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Recommendations for tick-borne encephalitis vaccination from the Central European Vaccination Awareness Group (CEVAG)

Dace Zavadska,[1,*] Ioana Anca,[2] Francis André,[3] Mustafa Bakir,[4] Roman Chlibek,[5] Milan Čižman,[6] Inga Ivaskeviciene,[7] Atanas Mangarov,[8] Zsófia Mészner,[9] Marko Pokorn,[6] Roman Prymula,[5,10] Darko Richter,[11] Nuran Salman,[12] Pavol Šimurka,[13] Eda Tamm,[14] Goran Tešović,[15] Ingrid Urbancikova[16] and Vytautas Usonis[7]

[1]Department of Pediatrics; Riga Stradins University; Riga, Latvia; [2]Carol Davila University of Medicine and Pharmacy; Institute for Mother and Child Care; Bucharest, Romania; [3]Consultant; Chaumont-Gistoux, Belgium; [4]Department of Pediatrics; Division of Pediatric Infectious Diseases; Marmara University School of Medicine; Istanbul, Turkey; [5]Faculty of Military Health Sciences; University of Defence; Hradec Kralove, Czech Republic; [6]Department of Infectious Diseases; University Medical Centre; Ljubljana, Slovenia; [7]Faculty of Medicine; Vilnius University Clinic of Children's Diseases; Vilnius, Lithuania; [8]Infectious Diseases Hospital; Sofia, Bulgaria; [9]National Institute of Child Health; Budapest, Hungary; [10]University Hospital; Hradec Kralove, Czech Republic; [11]Department of Pediatrics; University Hospital Center; Zagreb, Croatia; [12]Division of Infectious Disease and Clinical Microbiology; University of Istanbul; Istanbul Turkey; [13]Pediatric Clinic; Faculty Hospital; University of Trencin; Trenčín, Slovakia; [14]Children's Clinic of Tartu University Hospital; Tartu, Estonia; [15]Paediatric Infectious Diseases Department; University of Zagreb School of Medicine; Zagreb, Croatia; [16]Department of Paediatric Infectious Diseases; Children's Faculty Hospital; Košice, Slovakia

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Tick-borne encephalitis (TBE) is a viral neurological zoonotic disease transmitted to humans by ticks or by consumption of unpasteurised dairy products from infected cows, goats, or sheep. TBE is highly endemic in areas of Central and Eastern Europe and Russia where it is a major public health concern. However, it is difficult to diagnose TBE as clinical manifestations tend to be relatively nonspecific and a standardised case definition does not exist across the region. TBE is becoming more important in Europe due to the appearance of new endemic areas.

Few Central European Vaccination Awareness Group (CEVAG) member countries have implemented universal vaccination programmes against TBE and vaccination coverage is not considered sufficient to control the disease. When implemented, immunization strategies only apply to risk groups under certain conditions, with no harmonised recommendations available to date across the region. Effective vaccination programmes are essential in preventing the burden of TBE. This review examines the current situation of TBE in CEVAG countries and contains recommendations for the vaccination of children and high-risk groups.

For countries at very high risk of TBE infections, CEVAG strongly recommends the introduction of universal TBE vaccination in children > 1 y of age onwards. For countries with a very low risk of TBE, recommendations should only apply to those traveling to endemic areas. Overall, it is generally accepted that each country should be free to make its own decision based on regional epidemiological data and the vaccination calendar, although recommendations should be made, especially for those living in endemic areas.

