Review of tick-borne encephalitis and vaccines
Smit, Renata; Postma, Maarten J

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Tick-borne encephalitis (TBE) disease is an increasing burden not only locally but also globally. In most endemic countries, vaccination coverage is too low to reduce the TBE burden significantly; however, vaccination is the most effective protection against TBE, with various vaccines currently available. In spite of rising awareness of TBE, little attention is directed toward the health economics of the disease. The purpose of the present review is to compile information on TBE and its explicit clinical and economical aspects. Given the scarcity of studies, the authors conclude that more attention is needed for health economics of TBE. Notably, this would help establish guidance on efficient policies for TBE prevention, reduce disease burden and achieve population health benefits.

**KEYWORDS:** health economics • tick-borne encephalitis • vaccination • vaccines

Three genetically closely related subtypes of the tick-borne encephalitis virus (TBEV) cause TBE; that is, the European, Siberian and Far-Eastern subtypes [1]. The European subtype of the virus is mostly found in Europe, the Siberian subtype occurs mainly in the Urals, Siberia and Far-Eastern Russian provinces and the Far-Eastern subtype is prevalent in Far-Eastern Russia, China and Japan [1,2]. All three subtypes co-circulate in the Baltic states and Finland [3,4]. The tick *Ixodes ricinus* is the main transmitter of the European, whereas *I. persulcatus* spreads the two other subtypes [1,5]. Next to being directly tick-borne and tick-transmitted, TBEV can also be transmitted by unpasteurized dairy products [5].

TBE is a serious viral infectious disease of the CNS, which may lead to long-term or permanent neurological sequelae or even death [6]. Sequelae of the disease may affect the patients’ quality of life and may require changes in their lifestyle [6]. Course of the disease, disease severity and fatality because of TBE depend on virus subtypes [1]. Disease caused by the Far-Eastern subtype of the virus is usually severe, frequently with encephalitic symptoms and mortality rates between 5 and 35% [1]. Disease with the Siberian subtype is less severe, with a tendency to develop chronic infection with diverse neurological symptoms and mortality rates between 1 and 3% [1]. The European subtype of the virus usually causes a biphasic course of the disease [1]. The first stage of the disease is characterized by symptoms similar to flu and the second stage of the disease often manifests as meningitis, meningoencephalitis or meningoencephalomyelitis [1]. Mortality rate due to TBE in adults caused by European subtype of virus is less than 2% [1].

In many parts of Europe, Asian Russia, Siberia and the Far East, the incidence is increasing and new foci have appeared because of increasing mobility, changes in lifestyle, human leisure activities, agricultural practices and effects of climate changes on vectors and reservoir hosts [2,7]. TBE is becoming a high burden locally as well as globally. It is believed that the incidence of TBE is underestimated [1,2,7] and the true burden of TBE can therefore not be known [8]. Yet recently, the real burden measured in disability-adjusted life years (DALYs) was estimated for Slovenia, inclusive of correction for underestimation, to
show the true burden of the disease in this Central European country [9].

Currently, national guidelines, specific recommendations and public-health interventions for prevention and control of TBE differ between countries and even within one country [10]. However, consistently in most endemic countries, vaccination coverage is very low and inefficient to adequately reduce the TBE burden [11,12]. Yet, TBE vaccines are safe, efficacious and well tolerated and present the only real option of effective and successful prevention [2,13,14]. Currently, four registered vaccines exist: FSME-Immun® (Baxter, Vienna, Austria) and Encepur® (Novartis Vaccines, Marburg, Germany) are based on the European subtype and are used mainly in Europe (further referred to as Western European vaccines), whereas the TBE-Moscow vaccine® (Chumakov Institute, Moscow, Russia) and EnceVir® (Scientific Production Association Mirogen, Tomsk, Russia) are based on the Far-Eastern subtype and are used mainly in Russia (further referred to as Russian vaccines) [2,14]. Ways to protect against the disease is wearing suitable clothes and shoes, using repellents, avoiding tick-infected areas and consuming adequately pasteurized dairy products. However, vaccination is the most effective and potentially most successful route to prevent TBE [12] and thus reducing the burden of TBE.

Slovenia is an endemic country with a high incidence rate of TBE and low vaccination coverage [2,11]. TBE causes high costs for healthcare insurances and the society because of hospitalization and frequent long-term and permanent neurological sequelae [2]. One recent cost–effectiveness study of vaccination was directed at Slovenia [15]. In many countries, including Slovenia, cost–effectiveness of vaccines represents an important criterion for inclusion in national immunization programs. Therefore, also for Slovenia, an economic evaluation on TBE vaccination was clearly needed to help decide whether TBE vaccination could be included into the national immunization program. The cost–effectiveness of TBE vaccination for adults was evaluated for Slovenia, using a Markov model constructed on the basis of the natural history of the disease [15]. The results were shown as the cost per quality-adjusted life year (QALY) gained of vaccination from the view of the healthcare payer and the society [15]. On the basis of the study [15], Slovenia took a positive decision on the inclusion of the vaccine in the national program. Also, based on the study [15] and applying its model [15], the County Council of Sornland in Sweden decided positively on vaccination against TBE [16]. Also other countries are encouraged to evaluate the cost–effectiveness of TBE vaccination [14], so that health authorities decision making on programmatic vaccination can be adequately informed by analyses of the cost–effectiveness in those countries as well.

