own body weight in blood, thus increasing its volume approximately 120 fold. *I. ricinus* is equipped with piercing and sucking mouth parts (chelicerae and hypopharynx) (Figure 5). The saliva of blood-feeding ticks contains numerous bioactive components with a broad spectrum of pharmacological properties, among them anti-coagulants, enzymes and inhibitors, local anesthetics and anti-inflammatory compounds, toxins and other secretions, such as cement for anchoring the mouth parts in the host's skin. By use of sense organs, the tick can react to thermic, chemical, and physical stimuli, such as vibrations or changes in temperature caused by a passing host. The CO$_2$ and butyric acid discharged by the host are also thought to play a role.

2.4.1. Developmental cycle

The common castor-bean tick *I. ricinus* spends most of its life free-living on the ground or among vegetation. The ticks are characterized by a comparatively long life cycle, lasting several years during which the infecting virus may be maintained from one developmental stage of the tick to the next (Figure 6). Hence, ticks act as highly efficient reservoirs of flaviviruses. Many tick-borne flaviviruses are transmitted vertically, from adult to offspring, although the frequency is too low to maintain the viruses solely in the tick population. Instead, the survival of tick-borne flaviviruses is dependent on horizontal transmission, both from an infected tick to a susceptible vertebrate host and from an infected vertebrate to uninfected ticks feeding on the animal.

Copulation usually takes place on a host prior to blood feeding. Following copulation, the female spends six to eleven days feeding on blood and during subsequent months deposits 500 to 5,000 eggs (Figure 7) in several places in the loose top layer of the soil. Several weeks later, larvae measuring 0.6-1.0 mm hatch from the eggs. Unlike the subsequent developmental stages (nymph and imago), larvae only have three pairs of legs, no stigmata, and no sexual openings.

In each stage of development from larva to nymph and imago, ticks have to feed on a vertebrate host at least once before they can develop into the next stage. Male ticks do not feed on blood, but take only a small amount of tissue fluid during a short feed. Larvae feed on a host for two to five days before they drop off and molt into nymphs. These feed on a vertebrate host again for two to seven days and metamorphose into adults (imagos).
The duration of the developmental cycle of one tick generation from egg to oviposition by a fertilized female varies, according to the literature, between six months and eight years. The average time in Central Europe is thought to be two years (Figure 6), although in adverse environmental conditions each stage of development may take longer.

2.4.2. Seasonal tick activity

All developmental stages of I. ricinus hibernate under leaf litter in places where the temperature may be as low as 0°C, or for short periods even lower, and where relative humidity amounts to at least 92%. Eggs and starved larvae perish at temperatures below –7°C. Tick activity starts when the soil temperature rises to 5–7°C in March or April and ends late in the year when the average air temperature has declined to about the same values in October or November.

The seasonal peaks of tick activity depend on climatic factors. In Central Europe, a two-peak incidence curve has been observed for all developmental stages, with maximum activities in May or June and September or October (Figure 8). In Northern Europe and in mountain regions, these two peaks converge into a single maximum in the summer months. In Mediterranean areas, maximum tick activity occurs between November and January.

Wet summers and mild winters tend to increase the tick population density. Warmer springs (March-May) might permit an earlier onset of questing activity, while raised temperatures throughout the spring-autumn period (March-September) would accelerate inter-stadial development.

Female ticks feeding in spring start to deposit eggs in early July. The larvae hatch in the same year, but mostly find their host in the following spring. Larvae and nymphs feeding in spring or early summer undergo metamorphosis and, in the same year, appear as the next stage of development. The activity of the larvae of I. ricinus usually starts one month later than that of nymphs and adults.

2.4.3. Mechanism of transmission

The TBE virus in I. ricinus can be transmitted either from one development stage to the next (trans-stadial transmission) or from fertilized female to egg (trans-ovarian transmission) (Figure 9). Usually, larvae and nymphs become infected by feeding on viremic hosts. As nymphs or imagos, they then pass on the virus to other warm-blooded vertebrates. Ticks themselves do not develop the disease. The virus hibernates in ticks. Once a tick is infected, it carries the virus for life. In the period that precedes molting, the virus multiplies in the tick and invades nearly all its organs.

Female ticks usually transmit the virus to a single host only. Male ticks feed more often and, in this way, may infect several vertebrates. After attachment to the host, twelve hours may pass until the tick starts feeding. On humans, ticks prefer to attach themselves to the hair-covered portion of the head, behind the ears, to
Figure 7: Some time after copulation, the female, having expanded to 200 times of its former volume, deposits up to 5,000 eggs before dying. The second picture shows a larva crawling on eggs.

the elbows and backs of knees, hands, and feet. Owing to the anesthetizing effect of the tick’s saliva, which contains analgesic, anti-inflammatory, and coagulation-inhibiting substances, the procedure causes no pain and often passes unnoticed by the host.30)

The TBE virus is transferred to the host through the saliva of an infected tick. Conversely, TBE virus contained in host tissue enters the tick’s intestine with blood feeding. A tick does not need to feed for a long time to pass on the infection – a short feed of tissue fluid by a male tick may suffice to transmit the virus.41) Tick bites often go unnoticed, which may be the main reason why persons with manifest TBE frequently cannot remember having been bitten by a tick.

2.4.4. Mixed infection of ticks

The spread of mixed infections with natural focality transmitted by ixodid ticks is a well recognized phenomenon.42) I. ricinus ticks coinfectected by Borrelia burgdorferi, Babesia microti, and Ehrlichia phagocytophila are common. Various combinations of pathogens simultaneously infecting the same ixodid tick have been described. The main combinations are TBE virus and Borrelia spp. or TBE virus and Coxiella burnetii.43)

A Russian survey found that more than one-third of all infected tick individuals were multi-infected. Among these, more than 80% were dually infected and 13% contained three species of pathogens simultaneously. The prevalence of mixed infection by Borrelia and TBE virus in adult ticks varies depending on tick species and natural focus, reaching 5-10% in some places.44) The presence of Borrelia in ticks has no apparent effect on the TBE virus and vice versa, showing that these pathogens do not interfere with each other within the tick.44)

2.5. Hosts

The common castor-bean tick acts as a parasite on more than 100 different species of mammals, reptiles, and birds. Tables 2a and b give a selection of the most important hosts. TBE virus infection of I. ricinus by a host harboring the virus is only possible during the viremic stage in the host and if the TBE virus titer in blood is high enough. For most hosts, the TBE virus is apathogenic, i.e., these hosts hardly ever develop the disease.
An infected host develops specific antibodies to the TBE virus and then remains immune to re-infection for life. Under these conditions, TBE virus circulation in nature would soon come to an end. Thus, virus persistence in a natural focus depends on the following conditions:

- a population of hosts with a sufficient duration of viremia and a high virus titer,
- a sufficient number of young animals susceptible to infection,
- different species of hosts,
- large vertebrate hosts serving as feeding targets for numerous ticks.

**Duration of viremia:** In small mammals, such as the yellow-necked field mouse, the red-backed mole, the common mole, and the hazel mouse, a long viremic stage (2 to 8 days) and high virus titers are observed. Therefore, ticks are most likely to become infected by feeding on these hosts, in which the TBE virus can even hibernate.