Introduction

Tick-borne encephalitis (TBE) is a pathogenic human infection caused by the TBE virus (TBEV), a flavivirus, which is transmitted by infected ticks and by unpasteurized dairy products from infected cows, goats, or sheep. TBE occurs focally in the non-tropical Eurasian forest belt with most cases occurring in Russia and in Central and Eastern parts of Europe. In endemic areas, TBEV is one of the most important causes of viral meningitis/encephalitis and is a major public health problem.[1]

Approximately, 10,000–12,000 clinical cases of TBE are reported worldwide each year.[2-4] In Europe, between 1990 and 2009, 8,755 cases were reported annually. Of these, 2,815 cases (33.1%) occurred in Central and Eastern Europe, excluding Russia. However, this figure is believed to be underestimated, mainly due to insufficient routine diagnostics and surveillance.[1,5] Overall, in the last three decades, reported cases of TBE have increased by 317.8% in Europe and Russia, and by 193.2% in Europe alone.[1,5,6]

The epidemiology of TBE is, however, very focal in nature. Even in the most affected regions, the disease is usually limited to a specific area. As a result, prevalence figures vary considerably, even within countries.

The proportion of ticks infected with TBEV varies markedly in each region. While TBEV prevalence in ticks reaches 20–40% in highly endemic areas, it can be as low as 0.1–0.5% in other areas.[2,7] Therefore, seroprevalence data are not sufficiently reliable or meaningful and should be more localized to reveal the true epidemiological picture of TBE within the affected region. Small rodents can be used as a useful indicator of the circulation of TBE in an area.[8] While transmission

*Correspondence to: Dace Zavadska; Email: dzavadska@apollo.lv
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seasons vary, ticks are most active from early spring to late autumn (March to November) and seasonal TBE incidence usually coincides with increased exposure during this period.[9]

Three main TBEV subtypes cause the human disease: the Western or European subtype, transmitted primarily by the tick *Ixodes ricinus*; the Far-Eastern subtype, transmitted mainly by *I. persulcatus*; and the Siberian subtype, transmitted mostly by *I. persulcatus*. All three subtypes co-circulate in the Baltic region.[1,2]

TBE Diagnosis and Case Definitions

Following a tick bite, only 10–30% of susceptible cases become infected with TBEV and 90% of these develop flu-like symptoms.[2] The remaining 10% of infections lead to more serious illnesses such as meningitis, meningoencephalitis and meningoencephalomyelitis.[2] TBE can be fatal, with 1–2%, 6–8% and 20% of patients reportedly dying from the European, and Siberian and Far-Eastern subtypes, respectively. Up to 46% of TBE patients suffer from long-term sequelae.[10]

Etiological diagnosis of TBE requires laboratory confirmation because clinical manifestations tend to be relatively nonspecific and are not usually sufficient for diagnosis.[11] Moreover, there is no clear internationally standardized case definition of TBE, and apart from Austria, no clear perception of TBE risk.[1]

At-Risk Populations

TBE is more common in males than females.[2] All age groups can be affected but case distributions vary by region. People living in rural areas or at altitudes below 1400 m are at increased risk of TBE compared with those in urban areas. Most infections are caused by tick bites in forested areas. Professional occupation (military personnel, farmers and forestry workers) and/or interest in recreational outdoor activities in endemic areas increases exposure to tick bites. Moreover, new endemic areas appear as changes in climate occur and recreational activities increase. As a result, TBE is a growing problem for unvaccinated travelers in areas where the disease is endemic.[4,12]

The incidence and severity of TBE are highest in persons aged > 50 y with increase starting from 40 y, but a small number of cases occur in children and adolescents, in whom the signs of meningitis are dominant.[1] In children aged < 7 y, TBE tends to be less severe and permanent sequelae are uncommon;[13] however, there are few high quality TBE studies in children.[4,12] Most TBEV infections occur through a tick bite although a small number are associated with the consumption of unpasteurized milk products.[2,14]

The risk of TBE infection can be reduced by the use of personal measures in endemic areas, such as the wearing of appropriate protective clothing and daily inspection for tick bites. These preventive measures are, however, not sufficiently reliable and vaccination is the most effective way to prevent TBE infection.

TBE vaccines, manufactured in Austria and Germany, provide protection against European TBEV subtypes and have been highly successful over recent decades.[1,2] In Austria, where the vaccination coverage in the general population has reached approximately 88%, the annual number of clinical TBE cases has declined by 90% compared with the prevaccination era.[1,2] However, national vaccination campaigns are not implemented in most European countries where TBE is endemic, resulting in low vaccine coverage and high disease incidence.[1] Defined regional guidelines are therefore important for vaccine implementation and uptake.