Even though awareness about TBE is increasing, too little attention seems to be oriented toward health economics of the disease. Yet, such studies can help to formulate more specific guidelines for efficient prevention and control of TBE to reduce the disease burdens locally and globally. The purpose of the present review is to compile information on TBE and its health economic aspects.

Epidemiology

TBE is endemic in areas from Alsace-Lorraine and Scandinavia to the North-Eastern parts of China and Northern Japan [2,17,18,19]. Surveillance in TBE endemic areas is based mostly on the number of TBE reported cases [18,19]. Within Europe, Slovenia, Estonia, Lithuania, Latvia and Russia are countries with the highest incidence of TBE reported cases [2,20]. Between 2005 and 2009, the incidence rate in the whole country of TBE reported cases per 100,000 population was 14.07 in Slovenia, 11.10 in Estonia, 10.59 in Lithuania, 8.76 in Latvia, 7.02 in the Czech Republic, 2.15 in Switzerland, 1.99 in Sweden, 1.16 in Slovakia and 0.94 in Austria (relatively low because of high proportions already vaccinated populations [19]; notably, 6.02 in the nonvaccinated population) [21]. Lower incidence rates are found in some other countries: 0.66 in Poland, 0.60 in Hungary, 0.44 in Germany and 0.39 in Finland [19]. Russia not only has areas of high incidence of TBE reported cases but also large nonendemic areas [19]. In 2006, the national average incidence rate was 2.44, but in Siberia the incidence was more than 5-times higher, including some areas where it was even 10-times higher than the national average [2,18]. High incidence rates of TBE were also reported from North-West Russia [18,19].

In his studies [18,19], Süss described the epidemiological overview of TBE in Europe, the Far East and Asia. He presented the number of TBE reported cases in endemic countries, such as Austria, Croatia, the Czech Republic, Denmark, Estonia, Finland, France, Germany, Hungary, Italy, Latvia, Lithuania, Norway, Poland, Russia, Slovakia, Slovenia, Sweden and Switzerland, as well as in the non-European TBE endemic countries China, Kazakhstan, Mongolia, Japan, South Korea and Kyrgyzstan in different time periods of observation, described fluctuations in TBE cases and emergence of new TBE foci. Between 1990 and 2007, a total of 157,584 TBE reported cases were documented in Europe. Of these, 50,486 reported cases were registered in Europe without Russia [18]. Between 1976 and 1989, a total of 38,572 TBE reported cases were documented in Europe, and of these, 20,328 TBE cases were reported in Europe without Russia [18]. The comparison of these two periods shows an increase in TBE reported cases over 300% in Europe and almost 200% in Europe without Russia [18]. Since 1990, the number of TBE reported cases has drastically increased [18], partially because of the introduction of mandatory reporting of TBE cases in some countries, better surveillance and improved diagnosis, particularly in the less developed countries of Europe, where the health systems have improved substantially over these years [2]. As indicated, one exception referred to Austria where the number of TBE reported cases has decreased with an increase in vaccination coverage [21–24].

The number of TBE cases fluctuates annually between and within countries [18,19]. In 2006, 7424 TBE cases were reported in Europe and 3914 in Europe without Russia, while in 2007 the number of reported TBE cases fell to 5462 in Europe and 2364 in Europe without Russia [18]. This corresponds to a reduction of 60% [18]. From 2006 to 2007, a decrease in the
number of TBE reported cases was seen in almost all European countries except in Sweden, Norway and Hungary, where the number of TBE reported cases further increased and in Latvia where no changes in the number of TBE reported cases was observed [18]. Furthermore, for the Czech Republic, Germany, Poland, Lithuania, Slovakia, Slovenia and Switzerland, the number of TBE reported cases for 2008 was the same as for 2007 [18]. Annual TBE fluctuations are a well-known phenomenon as described both by Mantke et al. [25] and Heinz et al. [21]. Fluctuations in TBE cases may be caused by several factors, of which the most important are behavioral and environmental changes [26].

Consistently, over the past years, endemic areas have spread north- and westward in Europe and within already affected countries [27]. New foci have emerged in Denmark [28], Finland [4,19], Sweden [29], Norway [30], Austria [31], Germany [32], Switzerland [33], Slovakia [34], Russia/Siberia [34] and Romania [8]. TBE endemic areas are also expanding to higher altitudes as reported for Austria [35] and for the Czech Republic [36]. The spread of endemic areas is expected to continue further to currently still nonendemic areas [37].