In large mammals (roe, goat), viremia is short-lived, and only low virus titers are reached. However, recent findings suggest that with several ticks feeding on large mammals, non-viremic transmission of the virus to ticks may also play a role in the virus cycle. During the viremic stage, milk from goats, cows, and sheep contains the virus and may be a source of infection for man. Birds only pass through a very short viremic stage and play no role as reservoirs of TBE virus. However, they often serve as hosts for the immature stages of *I. ricinus* and may contribute to the spread of infected ticks.

Man is only of minor importance for ticks as a source of sustenance and infection. In the chain of virus transmission, man is a dead-end host.

### 2.6. The biotope

TBE focal areas normally exist in biotopes where *I. ricinus* and its hosts find optimal living conditions. Infected ticks are frequently found on forest fringes with adjacent grassland, glades, riverside meadows and marshlands, forest plantations with brushwood and shrubbery, on the transition between deciduous and coniferous forests, or between timber and coppice. Oak and hornbeam as well as beech and fir woods with rich undergrowth of weeds, ferns, elder, hazel, and bramble bushes provide an ideal habitat for ticks (Figure 10). Sites of infestation are frequently situated on sunny slopes facing south and having a low plant cover of shrubs and hedges.

Such rural landscapes, especially when benches, cross-country tracks, or barbecue pits are provided, attract many people so that an increased risk of infection must be expected. It has been shown in various studies that TBE natural foci are usually not eliminated by cultivation of the landscape. Exposure to ticks is also possible in newly created gardens. Ticks may also be transported to homes by way of dogs, flowers, branches, or on clothing. Reducing the habitats of small mammals to a few areas not suitable for cultivation also leads to an increased circulation of TBE virus, because the probability of virus transmission rises with the population density of the hosts.

Contrary to a widespread belief, ticks do not sit on trees and jump down onto their hosts, but rather prefer vegetation that is closer to ground level. Larvae are usually found on grass up to a
Vertebrate hosts of *Ixodes ricinus* which may transmit the virus - Wild animals

Ticks may bite birds or bats, thus becoming airborne.

Many ground-dwelling animals, such as various species of mice and lizards, attract ticks.

Hosts below and above ground include mole, weasel, marten, badger, porcupine, and squirrel.

Predators and prey alike attract ticks - from insectivores, such as hedgehog or shrew, to carnivores, such as fox and hare.

Ticks also feed on larger mammals, such as wild boar, mouflon, roe deer, and red deer.

Table 2a
level of 30 cm, nymphs on herbs and plants of less than 1 m, and imagos on weeds or shrubs up to 1.5 m high.\textsuperscript{39}

Keeping to the underside of foliage, ticks mostly sit at the ends of leaves or branches next to footpaths and the trails of wild animals, from where they drop onto their hosts or are brushed off by them. In adult humans, ticks tend to attach themselves to the legs or the gluteal and genital regions. In children, 75\% of tick bites are observed on the head. In the remaining cases, legs and arms, the trunk, and the gluteal and genital regions are affected.

Vertebrate hosts of Ixodes ricinus which may transmit the virus -
Domestic animals

Table 2b

Ticks suck blood from animals, such as dog, horse, sheep, goat, cattle - and, of course, humans.

Figure 10: Typical TBE biotope
Knowledge about the distribution, persistence, and intensity of tick-borne diseases enables us to characterize and predict transmission foci and to recommend preventive measures. To investigate the epidemiology of TBE, several methods can be employed:

- Describing clinical cases and their geographical localization
- Examination of ticks for the presence of the TBE virus (by PCR)
- Serological screening of tick-exposed persons

3.1. Distribution of TBE natural foci

The distribution of the TBE virus in ticks and vertebrate hosts covers almost the entire southern part of the nontropical Eurasian forest belt, from Alsace-Lorraine in the west to Vladivostok and the northern and eastern regions of China in the east (Figure 11). The true extent of TBE infections has only become clear during the past few years. Little is known about the rate of infection in China. In 1998, an isolated endemic area was identified in Hokkaido, Japan. The development of new natural foci and the stability of known endemic areas are determined by the factors listed in Table 1. The number of infected ticks in known natural foci may vary from year to year.

Widely differing figures are also given for TBE virus prevalence in the tick populations in the endemic areas of various European countries (Table 3). Usually, questing ticks are collected by flagging in special tick monitoring sites, and TBEV prevalence is investigated by examining individual ticks or tick pools. When investigations are carried out on ticks removed from humans, the TBEV prevalence can be up to ten times higher. The techniques of investigating TBEV prevalence in unfed versus partially engorged ticks are not standardized. Therefore, the prevalence values cannot be compared across Europe. Because ticks are usually infected for life, the degree of virus prevalence increases during their development from egg to adult arthropod. Compared to nymphs, 3 to 5 times more adult ticks are infected with the TBE virus.

<table>
<thead>
<tr>
<th>Country</th>
<th>Prevalence %</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Austria</td>
<td>&gt;0.44 (max. 6.2)</td>
<td>55</td>
</tr>
<tr>
<td>Finland</td>
<td>0.07-2.56</td>
<td>56</td>
</tr>
<tr>
<td>Italy</td>
<td>0.05</td>
<td>57</td>
</tr>
<tr>
<td>Sweden</td>
<td>0.1-1</td>
<td>58, 24</td>
</tr>
<tr>
<td>Switzerland</td>
<td>0.10-1.36</td>
<td>46</td>
</tr>
<tr>
<td>Germany (high-risk areas)</td>
<td>0.3-5.3</td>
<td>52</td>
</tr>
<tr>
<td>Latvia</td>
<td>1.7-26.6 (I. ricinus) 0-37 (I. persulcatus)</td>
<td>51, 52</td>
</tr>
<tr>
<td>Slovakia</td>
<td>13.7</td>
<td>15</td>
</tr>
</tbody>
</table>

Table 3
In a number of hosts, the TBE virus prevalence is much higher than in the tick population (Table 4). On account of their longer life span, large mammals can be repeatedly infested by infectious ticks. Also, due to their size they often serve as feeding targets for several ticks at a time. Either of these factor is conducive to the transmission of the TBE virus.

The risk of contracting TBE in the most affected countries increased considerably between 1974 and 2003 (Figure 12). For example, in Lithuania the incidence increased by an amazing 1,033% and in Germany by 574%. In addition to the already known risk areas, new risk areas formed in Norway and possibly in the southern part of Sweden. Also, more and more single TBE cases have recently been reported in non-risk areas. Along with the shift of I. ricinus to higher altitudes, a corresponding shift of TBE to higher altitudes has been expected. The only exception to this increase in TBE incidence is Austria, where national vaccination campaigns have lead to consistent immunization, reducing the number of new infections from 600 to about 60.

The increases in the frequency of hospitalization are based on a multitude of factors. Evidently, various factors work alongside, and this makes interpretation of strongly differing annual hospitalization and virus prevalence patterns difficult. The warming of the climate has been discussed...
as one of the reasons for an increase in tick prevalence. Table 5 summarizes ascertained contributing factors.