The aim of this review is to reinforce existing knowledge of TBE burden, highlighting the current situation in Central European Vaccination Awareness Group (CEVAG; http://www.cevag.org/) countries and how CEVAG perceives TBE risk, and developing a formal CEVAG guidance statement on TBE vaccination. CEVAG consists of regional experts from 12 Central European countries: Bulgaria, Croatia, the Czech Republic, Estonia, Hungary, Latvia, Lithuania, Poland, Romania, Slovakia, Slovenia and Turkey. The aim of CEVAG is to encourage the efficient and safe use of vaccines to prevent, control and, if possible, eradicate infectious diseases. This will be addressed by raising awareness of vaccination and by compiling and distributing appropriate information. CEVAG is an established voluntary association of national representatives and legal entities, which shares an interest in promoting vaccination in Central Europe. CEVAG is organizationally independent of state administration and self-administration bodies, political parties and other civic associations and initiatives. The association does, however, cooperate with these groups during the realization of common plans and promotion of matters of common interest.

The Disease Burden in CEVAG Countries

Currently, TBE is a notifiable disease in 10 of 12 CEVAG member countries. In Bulgaria, clinically defined encephalitis cases are reportable, irrespective of the cause and in Turkey, very little information is available (**Table 1**).

TBE is considered endemic in many regions within CEVAG countries. The Czech Republic, Estonia, Latvia, Lithuania and Slovenia have highly endemic areas (incidence > 10 per 100,000 population). Estonia, Latvia and Lithuania are considered particularly high risk.[6,15] TBE is also an important issue in Poland, Slovakia and Hungary.[16]

In recent decades, the number of TBE cases in CEVAG countries has increased, which may be in part attributable to the introduction of mandatory reporting, better surveillance and improved disease diagnosis linked to healthcare improvements. The incidence rates of TBE (per 100,000 population) vary significantly not only between countries, but also within regions.[1]

According to a 2011 report published by the World Health Organization (WHO), some of the highest rates of TBE are being reported in the Baltic states, including Estonia, Latvia and Lithuania (from north to south) and Slovenia.[2] In 2009, the highest rates of TBE were reported in Estonia (18.7/100,000)[17] and Lithuania (17.8),[18] followed by Latvia (14.6)[19] Slovenia (9.90), and Czech Republic (7.8)[16] and the lowest rates in Hungary (0.60).[1] The highest rates of TBE have been reported in Latvia: 21.97/100,000 in 2010 and 18.70 in 2011 (as reported in November).[19] In Slovakia, the rate was 2/100,000 in 2011.[20]

Table 1. Overview of TBE in CEVAG countries[1,16]

Country	Notifiable disease	Natural foci	Case definition	Incidence rates (cases per 100,000 population)[a]
Bulgaria	No	Of negligible epidemiological significance	No official TBE case definition. Encephalitis cases are reported in bulk irrespective of the cause	N/A
Croatia	Yes, mandatory since 2007	Northwestern and eastern regions New foci emerging south of the river Sava	N/A	2006–2011: 1.1 (Zagreb region)
The Czech Republic	Yes, since 1954 (since 1971 laboratory confirmed cases only)	Endemic in most areas Highly endemic areas include: Southern Bohemia, Berounka	Clinical symptoms (signs of aseptic meningitis/meningoencephalitis with proven neuroinfection in CSF) Presence of specific anti-TBEV antibodies	2009: 7.8 2010: 5.6 2011: 8.2
Estonia	Yes, since 1949	Endemic Highly endemic areas include: western (Pärnumaa, Läänemaa), and eastern (Ida-Virumaa) regions, Saaremaa and Hiiumaa (Western islands) and southeastern region (Polvamaa, Tartumaa)	Possible: typical case history (biphasic infection) with epidemiological links (e.g., tick attack). Confirmed: clinically compatible case with positive laboratory tests. Laboratory testing: ≥ 4-fold increase in antibody titer in paired serums or IgM antibodies in serum/CSF or positive PCR	1998: 27.0 2008: 6.7 2009: 13.3 2010: 15 2011: 18.7
Hungary	Yes, since 1977	Endemic Highly endemic areas include: western region and along the river Danube (Zala, Somogy and Vas), northern region (Nógrád) and around Lake Balaton	Aseptic meningitis, encephalitis or meningoencephalomyelitis laboratory confirmed. Hospitalization is not necessary for diagnosis	Until 1996: 1.3–3.8 1997–2000: 0.67
Latvia	Yes, since 1955	Endemic Highly endemic areas include: northwestern regions (near the coast) of Talsu and Ventspils	No official case definition	2002: 6.52 2003: 15.66 2005: 6.2 2006: 7.41 2007: 7.5 2008: 8.10 2009: 14.6 2010: 21.97 2011: 97.21 (Kuldīgas region)