Furthermore, TBE spread was illustrated in recent findings of Süss [34], comparing the number of TBE reported cases between 1991 and 2000 with those between 2001 and 2010, showing an increase of TBE reported cases by approximately 100% in Scandinavian countries (Sweden, Finland and Norway) and 144% in Central European countries (Czech Republic, Germany, Switzerland and Poland). Yet, decreases were reported for the Baltics states (Estonia, Latvia and Lithuania) by 65% and by 42% in Russia [34].

In non-European endemic countries, such as China, Kazakhstan, Mongolia, Japan, South Korea and Kyrgyzstan, the epidemiological picture is not reliable, mainly because of inaccurate reporting of TBE, diagnostics not being performed regularly and very low awareness of the disease [19].

Yet, TBE is well-known to be endemic in China, with endemic foci having been identified mostly in the North-Eastern North-Western and South-Western parts of the country [19]. Notably, main endemic areas are in the province of Heilongjiang [19]. From 1980 to 1998, 2202 TBE cases were registered; however, absolute numbers of TBE cases are not representative because TBE is not a notifiable disease in China and cross reactivity with other flaviviruses, especially Japanese Encephalitis virus, hampers proper diagnosis [19,38]. In Kazakhstan, endemic areas are identified in the eastern parts of the country and in the region of Almaty. From 2004 to 2009, in total, 245 TBE cases were reported in Kazakhstan [19]. However, it is believed that this number is significantly affected by underreporting [19]. In Mongolia, some endemic areas were described closely to the Russian border, in the North of the country, in the provinces of Selenga and Bulgan and around the capital city Ulanbataar [39]. In 2008, the first patient died with a formal diagnosis of TBEV meningoencephalitis. The TBEV was isolated from the brain and was identified as genetically closest related to the Far-Eastern subtype of virus [39,40]. In Japan, in 1993 one TBE case was reported from the southern part of Hokkaido. TBEV serosurveys in domestic animals and virus isolations from ticks also suggested TBE foci in Hokkaido [19,41]. In South Korea, TBEV has been isolated from ticks (Haemaphysalis longicornis, I. nipponensis) in several regions and surprisingly was found to be the European subtype of virus [42]. In Kyrgyzstan, TBE cases have not been reported yet [19].

Although it is believed that the incidence of TBE is underestimated, the epidemiological overview on TBE in Europe, the Far East and Asia presented by Süss demonstrates the importance of TBE from the individual as well as the healthcare perspective even at its currently measured level [18].

Surveillance and notification schemes are not uniform, not always mandatory and affect the incidence and prevalence estimates of disease in endemic areas [125]. Surveillance of TBE endemic areas based on TBE cases is not reliable because the number of TBE reported cases do not adequately reflect prevalence of TBEV and, therefore, the risk of infection [18,19]. This is illustrated by a high vaccination coverage in Austria and a low number of TBE reported cases, while a significant risk of infection still exists [8,23]. Although TBE was already mandatorily notifiable in 16 EU/EEA countries in 2011 [25], numbers of TBE reported cases are not fully comparable between endemic countries, because of significant differences in the quality and quantity of the diagnostics, case definitions and reporting in different endemic countries [1,25,43]. Many countries with mandatory notification use a case definition based on clinical and laboratory data; however, these definitions vary between countries [19]. Some endemic countries, such as Switzerland, Russia, Latvia, Lithuania, Slovakia and Norway, do not have a formal case definition at all [19]. Therefore, the overall epidemiology and burden of TBE at the European level remains unclear [43]. From 2012 onward, TBE is a notifiable disease in the EU with a new common case definition to allow comparability of numbers of TBE reported cases between countries, to improve knowledge about the disease and to provide better mapping of the disease, thus providing a clearer view on the epidemiology of the virus and the corresponding burden of TBE [43].

Burden measured in DALYs

Mostly, the disease burden is expressed in terms of the incidence [2,10]. However, the burden of the disease can be better estimated by DALYs, which integrate data on incidence/prevalence, mortality, seriousness of disease and sequelae and, therefore, give a more comprehensive insight into the burden of the disease than, for example, incidence alone [44]. According to the WHO, DALYs are defined as lost years of healthy life [45].

In the report of the Dutch National Institute of Public Health & the Environment, it was shown that the relative burden measured in DALYs is different when compared with the relative burden measured just by incidence or mortality data for seven selected infectious diseases (influenza, measles, HIV, campylobacteriosis, infection with enterohemorrhagic Escherichia coli, salmonellosis and tuberculosis) in selected European countries [44]. Notably, for these diseases, the incidence is not
considered to provide an overall and complete view of the burden of the disease [44]; this is likely similar for TBE.