**Factors augmenting the incidence, prevalence, and distribution of vector-borne disease**

1. Increase in the human population
2. Increased population density (urbanization)
3. Migration of populations to suburban areas
4. Changing leisure habits  
   3. + 4.: Greater exposure to vectors, i.e., ticks  
      Greater exposure to animal reservoir of infections
5. Displacement of human populations as a result of conflicts; introduction of exotic diseases
6. Changes in agricultural practices
7. Increased reforestation  
   - increased density of deer population  
   - increased deer tick population  
   - increased incidence of Lyme disease and babesiosis

Table 5

### 3.2. TBE incidence in man

#### 3.2.1. Seroprevalence

Data on TBE seroprevalence in the general population and among the inhabitants of endemic areas are presented in Table 6. In endemic areas of Austria and Southern Germany, TBE prevalence has been found to be 4-8%. In the most severely affected areas in the east and southeast of Austria, a prevalence of up to 14% may be reached. Prevalence is also extremely high in some areas of the former USSR and former Czechoslovakia. A much higher percentage of TBE positive individuals has been observed among risk groups such as:

- Individuals working in agriculture and forestry
- Hikers, ramblers, people engaged in outdoor sports
- Collectors of mushrooms and berries.

Today, most people (90%) who will ultimately develop the disease come to TBE endemic areas in pursuit of recreational activities. In Central Europe and the Baltic states, recent increases in TBE may have arisen largely from changes in human behavior that have brought more people into contact with infected ticks. In Russia, the rigorous treatment of TBE natural focus territory was discontinued for environmental concerns in the 1980s. This may partly explain the increase in the tick population and rate of infective ticks in this region.

Infection with TBE virus may also happen at home, when infected ticks are inadvertently carried in with bunches of wild flowers, Christmas trees, clothes, or by dogs. Moreover, TBE virus infections are more and more frequently reported to have occurred in the patients’ own gardens, even in urban areas.
3.2.2. **TBE incidence in different age groups**

The lowest incidences of TBE have been found in children less than 3 years of age, with incidence rising with increasing age. The highest incidence reported in children was in the Khabarovsk region in Russia, where 26% of TBE cases had occurred in children aged 0-14 years.69) In Slovenia, children represented 23.5% of all confirmed TBE cases in the period between 1959 and 2000.70) In Austria, the 7- to 14-year-olds used to be the age group with the greatest annual incidence of TBE (19% of all cases). Today, due to the Austrian vaccination program and particularly the vaccination campaign in schools, children between 7 and 14 years are among the best-protected age groups (Figure 13). In Austria, most cases of TBE now occur in older age groups.71) In Sweden, about 10% of patients are younger than 15 years.72)

The youngest patient known thus far was a 6-week-old infant. The oldest patient was 83 who ultimately died, showing signs and symptoms of meningoencephalitis.73) As for TBE prevalence in the different age brackets, an increase with advancing age has been observed in TBE focal areas, although the prevalence in different endemic areas may vary.74)

3.2.3. **Seasonal variations of TBE incidence**

In many countries, two peaks of seasonal tick activity are observed, i.e., in spring and fall. The incidence of clinical cases of TBE lags about 4 weeks behind the seasonal tick activity (Figure 14). In some countries, including Poland, Germany (Baden-Wuerttemberg), Sweden, the Czech Republic, and recently also in Austria, only one peak of TBE incidence has been observed, occurring in July and August.75, 76)

3.2.4. **Risk of contracting TBE**

Exact calculations of the risk of infection and the resulting morbidity rates are extremely difficult to carry out, because tick bites often go unnoticed. In areas endemic for TBE, virus transmission may be estimated to occur in one of about 3-200 tick bites, depending on the prevalence of TBE virus in ticks (Table 3). In the different TBE endemic areas, the risk of human infection after a single tick bite varies between 1:200 and 1:1,000.26)

According to estimates by Roggendorf et al. in 1989, the risk of infection in German endemic areas was 1:900.80) It may be suspected that the risk of infection in Germany is much higher today. In a study of endemic areas in Sweden, the annual incidence was found to be between 1.2% and 2.4%, and the risk of infection following a tick bite was estimated to be about 1:600.81)
3.2.5. Annual TBE morbidity

Between 1997 and 2000, the average TBE incidence rate in Germany with 82.2 million inhabitants and 533 clinical cases was 0.17 per 100,000 per year. In 2005, the TBE incidence in Germany was 19.1 per 100,000 population, and based on preliminary data was even higher in 2006. In the German high-risk foci, the average incidence rates were 0.29 in Bavaria and 0.87 in Baden-Wuerttemberg. In Latvia, with 2.6 million inhabitants and 2,797 cases in the last four years, the average annual incidence rate was 26.9 per 100,000 population, placing Latvia among the countries with the highest TBE incidence world-wide.53)

Table 7 gives data on the annual morbidity of TBE in several European countries. It is evident that, in the past, morbidity among forestry workers in Austria was much higher than in the general population. Since regular vaccination campaigns have been carried out by the vocational organizations involved in combating TBE, morbidity in the most exposed groups has been impressively reduced (see also Section 3.2.1.).

Before the annual vaccination campaign was introduced in 1981, the incidence of TBE in Austria was in the range of 600 cases per year. As a result of the vaccination campaign with the Austrian TBE vaccine, the incidence has declined significantly, with only about 50 to 60 cases recorded annually.86) These figures clearly demonstrate the field effectiveness of the FSM E-
IMMUN vaccine by Baxter. At the time the campaign started, it was the only TBE vaccine in use.

3.2.6. Mortality

In very severe cases of TBE, death may occur within the first week after onset. It has been suggested that the Far-Eastern TBEV subtype is more pathogenic for humans than the European subtype, because the mortality rates in areas where the Far-Eastern subtype is prevalent have been reported to be significantly higher (5-20%) than in Europe (0-3.9%).

However, the data of seroprevalence studies do not support these findings. The prevalence of antibodies to TBEV in populations living in the endemic areas in Europe and Russia are in the range from 1% to 20% and from 30% to 100%, respectively. This suggests that a large proportion of mild diseases may not be diagnosed or may be underreported in some areas of Russia. The apparent difference in the severity of TBE in different areas may either reflect the true difference in the clinical presentation or be a result of different diagnostic criteria and patient selection in the studies.

![Figure 14: Relationship between tick activity and incidence of CNS disease in a TBE endemic area in Austria](image)

![Figure 15a-c: A German TBE-patient – he too was in need of artificial respiration](image)

### Annual morbidity from TBE in various European countries

<table>
<thead>
<tr>
<th>Country</th>
<th>Morbidity (incidence per 100,000)</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Austria</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• unvaccinated</td>
<td>5.0</td>
<td></td>
</tr>
<tr>
<td>• general population</td>
<td>98-100</td>
<td></td>
</tr>
<tr>
<td>• forestry workers</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Czech Republic</td>
<td>5.9</td>
<td></td>
</tr>
<tr>
<td>Switzerland</td>
<td>0.4-7</td>
<td></td>
</tr>
<tr>
<td>Germany</td>
<td>0.2-5</td>
<td></td>
</tr>
<tr>
<td>Slovakia</td>
<td>0.2-1.6</td>
<td></td>
</tr>
<tr>
<td>Russia</td>
<td>1-6.5</td>
<td></td>
</tr>
</tbody>
</table>

Table 7
4. Clinical Description

4.1. Clinical course and manifestations

The typical course of TBE is diphasic in at least two-thirds of patients. The incubation period is 7 days on average but may last between 2 and 28 days. The first stage, which may last for 2 to 8 days, corresponds with the viremic phase. It is associated with non-specific systemic signs and symptoms such as fatigue, headache, aching back and limbs, nausea, and general malaise. In most cases, the temperature rises to 38°C or higher. Sometimes exceptionally high initial temperatures above 40°C may occur (Figure 16). The first stage of TBE is followed by an afebrile interval lasting between 1 and 20 days. During this time, patients are usually free of symptoms. Another sudden and significant increase in temperature marks the beginning of the second stage (Figure 16).