CSF, cerebrospinal fluid; N/A, Not available; PCR, polymerase chain reaction; TBE, tick-borne encephalitis; TBEV, tick-borne encephalitis virus.
[a]Nationwide rates, at least specified.

In some countries, such as the Czech Republic, Hungary and Slovenia, TBE is clinically defined as aseptic meningitis, meningoencephalitis and/or meningoencephalomyelitis. In most countries, TBE is routinely diagnosed by detecting specific antibodies in serum and cerebrospinal fluid (CSF) using the enzyme-linked immunosorbent assay (ELISA).

Bulgaria

In Bulgaria, clinically defined encephalitis cases are reportable, irrespective of the cause. Although TBEV has been found near to natural foci, the epidemiological significance of TBE is negligible (A. Mangarov, unpublished data). The geographical characteristics of Bulgaria probably contribute to the atypical epidemiology of TBE compared with other CEVAG countries. Bulgaria does not have a specific surveillance system for TBE. Encephalitis cases are registered in bulk as seasonal encephalitides with no separate record of TBE cases, and as a result, very few human cases have been reported. Four laboratory confirmed cases of TBE have been reported in the last two years.[21] AlthoughTBE is not endemic in Bulgaria, physicians should be aware of this infection in patients with manifestations of viral meningitis.

Croatia

In Croatia, TBE was first described in 1953 and since 2007 it has been an obligatory reportable disease. However, the reporting of cases still depends on the "goodwill" of clinicians. From

Table 1. Overview of TBE in CEVAG countries[1,16] (continued)

Country	Notifiable disease	Natural foci	Case definition	Incidence rates (cases per 100,000 population)[a]
Lithuania	Yes, since 1960	Endemic Highly endemic areas include: Kaunas, Panevėžys and Šiauliai	No official case definition, but reported cases are serologically proven hospitalized TBE cases	2003: 100 (Panevėžys) 2004–2008: 6.9–13.5 2009: 17.4
Poland	Yes, since 1970	Endemic in much of the country Highly endemic areas include: northeastern (Bialystock) and southwestern regions	Possible: clinically compatible case and onset of illness during periods of increased tick activity (April–November). Probable: clinically compatible case and increased probability of infection during previous 6 weeks (living in or visiting to endemic areas), and demonstration of specific IgM antibodies in serum, with no history of vaccination against any flaviviral disease during the previous 3 mo Confirmed: clinically compatible case and demonstration of specific IgM and IgG antibodies in serum, or demonstration of intrathecal synthesis of specific IgM or IgG antibodies, detection of specific anti-TBEV antibodies by neutralization test, or positive virus isolation from tissues, blood or CSF	2003: 0.89 2009: 0.52
Romania	Yes, since 1996	Endemic emergent course and natural foci in full territorial expansion Highly endemic areas include: Tulcea district, Transylvania at the base of the Carpathian Mountains and the Transylvanian region	No official case definition. Clinical manifestation and diagnostic tests	N/A
Slovakia	Yes, since 1950	Endemic Highly endemic areas include: Trencín region in the northwest New foci identified in the East	No official case definition	2006: 1.7 2007: 1.1 2008: 1.5 2009: 1.4 2010: 1.7 2011: 2.0 (8.35 in the Trenčín region)
Slovenia	Yes, since 1977	Endemic Highly endemic areas include: Gorenjska and Koroska	Confirmed TBE case: fever, clinical signs/symptoms of meningitis or meningoencephalitis, elevated CSF cell count (> 5 x 105 cells/l), and serum IgM antibodies to TBEV and/or IgG seroconversion	1991–2011: 57.2–76.9 (Gorenjska and Koroska) 2000–2009: 7.6–18.6 2006: 33.4 (aged 55–64 y)
Turkey	No	Very scarce data on TBEV and no published diagnosed/reported cases	No official case definition	N/A