In 2014, the burden of TBE measured in DALYs was estimated for Slovenia, by using the updated DALYs methodology first introduced by Murray et al. in the Global Burden of Disease project [9]. According to the methodology of Murray et al., DALYs are sum of the number of life years lost due to premature death and the number of life years lost due to disability, weighted with a factor between 0 (perfect health) and 1 (death) that reflects the severity of the disability [45]. The DALYs calculations for Slovenia were based on the health outcomes of the natural course of TBE [9]. Corrections for under-ascertainment and under-reporting were included to show the true burden of the disease [9]. The study showed that from the population perspective total DALYs amount to 3450, while from the individual perspective, they amount to 3.1 per case [9]. It was concluded that TBE presents a relatively high burden from both these perspectives in Slovenia and that the neurological sequelae have the largest impact on the overall TBE burden [9].

Burden of TBE expressed in QALYs, taking into account both the quantity and quality of life for the whole population [46], was also calculated for adults in Slovenia using a Markov model [15]. Notably, the exact scope of the study was discussed in letter [47]. Findings of these DALY and QALY studies [9,46] showed that the burden of TBE in Slovenia is centered in adults, with age having a strong influence on TBE burden. The exact course of TBE and case fatality depend on various components; for example, increasing severity of disease with increasing age and death risk depending on virus subtypes, resulting in differences in specific estimates of DALYs and QALYs. QALYs and DALYs reflect criteria, next to various others, that can be used for effective planning and prioritizing of limited public health resources [44].

Diagnosis

All three human pathogenic subtypes of TBEV can cause TBE with a wide spectrum of symptoms, from subclinical to biphasic courses, characterized by a first stage with symptoms similar to flu, followed by an asymptomatic period and in approximately one-third of cases, a second stage of the disease characterized with CNS involvement [1]. The second stage of TBE manifests with signs of meningitis, meningoencephalitis or meningoencephalomyelitis and the appearance of specific antibodies in the serum and cerebrospinal fluid (CSF) [1]. Routine laboratory diagnosis of TBE is mainly based on detection of specific antibodies by serological methods, usually ELISA [48-50]. However, reverse transcription-PCR (RT-PCR) techniques, based on TBEV detection, can also be valuable tools for TBE diagnosis [49,50].

In the first stage of the disease, TBE can be diagnosed by TBEV isolation from the blood or by virus RNA detection in blood or CSF, using RT-PCR techniques [48]. During the second stage of the disease, CNS complications occur and most patients are hospitalized [48]. IgM and IgG antibodies appear at the same time with the occurrence of the neurological symptoms [48]. These antibodies can be detected in serum or CSF by serological methods, using ELISA, neutralization tests or immunofluorescence assay [49]. During the second stage of the disease, the TBEV isolation and the RT-PCR techniques are only of limited value for TBE diagnosis because TBEV may not be present anymore in the blood and CSF [48].

Yet, RT-PCR techniques can be valuable for the early diagnosis of TBE in the first stage of the disease, early differentiation of TBEV infections from other tick-transmitted infections (Lyme borreliosis, anaplasmosis), discrimination among TBEV subtypes, as well as for those patients where antibodies are not detectable [49,50]. These techniques are important for epidemiological studies [50]. In fatal cases, RT-PCR techniques can be used for TBEV detection from the brain and other organs [47].

IgM antibodies may persist for many weeks after TBEV infection or after the first and second TBE vaccination [2]. Without information on history of TBE vaccinations, positive serological findings caused by recent vaccination may lead clinicians to suspect TBE also in cases of non-TBEV-related CNS manifestations [2]. Therefore, confirmation of the diagnosis of TBE by detection of IgG antibodies is recommended, but it is necessary to monitor increased IgG titers 1–2 weeks later as well, which is rarely performed [49].

The major limitation of ELISA is that cross-reacting antibodies in IgG ELISA might be shown in persons who were previously exposed to other flaviviruses through infections or vaccination, potentially leading to false-positive results [2,48,49]. This is an increasing problem in Europe because many people travel to countries where other flavivirus are endemic [48]. In persons where cross-reacting antibodies are suspected, a highly specific neutralization test that requires specialized laboratories for detection of TBEV is recommended [2,14,49]. Although PCR techniques are very valuable methods for TBEV diagnosis, they are not used much in practice [50].

Vaccines

The outbreaks of the disease in the former Soviet Union presented huge public health concerns in 1937, and the first vaccine against TBE was prepared from the mouse brain around that time [14]. The first generation of vaccines was efficacious, but it caused frequent adverse events, which stimulated the development of modern, more purified and safe vaccines [13,14,37].

These modern vaccines are the Western European vaccines FSME-Immun and Encepur, both based on the European subtype of virus, the Russian TBE-Moscow vaccine, EnceVir [2,14,37] and the Chinese vaccine (Changchun Institute of Biological Products, China) [38]; all three are based on the Far-Eastern subtype of virus [2,51]. Notably, on the composition, safety, efficacy of the Chinese vaccine, only very little is published (and this vaccine will not be addressed anymore below).