Not all individuals infected with the TBE virus go through the entire course of the disease. In approximately two thirds of infected individuals, the infection remains either silent even though viremia can be demonstrated or shows the clinical picture of the initial stage of TBE (Table 8), with symptoms subsiding without developing into the second stage.

About one-third of symptomatic patients proceed into the second stage of the disease after the virus has spread to the CNS. 50-77% of these patients go through the typical biphasic course of the infection. In the remaining 23-50%, the infection is not apparent during the first stage and the onset of clinical illness coincides with the beginning of the second phase of the disease.

The course of infection with the Far-Eastern variety clinically differs from the European form. The onset of illness is more often gradual than acute, with a prodromal phase including fever, headache, anorexia, nausea, vomiting, and photophobia. These symptoms are followed by a stiff neck, sensorial changes, visual disturbances, and variable neurological dysfunctions, including paresis, paralysis, sensory loss, and convulsions. In fatal cases, death occurs within the first week after onset. The case-fatality rate is approximately 20%, compared to 1-2% for the European form, but these figures may be

---

“With increasing age severe courses of disease accumulate, neuropsychiatric sequelae frequently persist.”

(R. Kaiser, MD, Pforzheim)
biased by the different standards of medical treatment available in Western and Eastern Europe. It is supposed that, in contrast to the European form, the disease caused by the Far-Eastern variety is more severe in children than in adults. Neurological sequelae occur in 30-80% of survivors, especially residual flaccid paralyses of the shoulder girdle and arms. Little information is available on the virulence of the recently described Siberian subtype with respect to the course of disease in humans. However, animal studies have demonstrated that the limited number of Siberian subtype strains studied have higher virulence in mice than Far-Eastern strains.94)

4.1.1. Stages of the disease

- **Incubation period**: The incubation period prior to the onset of the first stage in most cases is between 7 and 14 days, but may last from 2 to 28 days.

- **First stage**: On average, the first stage lasts for 2 to 4 days (durations of 1 to 8 days have rarely been observed) and corresponds with the viremic phase. It is associated with uncharacteristic flu-like symptoms (Table 8) and with an increase in temperature to 38°C in most cases. Sometimes, exceptionally high initial temperatures may occur.

- **Asymptomatic interval**: The first stage is followed by an asymptomatic interval lasting for about 8 days (durations between 1 and 20 days have been observed). During this period, patients are usually without symptoms.

- **Second stage**: About 2 to 4 weeks after infection, one third of patients passes into the second stage of the disease, which is characterized by CNS involvement.95) The clinical picture is that of meningitis, encephalitis, meningoencephalomyelitis, or meningoencephaloradiculitis (Table 9). The mortality rate in adult patients in Europe is about 1% and increases to about 3% in patients with a severe course of TBE including meningoencephalitis, meningoencephalomyelitis, and dysfunction of the autonomic nervous system.96) These patients have temperatures that are often higher than temperatures associated with other forms of viral meningitis or meningoencephalitis.97) The age distribution of the clinical manifestations of the disease is shown in Figure 17.

The main symptoms of meningitis are severe headache, nausea and retching, nuchal rigidity, and high fever (Table 10). Special attention should be paid to the lack of meningeal symptoms in 10% of patients diagnosed with TBE.75) Lack of meningeal signs in the course of TBE does not exclude serious neurological complications.

Encephalitis is characterized by disturbances of consciousness, ranging from somnolence to sopor and, in rare cases, coma. Other symptoms include restlessness, hyperkinesia of muscles of limbs and face, lingual tremor, convulsions, vertigo, and speech disorders (Table 10).

When cranial nerves are involved, mainly ocular, facial, and pharyngeal muscles are affected. In
some cases, neuropsychiatric symptoms prevail, and the patient is sent to a psychiatric ward. The greatest extent of neurological abnormalities of TBE is found in the meningoencephalomyelitic manifestation of the disease, which is primarily characterized by flaccid paresis of the extremities. Since TBE viruses have a particular predilection for anterior horn cells of the cervical spinal cord, paresis usually affects the upper limbs, shoulder girdle and the head levator muscles. Mono-, para- and tetraparesis may develop, including paresis of the respiratory muscles. This clinical form of TBE closely resembles poliomyelitis. However, compared with poliomyelitis, paresis in TBE tends to have a proximal distribution and more often affects the upper than the lower extremities. If the lesion spreads to the lower portion of the brain stem, and particularly to the medulla oblongata, bulbar syndrome may develop, with the risk of sudden death due to respiratory failure or circulation disturbances. Bulbar syndrome can also be observed in the meningoencephalitic form of TBE without association of myelitis. It invariably is a sign of an adverse prognosis.

Table 9: Different courses of severity of TBE

<table>
<thead>
<tr>
<th>Reference</th>
<th>n</th>
<th>Meningitis</th>
<th>Meningo-</th>
<th>Meningo-</th>
<th>Meningo-</th>
</tr>
</thead>
<tbody>
<tr>
<td>98</td>
<td>286</td>
<td>161 (56.3%)</td>
<td>98 (34.3%)</td>
<td>27 (9.4%)</td>
<td></td>
</tr>
<tr>
<td>99</td>
<td>117</td>
<td>72 (61%)</td>
<td>28 (24%)</td>
<td>17 (15%)</td>
<td></td>
</tr>
<tr>
<td>100</td>
<td>805</td>
<td>398 (49%)</td>
<td>354 (43%)</td>
<td>23 (3%)</td>
<td>30 (4%)</td>
</tr>
<tr>
<td>101</td>
<td>549</td>
<td>393 (71.6%)</td>
<td>111 (20.2%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>102</td>
<td>38</td>
<td>20 (52.6%)</td>
<td>12 (31.6%)</td>
<td>6 (15.8%)</td>
<td></td>
</tr>
<tr>
<td>103</td>
<td>100</td>
<td>60 (60%)</td>
<td>32 (32%)</td>
<td>3 (3%)</td>
<td>5 (5%)</td>
</tr>
<tr>
<td>104</td>
<td>120</td>
<td>70 (58%)</td>
<td>39 (33%)</td>
<td>11 (9%)</td>
<td></td>
</tr>
<tr>
<td>105</td>
<td>152</td>
<td>51 (34%)</td>
<td>89 (59%)</td>
<td>12 (8%)</td>
<td></td>
</tr>
<tr>
<td>106</td>
<td>850</td>
<td>400 (47%)</td>
<td>356 (42%)</td>
<td>93 (11%)</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>3,017</td>
<td>1,625 (53.9%)</td>
<td>1,119 (37%)</td>
<td>272 (9%)</td>
<td></td>
</tr>
</tbody>
</table>