Western European and Russian vaccines are produced according to the WHO manufacturing requirements, with all TBE vaccines containing formalin-inactivated TBEV and aluminum hydroxide as an adjuvant [2]. The use of different
stabilizers and different strains of TBEV reflect the main differences among these four vaccines in the production process [2]. The stabilizer used in FSME-Immun and TBE-Moscow vaccine is human albumin, and sucrose is used as a stabilizer in Encepur and Encevir. FSME-Immun is based on the Neudörfel strain and Encepur is based on the K23 strain of TBEV. The TBE-Moscow vaccine is based on the Sofjin strain and EnceVir on the 205 strain of TBEV [2].

Western European vaccines are used in adults and children aged ≥1 years [14]. Registration schedules require a primary series of three doses for both Western European vaccines [14]. Conventional schedules require the second dose being administered 1–3 months after the first and the third dose 5–12 months after the second (for Encepur the third dose is given 9–12 months after the second) [14]. ‘Accelerated’ or ‘rapid’ schedules for both Western European vaccines are used in case of emergency mainly for travelers and armed forces, but still require at least 3 weeks to establish protection against TBE [52,53]. The ‘accelerated’ schedule requires the second dose to be given 14 days after the first, and the third dose 5–12 months after the second (for Encepur the third dose is given 9–12 months after the second) [14]. ‘Accelerated’ or ‘rapid’ schedules for both Western European vaccines are used in case of emergency mainly for travelers and armed forces, but still require at least 3 weeks to establish protection against TBE [52,53]. The ‘accelerated’ schedule requires the second dose to be given 14 days after the first, and the third dose 5–12 months after the second (for Encepur the third dose is given 9–12 months after the second) [14]. The ‘rapid’ schedule for Encepur requires the second dose after the 7 days, the third dose after 21 days and the fourth dose 12–18 months after the third [14]. For both Western European vaccines, the manufacturers recommend the first booster to be given 3 years after the primary series and subsequent boosters at intervals of 5 years for persons below 50 or 60 years of age [14]. For persons aged 50 or ≥60 years, it is recommended that subsequent booster intervals do not exceed 3 years [37,53–62], based on the fact that persons aged 50 or ≥60 years develop relatively lower antibody titers [63]. However, recommended intervals for subsequent booster doses vary by age and countries [64]. Currently, no standardized recommendations for booster intervals are available and adequate immunosenescence remains a challenge [14]. In Austria, 3-year intervals are recommended for persons aged ≥60 years [14]. In Switzerland, booster intervals of 10 years are recommended after the first three doses [65]. Extended booster intervals can be important for reducing costs of vaccination and improving patients’ compliance [14].

The Russian vaccines are used in adults and children aged ≥3 years [14]. Conventional schedules have the second dose 1–7 months after the first dose for the TBE-Moscow vaccine and for Encevir the second dose is given 5–7 month after the first dose [2]. For both Russian vaccines, the third dose is given 12 months after the second dose [2]. The first booster is given 3 years after the third dose, and subsequent boosters are recommended at 3-year intervals [2] For Encevir, there is also a ‘rapid’ schedule, where a second double dose is given 1–2 months after the first dose [2]. The third double dose is required 1–3 months after the second double dose [2]. A fourth dose is given after 6–12 months after the third double dose and first booster is given 3 years after the fourth dose and subsequent boosters are recommended at 3-years interval [2]. Vaccination schedules for TBE vaccines are presented in Tables 1 & 2.

### Safety

According to the Cochrane review [13] and the WHO position paper [14], TBE vaccines are safe. Side effects were common for all TBE vaccines, but none were severe or life-threatening [13,14]. This is stated by other studies as well [13,22,64,66–75], although there is relatively little data available for the Russian vaccines to support that [2,14]. According to the Russian National Regulatory Authority, both Russian vaccines are safe and well tolerated [2,14]. However, in both 2010 and 2011, EnceVir was associated with high fever and allergic reactions, particularly in children. Currently, EnceVir is not recommended for vaccination of children below the age of 17 years [14].

### Immunogenicity

The efficacy of TBE vaccines is determined based on their immunogenicity, measured by the induction of protective antibodies [2]. Protective antibodies appear after TBE vaccination, and serological tests such as ELISA, neutralization test or hemagglutination inhibition are used for antibody detection [2,48]. Both Western European and Russian vaccines are reported to be highly immunogenic [2]; however, data on TBE vaccines’ immunogenicity are not directly comparable because there is no international standardized test of immunogenicity [2]. Numerous observational studies as well as randomized controlled trials confirm the strong immunogenicity after the primary series of currently available TBE vaccines [13,22,23,56,57,68,70,74,76–84]. More data on immunogenicity are available for the Western European vaccines than for the Russian vaccines [14].