Figure 17: Age & clinical manifestation of TBE

Symptoms of polyradiculitis may occur 5 to 10 days after the remission of fever. These symptoms are usually accompanied by paresis of the shoulder girdle. Paralysis may progress for up to 2 weeks, followed by a moderate tendency of improvement. Cases with paresis due to myelitis have only a slight tendency to regression and are generally followed by pronounced muscle atrophy. In a German study, all of the 15 patients with myelitis were left with residual paresis.
Systemic manifestations in the second stage of TBE

Symptoms

<table>
<thead>
<tr>
<th>Meningitis</th>
<th>Meningoencephalitis</th>
<th>Meningomyelitis</th>
<th>Meningoencephalomyelitis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever</td>
<td>Meningeal symptoms</td>
<td>Meningeal symptoms</td>
<td>Meningeal symptoms</td>
</tr>
<tr>
<td>Headache</td>
<td>Lack of drive</td>
<td>Facial paresis</td>
<td>Facial paresis</td>
</tr>
<tr>
<td>Nausea</td>
<td>Increased inclination to sleep</td>
<td>Paresis of the upper and/or lower limbs</td>
<td></td>
</tr>
<tr>
<td>Vomiting</td>
<td>Disturbed sleep</td>
<td>Atonic paresis in the region of the shoulder girdle</td>
<td></td>
</tr>
<tr>
<td>Retching</td>
<td>Somnolence/unconsciousness</td>
<td>Phrenic nerve paresis</td>
<td></td>
</tr>
<tr>
<td>Vertigo</td>
<td>Nystagmus</td>
<td>Lesions of the medulla oblongata and the central portions of the brain stem</td>
<td></td>
</tr>
<tr>
<td>Photophobia</td>
<td>Tremor capitis</td>
<td>Bulbar paralysis</td>
<td>Toxic damage of the liver parenchyma*</td>
</tr>
<tr>
<td>Nuchal rigidity</td>
<td>Lingual tremor</td>
<td>Severe myocarditis*</td>
<td>Severe myocarditis*</td>
</tr>
<tr>
<td>Slight pharyngeal catarrh</td>
<td>Speech disorders</td>
<td>Life-threatening conditions</td>
<td></td>
</tr>
<tr>
<td>Presence of Kernig’s sign</td>
<td>Hyperesthesia</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Passive and intention tremor</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Gait ataxia</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hyperkinesia of the muscles of limbs and face</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Transient Babinski's sign</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Abnormal reflexes</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cranial nerve paralysis</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hemiplegia</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cerebropsychotic episodes</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pain in arms and/or legs</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cystoplegia</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Facial pareses</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ophthalmoplegia</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Disorders of the autonomic nervous system</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hallucinations</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mental disorders with severe psychosis</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* may occur in all manifestations
TBE is a serious case of acute central nervous system disease, which may result in death or long-term neurological sequelae in 35–58% of patients.


**Prognosis**

<table>
<thead>
<tr>
<th>Meningitis</th>
<th>Meningoencephalitis</th>
<th>Meningomyelitis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Usually full recovery.</td>
<td>In some patients sequelae have been reported to persist for several years, e.g.,</td>
<td>The following sequelae have been observed:</td>
</tr>
<tr>
<td>In individual cases sequelae may persist for several months, e.g.,</td>
<td>• Headache</td>
<td>• Spinal paralysis</td>
</tr>
<tr>
<td>• Headache</td>
<td>• Lack of concentration</td>
<td>• Facial paresis</td>
</tr>
<tr>
<td>• Lack of concentration</td>
<td>• Decreased vitality</td>
<td>• Cerebellar insufficiency</td>
</tr>
<tr>
<td>• Disorders of the autonomic nervous system</td>
<td>• Auton. nerv. system disorders</td>
<td>• Atrophic paresis, particularly in the region of the shoulder girdle</td>
</tr>
<tr>
<td>• 19% of patients reported some cognitive dysfunction affecting quality of life after one year.</td>
<td>• Mood disorders</td>
<td>In about 2% of patients the disease is lethal*.</td>
</tr>
<tr>
<td></td>
<td>• Psychic handicaps</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Ophthalmoplegia</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Facial paresis</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Hearing impairment</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Lethal courses</td>
<td></td>
</tr>
<tr>
<td></td>
<td>have been observed.</td>
<td></td>
</tr>
</tbody>
</table>

* may occur in all manifestations
Post-encephalitic syndrome: Post-meningoencephalitic syndrome may occur after TBE. It impairs the quality of life, causes high costs to health care systems with long periods of hospitalization and inability to work as well as long-lasting neurological symptoms and social distress of the patients.\(^\text{107}\) Although severe manifestations usually subside after 1 to 3 weeks, TBE may cause long-lasting, mainly cognitive, CNS dysfunction, and the convalescence period may be very long.\(^\text{110}\)

According to a literature review by M. Haglund and G. Günther in 2003, the incidence of sequelae following TBE varies between 35% and 58%.\(^\text{109}\) In Austria, 10% to 20% of patients with a severe course of TBE have been reported to develop long-term or permanent neuro-psychiatric sequelae, such as a severe headache, dizziness, lack of concentration, depression, disorders of the autonomic nervous system, hearing impairment, and mood disorders. Next in frequency are residual pareses and atrophies in 3% to 11%. The pareses usually tend to remit, but in rare cases muscular atrophies may persist. In some patients, a spasmophilic tendency has been observed for as long as 4 years following TBE infection.\(^\text{110}\)

TBE with hemorrhagic syndrome: 8 fatal cases of tick-borne encephalitis with an unusual hemorrhagic syndrome were identified in 1999 in the Novosibirsk Region. Hemorrhagic fever was associated with the Far-Eastern TBEV subtype.\(^\text{12}\)

4.1.2. Pathogenesis

The picture of manifest TBE depends on the virulence of the virus and the individual resistance of the patient. After the bite of an infected tick, the virus usually replicates in the dermal cells at the site of the tick bite. This replication in Langerhans cells, as well as in neutrophilic granulocytes, is unhindered because of an immunodeficiency induced by the tick’s saliva. Furthermore, the TBE virus does not only use Langerhans cells and granulocytes for replication but also as vehicles to reach regional lymph nodes via lymph capillaries.\(^\text{113}\) Thus, the virus spreads via the lymphatic system and, a few days later, reaches the bloodstream (viremia). It then invades other susceptible organs or tissues, especially the reticuloendothelial system (thymus, spleen, liver), where massive virus replication takes place. Only after this stage is it possible for the virus to reach the central nervous system. Because the capillary endothelium is not easily infected, high virus production rates in the primarily affected organs are a prerequisite for the virus to cross the blood-brain barrier. Once these endothelial cells have been invaded from the lumen, the virus replicates and enters the central nervous system by seeding through the capillary endothelium into the brain tissue. The TBE virus may also spread along nerve fibers. This route may be especially relevant in laboratory infections by aerosols. After infecting the neuroepithelial cells of the nasal mucous membrane, the virus directly enters the brain via the...
fila olfactoria. Considering the short incubation period and the often extremely severe course of such infections, this route of entry seems likely. However, in arthropod-borne infections, neural spread of the virus is of little importance.