Several observational studies demonstrated the duration of protection to be 3 years and above after the primary series of

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### Table 1. Conventional schedule for tick-borne encephalitis vaccines.

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Primary series</th>
<th>First booster</th>
<th>Subsequent boosters</th>
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<tr>
<td>FSME-Immun&lt;sup&gt;®&lt;/sup&gt;</td>
<td>Index date</td>
<td>1–3 months</td>
<td>3 years</td>
</tr>
<tr>
<td>Encepur&lt;sup&gt;®&lt;/sup&gt;</td>
<td>Index date</td>
<td>1–3 months</td>
<td>3 years</td>
</tr>
<tr>
<td>TBE-Moscow vaccine&lt;sup&gt;®&lt;/sup&gt;</td>
<td>Index date</td>
<td>1–7 months</td>
<td>12 months</td>
</tr>
<tr>
<td>Encevir&lt;sup&gt;®&lt;/sup&gt;</td>
<td>Index date</td>
<td>5–7 months</td>
<td>12 months</td>
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</table>

For patients aged ≥50 or 60 years, it is recommended by the manufacturers that subsequent booster intervals do not exceed 3 years.

For patients aged ≥60 years, the 3-year interval is recommended.

For patients aged ≥50 years, the 3-year interval is recommended.

†For patients aged ≥60 or 60 years, it is recommended by the manufacturers that subsequent booster intervals do not exceed 3 years.

‡For patients aged ≥60 years, the 3-year interval is recommended.

†For patients aged ≥50 years, the 3-year interval is recommended.

TBE: Tick-borne encephalitis.
currentl available vaccines in adults and children [58,72,85,86]. Findings by Schosser et al. [79] suggest that extended intervals between the first two or three vaccinations with Western European vaccines do not deteriorate the success of the subsequent vaccination. According to recent studies by Schosser et al. [87], and Asling et al. [88] single vaccination with FSME-Immun resulted in adequate TBEV antibody titers in the majority of subjects, in which the intervals after the last vaccination was longer than recommended. These data suggest that subjects with irregular vaccination histories can attain protection after a single catch-up vaccination and do not need to repeat the primary vaccination course. In addition, although Heinz et al. [21] reported high field effectiveness in irregularly vaccinated people, the field effectiveness in regularly vaccinated people was found to be superior with high statistical significance.

**Field effectiveness**
In 1981, an extended vaccination campaign was launched in Austria, with subsequent implementation of a universal vaccination program [23]. Vaccination coverage of persons receiving at least one dose of vaccine increased from 6% at the beginning of the program to 88% in 2006, leading to drastic reductions in TBE [22,23]. Studies on field effectiveness in Austria between 1994 and 2001 showed effectiveness of 96 and 100% after two and three doses of FSME-Immun, respectively [23]. Studies on field effectiveness of TBE vaccination in Austria between 2000 and 2006 showed the overall effectiveness in regularly vaccinated persons at 99% with no statistically significant differences between age groups [22]. In Austria, both Western European vaccines are available, but FSME-Immun is predominately used. The general notion is that both Western European vaccines can be used interchangeably [64]. Therefore, studies on field effectiveness of TBE vaccination are generally considered representative for both Western European vaccines [2]. During the period between 2000 and 2006, about 2800 TBE cases and 20 deaths were prevented by vaccination [22].

In their recent study, Heinz et al. [21] compared incidences in the highly endemic countries of the Czech Republic, Slovenia and Austria to estimate potential effectiveness of increasing vaccination coverage in Austria. For all three countries, extensive annual and longer range fluctuations and shifts in distributions of patients were found, suggesting major variations and complex interplay of factors influencing risk for exposure to the TBEV [21]. On the basis of these findings, they projected a strong decline in TBE incidence for Austria to about 16% of that of the pre-vaccination area because of vaccination [21]. The incidence in the nonvaccinated population would remain as high as it was during the pre-vaccination era [21]. In addition, it was shown that the field effectiveness of TBE vaccination in regularly vaccinated patients could be estimated at 96–99% [21]. During 2000–2011, vaccination was estimated to have prevented more than 4000 TBE cases and 15 to 30 deaths caused by TBE in Austria [21].

In the highly endemic Sverdlovsk region in Russia, vaccination against TBE has been mandatory since 1995, and a mass vaccination program was initiated in 1996 [81,89]. Since 2001, TBE vaccination has been obligatory for children aged ≥7 years and since 2008 for individuals aged ≥15 months [81,89]. Vaccination coverage increased from 35% at the beginning of the program to 88% in 2010, resulting in decreasing TBE and death caused by TBE [81,89]. Mandatory vaccination has prevented an estimated 3300 TBE cases, 63 deaths caused by TBE and 600 cases of disability [81,89].