Histopathological studies from lethal human cases revealed neuronal and glial destruction, spongiform focal necrosis, inflammation and perivascular infiltration, cellular nodule formation, and edema. Residual pathological lesions are characterized by neuronal loss and microglial scarring. Detection of viral RNA during the encephalitic stage of disease in cerebrospinal fluid (CSF) is difficult, which indicates that the main pathogenic mechanism may be due to inflammatory mediators, even if TBEV may be concealed in the neurons without leaking into the CSF.

4.1.3. Immune response

A TBEV infection confers life-long protection, and there is no known human case of symptomatic re-infection.

4.2. Laboratory findings

- **Blood count:** The typical changes in blood count in TBE are as follows: With the onset of the meningoencephalitic stage, the leukopenia observed during both the first stage of the disease and the asymptomatic interval disappears. It is followed by transient leukocytosis, with leukocyte counts that are considerably higher than in other forms of viral meningitis (6,600–14,600/mm³). Usually, leukocytosis changes into leukopenia before the blood count returns to normal. The blood sedimentation rate may be as high as 100mm/h. The frequency and extent of abnormal values do not correlate with the diagnosis or prognosis of TBE. Elevated C-reactive protein is detected in more than 80% of patients.

- **Cerebrospinal fluid:** Pleocytosis, mainly of lymphocytes, is observed in the CSF, reaching maximum values of 5,000/mm³ cells. Frequently, cell counts of several hundred mm³ as well as protein values between 50-200mg/dl are observed. Usually, it takes 4 to 6 weeks for the CSF lab parameter values to normalize, but in individual cases elevated values may persist for several months.

4.3. Prognosis

Hospitalization is usually required for about 3 weeks, even though in severe cases it may last up to several years. With increasing patient age, especially in persons over 60, TBE is more likely to take a severe course, leading to paralysis and sometimes resulting in death. With the exception of CSF cell counts, which may indicate the intensity of CNS infection and correlate with the severity of the disease, the results of laboratory examinations seem to have little predictive value with regard to prognosis. Similarly, TBE antibody concentrations as detected by ELISA do not correlate with the outcome of the infection, whereas the neutralizing antibody titer — together with the CNS cell count — seems to be more predictive of the clinical outcome. At the onset of the disease, the presence of low concentrations of neutralizing antibodies in serum and a high cell count in CSF might indicate an unfavorable course of TBE.
4.4. Pediatric clinical description

TBE in children can run a severe course and may lead to permanent sequelae. In children and juveniles, meningitis is the predominant form of the disease, which is why the infection usually takes a milder course with better prognosis than in adults. Retrospective studies have shown TBE infection to occur in infants as young as 3 months. A higher incidence of TBE was reported in boys (ratio 7:3), who more often show signs of focal encephalitis. There is a clear tendency for a more severe course of TBE above the age of 7 years. Severe cases have been reported even in young children with permanent neurological sequelae, mild or severe, such as headache, behavioral disorders, seizures, and pareses. The most common symptoms and signs of acute TBE in children are raised body temperature (38°C), headache and meningeal signs, fatigue and vomiting. Cizman also reports an unusually high rate of children aged 0-15 years who were hospitalized (n=133) due to severe TBE virus infection in Slovenia between 1993 and 1998 (Table 11). Symptoms of sequelae in children are headaches, sleep and concentration disturbances, vertigo, fatigue, and epileptic disorders.

<table>
<thead>
<tr>
<th>Hospitalized children in Slovenia aged 0-15 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>48.5% had aseptic meningitis</td>
</tr>
<tr>
<td>48.5% had meningoencephalitis</td>
</tr>
<tr>
<td>3.0% had meningoencephalomyelitis</td>
</tr>
<tr>
<td>5.2% were admitted to the intensive care unit</td>
</tr>
</tbody>
</table>

Table 11

4.5. Mixed infections

Co-infections involving various combinations of pathogens have frequently been described, and some tend to be particularly severe. Diseases caused by mixed TBE virus-Borrelia infections have already been reported in several countries of Central Europe. Co-infection with Borrelia burgdorferi is reported in about 15% of patients on the basis of seropositive results in serum and/or CSF. In the majority of patients with concomitant infections, the clinical features at presentation were characteristic of, or consistent with, TBE. It is suggested that in confirmed cases of TBE in patients with acute lymphocytic meningitis or meningoencephalitis originating in TBE and Lyme borreliosis endemic regions, an additional infection with Borrelia should be considered. If present, borreliosis can be successfully treated with antibiotics. There is some information in the literature that co-infection with B. burgdorferi sensu lato might contribute to a more severe course of TBE. Similar findings of mixed infections have been described in children, most commonly TBE and Lyme borreliosis. Double infections occur more frequently in areas where I. persulcatus ticks are abundant. A study from the Czech Republic demonstrated that TBE-human granulocytic ehrlichiosis (HGE) co-infections can also be encountered in Central Europe.

4.6. Incidence and severity of TBE in relation to other CNS viral diseases

According to a study conducted in 1958, the proportion of TBE in the total number of CNS viral diseases in Austria was 56% (Figure 19). Before the start of the vaccination program, it was the most significant and most frequent disease of this type in adults, with several hundred cases reported every year.

In Switzerland, TBE ranked fourth among viral infections of the central and peripheral nervous system in 1981, with only picorna, mumps, and Varicella zoster infections being more frequent. In some cantons, TBE was even the most frequent cause of CNS diseases. In Germany, TBE accounts for up to 50% of all viral diseases and in Lithuania, TBE accounts for more than half (53%) of all CNS infections.

Figure 20: In Austria, a significant number of cases of viral encephalitis can now be avoided.
5_ Therapy

"The bad news: You cannot abstain from TBE and therapeutic possibilities are poor. But there is good news regarding prevention."

(M. Kunze, MD, Vienna)

No specific therapy for TBE is known so far. Since there is no specific treatment targeting the virus itself, symptomatic treatment of patients with TBE is required. Strict bed rest for at least 10 days is imperative. In many Austrian hospitals, encephalitis patients are referred to intensive care units for continuous surveillance as a precaution. Only when their temperature is down to normal and neurological symptoms have subsided may the patient start to leave bed briefly for washing and using the toilet. For another 1 to 2 weeks, predominant bed rest is recommended to avoid complications. Maintenance of the water and electrolyte balances, sufficient caloric intake, and the administration of analgesics, vitamins, and antipyretics are the most important lines in the clinical management of patients. Physiotherapy of paralyzed limbs is essential to prevent muscular atrophy.

6_ Diagnosis

"It will only be possible to clearly identify the endemic TBE areas in Europe when every case of meningitis is tested for a pathogen."

(A. Mickiene, MD, Kaunas)

The diagnosis of TBE rests on the following pillars:112)
- Epidemiological information: stay in a TBE risk area, facultative history of a tick bite
- Clinical data: uncharacteristic and usually not sufficient for diagnosis
- Demonstration of TBE-specific IgM and IgG antibodies in serum (adequate evidence of infection) and CSF

6.1. Laboratory diagnosis

Because of the nonspecific clinical features of TBE, the definite diagnosis must be established in the laboratory. The laboratory results have no influence on the therapy of TBE and mainly serve to differentiate a TBE virus infection from other causes of meningoencephalitis, which may require special treatment.

The method of choice is the demonstration of specific IgM and IgG serum antibodies by enzyme-linked immunosorbent assay (ELISA).113) As the symptoms affecting the CNS are not usually observed until 2 to 4 weeks after the tick bite, the antibody test is almost invariably positive at the time of admission to hospital. Soon after infection, IgM antibodies are more specific,
while later, IgG antibodies are more reactive (Figure 21). A recent infection can be established by the qualitative determination of IgM. Specific IgG antibodies and rheumatoid factors do not interfere with the test. However, in cases of other flavivirus contacts (e.g., vaccinations against yellow fever or Japanese encephalitis; dengue virus infections) the performance of a neutralization assay (e.g., RFFIT, rapid fluorescent focus inhibition test) is necessary for assessing immunity due to the interference of flavivirus cross-reactive antibodies in ELISA and hemagglutination inhibition test. In the past, antibody identification relied on four tests, i.e., the hemagglutination inhibition, complement fixation, plaque reduction neutralization, and indirect fluorescent antibody (IFA) tests. Positive identification using these IgM- and IgG- based assays requires a four-fold increase in titer between acute and convalescent serum samples. The sensitivity and specificity of new assays, e.g. IIFT (indirect immunofluorescence test), ELISA, and immunoblot test systems, are considerably higher than those of tests used in the past, and cross-reactivity with related flaviviruses is significantly reduced. In the viremic phase of the initial stage of the disease before seroconversion, TBE virus can also be identified by reverse-transcriptase polymerase chain reaction (RT-PCR), by electron microscopy, or by cultivation. In fatal cases, the virus can be isolated or detected by RT-PCR from the brain and other organs. Electron microscopy and cultivation are not suitable as routine diagnostic tools. In contrast to many other flaviviruses, the PCR method is not very useful for the laboratory diagnosis of TBE in clinical practice. The overall prevalence of TBE can be established serologically, since the infection leads to immunity for life and the presence of antibodies to the TBE virus in the patient’s blood.
6.2. Differential diagnosis

Fever, headache and meningism associated with signs of inflammation in serum (leukocytosis, elevation of the sedimentation rate and of C-reactive protein), and predominance of neutrophilic cells over lymphocytes in the CSF are main findings in patients with TBE, but are also highly indicative of bacterial meningitis. Consequently, most patients are treated with antibiotics – at least until the TBE serology is found to be positive.123)

Thus, many viral and bacterial infections have to be considered in the differential diagnosis of TBE (Table 12). Lyme disease (lyme borreliosis) has been recognized as the most frequent vector-borne disease in mild climate areas and has to be included in the differential diagnosis of TBE. Its causative agent, the Borrelia burgdorferi sensu lato complex (B. burgdorferi sensu stricto, B. garinii and B. afzelii), is transmitted by ticks and other arthropods. In our part of the world, the incidence of lyme borreliosis is higher than that of TBE. Contrary to TBE, the various stages and the manifestations of lyme borreliosis occur facultatively; transitions may be indistinct. High-dose administration of penicillin, cephalosporin, macrolide, or doxycycline is the therapy of choice.126)

Acute human granulocytic ehrlichiosis (HGE) is an emerging tick-borne disease, which should now be included in the differential diagnosis of febrile illnesses occurring after a tick bite in Europe. HGE is caused by Ehrlichia phagocytophila (anaplasma), gramnegative intracellular bacteria infecting white blood cells. Comparing the clinical signs and laboratory findings of adult patients with proven acute HGE with that of patients in the initial phase of TBE shows that the duration of fever in the initial phase of TBE is shorter (median 4 days vs. 7 days in patients with acute HGE). Clinical signs, including chills, myalgia, and arthralgia, and laboratory findings, e.g., elevated values for lactate dehydrogenase and C-reactive protein, suggest a diagnosis of acute HGE rather than the initial phase of TBE.127)

<table>
<thead>
<tr>
<th>Differential diagnosis of TBE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical Picture</strong></td>
</tr>
<tr>
<td>- Lyme disease</td>
</tr>
<tr>
<td>- Acute human granulocytic ehrlichiosis</td>
</tr>
<tr>
<td>- Poliomyelitis</td>
</tr>
<tr>
<td>- Coxsackie virus infection</td>
</tr>
<tr>
<td>- ECHO virus infection</td>
</tr>
<tr>
<td>- Parotitis</td>
</tr>
<tr>
<td>- Measles</td>
</tr>
<tr>
<td>- Herpes virus infection</td>
</tr>
<tr>
<td>- Lymphocytic choriomeningitis</td>
</tr>
<tr>
<td>- Japanese B encephalitis</td>
</tr>
<tr>
<td>- St. Louis encephalitis</td>
</tr>
<tr>
<td>- Eastern and Western equine encephalitis</td>
</tr>
<tr>
<td>- Adenovirus infection</td>
</tr>
<tr>
<td>- West Nile Fever</td>
</tr>
<tr>
<td>- Louping Ill virus infection</td>
</tr>
<tr>
<td>- Tuberculous meningitis</td>
</tr>
<tr>
<td>- Leptospiral meningitis</td>
</tr>
<tr>
<td>- Tularaemia</td>
</tr>
<tr>
<td>- Q-fever</td>
</tr>
<tr>
<td>- Tick typhus</td>
</tr>
<tr>
<td>- Tick paralysis caused by salivary toxin of ticks</td>
</tr>
<tr>
<td>- Bacterial meningitis caused by common pathogens</td>
</tr>
</tbody>
</table>

Table 12: Differential diagnosis of TBE
Elimination of TBE by controlling all vectors is not possible, and no effective or practicable tools are available for interrupting the virus cycle in nature. Prevention is the only effective means to combat the disease.

7.1. General preventive measures

- Avoiding tick-infested areas whenever possible
- Wearing light-colored clothing that shows ticks easily and covers arms and legs. Wearing long-sleeved shirts, tight at the wrists, long pants tight at the ankles and tucked into socks, and shoes covering the entire foot.
- Applying diethyltoluamide (e.g., DEET) to skin and permethrin to clothing. Do not apply permethrin to clothing while being worn and allow the clothing to dry thoroughly before wearing.
- Performing daily checks of skin for ticks. Check children 2-3 times a day. Check under waist bands, sock tops, under arms, and any other moist areas.
- Removing ticks by using fine-tipped tweezers (Figure 22). Grasp the tick firmly and as closely to the skin as possible. Using a steady motion, pull the tick’s body away from the skin without rotation. If parts of the tick remain stuck in the skin, they should be removed as soon as possible. Suffocating the tick with oil, cream, etc. may induce injection of more infectious material into the body - so do not use petroleum jelly, burning matches, cigarette ends, nail polish, or the like.