### Duration of protection & booster dose
Long-term serological studies show very low rates of waning of protective antibodies titers during first 3–5 years after the booster following the primary series with both Western European vaccines [90]. This demonstrates long-term antibody persistence following booster vaccination [2]. In 2009, an Austrian study indicated that protection against TBE persists for at least 6 years following a booster vaccination [73]. Increasing age has been shown to be associated with infection, as the immune system is weaker and elderly are more susceptible to infection [73,91]. Signs of immunosenescence, reflected by significantly lower antibody levels, were detected not only in

<table>
<thead>
<tr>
<th>Table 2. Accelerated and rapid schedules for tick-borne encephalitis vaccines.</th>
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<tr>
<td><strong>Primary series</strong></td>
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<tr>
<td>First dose</td>
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<td><strong>Accelerated schedule</strong></td>
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<td>FSME-Immun®</td>
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<td>Encepur®</td>
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<td><strong>Rapid schedule</strong></td>
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For patients aged ≥50 or 60 years, it is recommended by the manufacturers that subsequent booster intervals do not exceed 3 years.

†For patients aged ≥60 years, the 3-year interval is recommended.
‡For patients aged ≥50 years, the 3-year interval is recommended.
For Encevir® the second and the third doses are doubled.

For Encepur® the second and the third doses are doubled.
patients aged >60 years but also in the age group between 50 and 60 years [91]. In the case of TBE vaccination, TBE antibody titers are significantly lower in the elderly, suggesting that risks of antibody levels declining below the threshold of protection are higher in elderly [91]. In the study by Aberle et al. [92], it was shown that the number of antigen-specific memory B cells induced by primary vaccination was about threefold lower in the elderly and also the antibody response per memory B cell after revaccination was strongly reduced. However, according to a recent study by Stiasny et al. [93], healthy elderly people are able to produce antibodies in response to TBE vaccination with similar avidity and functional activity as young individuals, although at lower titers. WHO recommends regular booster doses according to the recommended vaccination intervals for the age group >50 years until more information becomes available [14]. Also, regular antibody titer controls in elderly are advisable [73].

In 2013, one other Austrian study showed that 8 years after booster vaccination, seroprotection rate was still 87% [91]. However, between 8 and 10 years after booster vaccination, high percentages of persons lost protective antibody titers, with levels declining below the threshold of protection, implying the need for a booster dose [91]. Data on persistence of antibodies levels beyond 3 years are not available for Russian vaccines [37].

**Cross-protection**

In mouse models, Western European and Russian vaccines show mutual cross-neutralization and protection against all three TBEV subtypes [37]; yet, clinical documentation is scarce [94]. *In vivo* mouse studies and *in vitro* studies by Hayasaka et al. [95] showed that FSME-Immun induces protection against all three subtypes of the virus. In 2007, Leonova et al. [96] concluded that Encepur for adults induces protection against European and the Far-Eastern subtypes of virus. In 2009, the same authors concluded that all TBE vaccines induced protection against the Far-Eastern subtype of the virus [83]. In 2011, it was concluded by Orlinger et al. [97] that FSME-Immun showed equally efficacious protection against the European, Siberian and Far-Eastern subtypes of virus. Further support for this conclusion was presented by Fritz et al. [98]. Western European vaccines can be interchanged; however, no such clinical evidence exists for the Russian vaccines [37].

**Vaccination coverage**

National guidelines, recommendations and public health interventions for prevention and control of TBE differ between countries and even within one country [10]. It has been documented that public health interventions in Austria and Sverdllovsk successfully increased vaccination coverage, and that TBE cases have correspondingly reduced significantly [22,23,31,89]. Within Europe, Latvia was one of the countries with the highest number of TBE cases for many years [99]. Currently, Latvia is one of the European countries with the highest vaccination coverage [8]. After 1999, numbers of TBE reported cases were decreasing because of intensive vaccination, while the vaccination coverage was increasing and reaching up to 39% for the whole population in 2009 and up to 22% in children nationwide, with maxima up to 77% in highly endemic regions. TBE cases in children, as percentage of all cases, decreased from 12.5% in 2001 to 3.6% in 2010, mainly because of recommendations and implementations within the national vaccination program for children [8]. In Switzerland, booster intervals of 10 years are recommended to increase TBE vaccination coverage [14]. However, the impact of this measure on TBE incidence has still to be seen with time.

In some endemic countries with high TBE incidence, vaccination coverage is too low to control the disease effectively [12]. In 2006, vaccination coverage in terms of persons receiving one or two doses of vaccine was 6% in Lithuania, 11% in the Czech Republic, 12% in Sweden, 13% in Germany, 13% in Switzerland and 14% in Estonia [100]. In 2007, increases in vaccination coverage in Switzerland up to 17% were seen [11]. In 2008, increased vaccination coverage was seen in Estonia up to 20%, Sweden up to 13% and Lithuania up to 10% [11]. In 2009, vaccination coverage in the Czech Republic was 16% and Slovenia 13% [11]. Therefore, these rates are relatively low compared with other vaccines and ample room for improvement still exists.