7.1.1. Control of tick populations

Ticks being the chief vector of TBE virus, past efforts to fight TBE concentrated on the control of tick populations in TBE-endemic areas. In former Czechoslovakia and the USSR, large-scale control measures using tetrachlorvinphos, DDT, or Hexachlor did not produce the desired effect.
As the virus persists not only in ticks, but also in wild animals, such measures are of no use in the elimination or even control of the disease.

7.1.2. Protective clothes and repellents

As ticks attach to any spot on the host, and from there try to reach an uncovered part of the skin, adequate clothing may help to make access to the skin more difficult for ticks. Protective clothes must be completely closed to be really effective, but this may be found intolerable by people spending their leisure time or holidays in endemic areas in the warm season. In former Czechoslovakia, forestry workers were given protective clothes impregnated with DDT and were regularly disinfested after work.\(^{128}\) However, these preparations afford protection for a few hours only. Moreover, there have been reports from the former USSR of ticks becoming resistant to repellents.\(^{34}\) All these preventive measures directed at ticks have offered only limited protection. It was realized quite early that a vaccine was required for protection against the causative agent itself, i.e., the TBE virus.

7.2. Active immunization

Currently, no causal treatment is known for TBE. However, TBE can be successfully prevented by active immunization. Prevention by special clothing and tick repellents has proven not reliable enough, and the registration of TBE-specific hyperimmunoglobulin for post-exposure prophylaxis has been suspended due to concerns about antibody-dependent enhancement of infection.\(^{130}\)

Baxter offers the most widely used TBE vaccine in Europe, FSM E-IM M UN 0.5 ml for adults from 16 years of age and FSM E-IM M UN 0.25 ml Junior for children and adolescents from 1 to below 16 years (Table 13). FSM E-IM M UN has been registered in Austria since 1976 and has been widely used for many years in 25 European countries and Canada. More than 90 million doses have been administered since then.

Residents of and travelers to TBE endemic areas, who are at risk of tick bites, are advised to receive TBE vaccination.\(^{80, 82}\) The Austrian example

<table>
<thead>
<tr>
<th>Age</th>
<th>Vaccination coverage (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-12</td>
<td>80</td>
</tr>
<tr>
<td>13-19</td>
<td>94</td>
</tr>
<tr>
<td>20-29</td>
<td>94</td>
</tr>
<tr>
<td>30-39</td>
<td>92</td>
</tr>
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<td>40-49</td>
<td>90</td>
</tr>
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<td>50-59</td>
<td>87</td>
</tr>
<tr>
<td>60-69</td>
<td>88</td>
</tr>
<tr>
<td>70-79</td>
<td>83</td>
</tr>
<tr>
<td>80+</td>
<td>79</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td><strong>88</strong></td>
</tr>
</tbody>
</table>

\(^{*}\) Fessel-GfK Austria 2007

Table 14
shows that containment of TBE is feasible by mass vaccination. In the pre-vaccination era, Austria had a very high recorded morbidity of TBE - probably the highest in Europe at the time. In high-risk areas, the average annual incidence in the population exposed to ticks in their working environment was 0.9 per 1,000.\textsuperscript{131)\textsuperscript{}} A mass vaccination campaign was started in 1982 and has since continued annually. The vaccination coverage of the total Austrian population is high and again reached 88\% in 2007. In some age groups, the coverage was as high as 94\% (Table 14). 64\% of the total population adhere to the recommended vaccination schedule, including regular booster vaccinations. The vaccination program for school children has proven to be particularly effective. TBE infection in this age group has decreased to a very low rate of 2.3\% of the total recorded cases (Figure 13).\textsuperscript{86)\textsuperscript{}}

The increased vaccination coverage has resulted in a marked decline of the morbidity of TBE in Austria. This development is unparalleled in Europe, with vaccination coverage still low in most countries. The incidence of TBE can only be lowered by an increasing vaccination coverage and is not fully controlled until general vaccination is undertaken.\textsuperscript{86)\textsuperscript{}} For more information on FSME, see the FSME-IMMUN Product Monograph and attached SmPCs.

### Pharmaceutical composition of FSME-IMMUN vaccines

<table>
<thead>
<tr>
<th>Component</th>
<th>FSME-IMMUN 0.5 ml</th>
<th>FSME-IMMUN 0.25 ml Junior</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active substance: formaldehyde-inactivated, sucrose gradient purified, TBE virus antigen</td>
<td>2.4 µg (target)</td>
<td>1.2 µg (target)</td>
</tr>
<tr>
<td></td>
<td>2–2.75 µg (range)</td>
<td>1–1.375 µg (range)</td>
</tr>
<tr>
<td>Adjuvant: aluminum hydroxide, hydrated</td>
<td>0.35 mg Al\textsuperscript{3+}</td>
<td>0.17 mg Al\textsuperscript{3+}</td>
</tr>
<tr>
<td>Stabilizer: human serum albumin</td>
<td>0.5 mg</td>
<td>0.25 mg</td>
</tr>
<tr>
<td>Buffer system</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sodium chloride</td>
<td>3.45 mg</td>
<td>1.725 mg</td>
</tr>
<tr>
<td>Na\textsubscript{2}HPO\textsubscript{4}·2H\textsubscript{2}O</td>
<td>0.22 mg</td>
<td>0.11 mg</td>
</tr>
<tr>
<td>KH\textsubscript{2}PO\textsubscript{4}</td>
<td>0.045 mg</td>
<td>0.0225 mg</td>
</tr>
<tr>
<td>Sucrose</td>
<td>Max. 15 mg</td>
<td>Max. 7.5 mg</td>
</tr>
<tr>
<td>Formaldehyde</td>
<td>Max. 5 µg</td>
<td>Max. 2.5 µg</td>
</tr>
<tr>
<td>Protamine sulfate</td>
<td>Trace</td>
<td>Trace</td>
</tr>
<tr>
<td>Neomycin and gentamicin</td>
<td>Trace</td>
<td>Trace</td>
</tr>
<tr>
<td>Water for injection</td>
<td>Ad 0.5 ml</td>
<td>Ad 0.25 ml</td>
</tr>
</tbody>
</table>

Table 13
REFERENCES

12) Chiba N et al., Vaccine 17: (1532-1539, 1999)
References


68) Vorobyeva M, Voroncova T, Arumova E: Federal Centre of Sanitarian-Epidemiological Control of the Ministry of health of Russia Federation.


74) Krohn E, Ackermann R: Present at 7th annual meeting of ISW-TBE in Vienna 2005.


References
LIST OF ABBREVIATIONS

CNS Central nervous system
DDT Dichlorodiphenyltrichloroethane (organochlorine insecticide)
ELISA Enzyme-linked immunosorbent assay
FSME Frühsommer-Meningoenzephalitis, German term for TBE
IgG Immunoglobulin G
PCR Polymerase chain reaction
RNA Ribonucleic acid
TBE Tick-borne encephalitis
TBEV Tick-borne encephalitis virus
VIE U/ml Vienna units/ml – TBE ELISA concentration unit

References

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Sources: pictures of ticks, patients and production: Baxter archive; animals: Museum of Natural History Vienna, Landesmuseum Niederösterreich (F. Gauermann); art, illustrations: MedNews archive.

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