**Economic burden & cost–effectiveness of vaccination**

In 1981, an extended vaccination campaign was started under the national universal vaccination program in Austria [23]. Interventions increased vaccination coverage and correspondingly reduced the number of TBE cases [22]. In 1993, the economic benefits of vaccination were evaluated [101]. The total economic benefits of vaccination campaigns in Austria between 1981 and 1990 was evaluated at €24 million through reducing costs for inpatients care, loss of productivity and premature retirement. Similarly, the estimated economic benefits of vaccination campaigns between 1991 and 2000 were €60 million [101]. Also, it was estimated that the TBE vaccine may be cost–effective in Austria and potentially other countries where TBE is widespread and highly endemic [101]. In 2003, it was concluded by Kunz [23] that TBE will no longer be a public health problem in Austria if the universal national vaccination program is continued. In 2005, cost–benefit of vaccination against TBE among French troops was calculated using a decision tree [102]. The results were shown as the net costs (saved) calculated as the difference in vaccination program costs and costs prevented by vaccination [102]. Results demonstrate that the net benefit is negative [102]. It was concluded that the vaccination program

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1In the original study [101], costs are expressed in Austrian Schillings (ATS). In the present review, these costs are converted to Euros (€), using the conversion calculator, available from www.unitconversion.org/eu-currency/austrian-schillings-to-euros-conversion.html [Last accessed August 2014].
against TBE for French military personnel should not be implemented [102].

In 2012, a study on the cost–effectiveness of TBE vaccination in Slovenia was undertaken, using a Markov model for the natural course of TBE [15]. The results were shown as the incremental cost–effectiveness ratios calculated as the difference in the cost of vaccination and no vaccination, divided by the difference in the QALYs corresponding to vaccination and no vaccination, respectively [15]. Analyses were performed from the views of both the healthcare payer and the society [15]. Results illustrate that vaccination against TBE is cost–effective for adults from the healthcare payer’s perspective, whereas from the societal perspective vaccination brings overall economic savings in Slovenia [15]. Findings of the study [15] also demonstrated that costs of hospitalization increase with the age and TBE may be considered to cause relatively high costs for both the healthcare insurance and the society as a whole in Slovenia.

**Expert commentary**

TBE is a CNS disease that may result in long-term or permanent neurological sequelae and death. These neurological sequelae can impair patients’ quality of life and require changes in their lifestyle. TBE is a spreading/emerging infectious disease and new foci are appearing and will further appear in the future, both in countries already affected and in 'new' countries. It is believed that incidence of TBE is underestimated. TBE presents an increasing burden, not only locally but also globally. Raising awareness of TBE, its consequences and the benefits of TBE vaccination in endemic as well as nonendemic countries, among travelers, professionals working outdoors and their employers is extremely important. Awareness may help to increase coverage of vaccination and so reduce the disease burden further. Consequences of TBE have significant impact on patients working capacity and potentially TBE could be identified as an occupational disease/hazard in the future if it is not already considered like that in some areas. There is no specific treatment for TBE, but effective, safe and well-tolerated TBE vaccines provide effective protection against TBE. The cost–effectiveness of TBE vaccination was evaluated for Slovenia. Also, other countries are encouraged to evaluate the cost–effectiveness of TBE vaccination, with the explicit suggestion to apply the Markov model [15] to other countries, such as Sweden. Ideally, consistent evaluation and comparison of incremental cost–effectiveness ratios could result at the European level.

TBE causes high costs for health insurance and society; therefore, potentials for a favorable health-economic profile exist in many settings.

**Five-year view**

In the coming years, it is expected that TBE will further spread to nonendemic areas. It is expected that standardization of reporting and diagnostics procedures will be developed, including international standard testing of immunogenicity. Furthermore, guidelines for exact booster intervals can be expected. More clinical studies in connection with immunogenicity and safety should be undertaken for the Russian and Chinese vaccines and health–economic studies on TBE should be performed. More efficient policies and interventions for prevention and control of TBE, occupational health policies and consensus of travel recommendations locally and globally will be developed, likely resulting in increasing vaccination coverage and decreasing burdens of the disease with time.

**Financial & competing interests disclosure**

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the article. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

**Key issues**

- Tick-borne encephalitis (TBE) is a CNS disease that may result in long-term/permanent neurological sequelae, relevant quality-of-life impacts and even death.
- TBE presents an increasing burden not only locally but also globally, ideally to be estimated in disability-adjusted life years.
- Vaccination is the most effective protection against TBE with effective, safe and well-tolerated vaccines being available; however, coverages are still relatively low.
- There is a need for efficient guidance, recommendations and policies for (cost-)effective prevention of TBE to reduce the disease burden.
- Scarce evidence (notably, for Slovenia) illustrates that TBE vaccines can be highly cost–effective.
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