CSF, cerebrospinal fluid; N/A, Not available; PCR, polymerase chain reaction; TBE, tick-borne encephalitis; TBEV, tick-borne encephalitis virus.
[a]Nationwide rates, at least specified.

1999–2009, the Croatian Institute for Public Health reported between 11–44 cases of TBE annually.[22]

Croatia has natural foci of TBE in the northwestern region, between the rivers Sava and Drava, and in the northeastern region, across a small area on the western outskirts of Osijek city. Recently, two new natural foci have emerged in the central mountainous region, south of the river Sava.[23,24]

According to seroepidemiology data collected over a 7-y period (2002–2008), a seroprevalence rate of 14.4/100,000 (range 1.6–66.6) was reported across all Croatian counties.[23] Another study,

conducted within a defined area along the river Sava, reported that 4.41% of forestry workers were IgG-seropositive while none of the volunteer controls tested positive.[25] Further data collected over a 5-y period (2006–2011) at the University Hospital for Infectious Diseases (UHID) in Zagreb, showed an average of 20 TBE cases per year and an annual incidence of 1.1/100,000 [G. Tešovic, unpublished data]. Most cases reported in this study were adults (86.7% aged > 18 y vs 13.3% of children and adolescents aged 1–18 y), with a peak incidence in June (20 cases) and July (26 cases). The similar age and seasonal case distributions were observed in the endemic regions of Koprivnica (Northern Croatia) and Osijek (Eastern Croatia).[26,27] Although some differences in clinical severity have been observed between Eastern Croatia and the rest of the country, mortality is generally low (< 3.3%). However, permanent neurological sequelae were present in 17.1% of adult patients.[27,28]

The Czech Republic

TBE has been recognized as a disease in the Czech Republic since 1948, but cases have only been reported since 1971. Two reporting systems have been established in the country.

TBE is endemic in most of the Czech Republic, but some areas have a much higher risk than others. The Southern Bohemia region and Prague are the two most affected areas, but TBE foci have also been identified in the southern Moravia and highland region.[29] In the east of the country, there has been a high reported incidence near Olomouc city.[29] The high number of cases reported in Prague has been associated with residents traveling to areas of greater risk and being diagnosed with TBE upon their return.

In 2000, 719 cases were reported (7.2/100,000), peaking in 2006 with 1029 cases (10/100,000).[16] In 2007, 546 cases were reported (5.42/100,000), increasing to 861 in 2011 (8.6/100,000). Currently, more than 130 cases of TBE are diagnosed in Czech children annually [R. Chlibek, unpublished data].

Although some children die of TBE, higher case-fatality rates are reported in adults. Up until 2007, TBE fatality rates ranged between 1.44–4.61% among older age groups (> 65 y) compared with 0.48% among children aged 1–4 y [Source: IPH-CEM (EPIDAT), by courtesy of C. Beneš, National Health of Public Health, Prague].

In the Czech Republic, TBE has a seasonality trend with most cases reported between April and December.[29] Most cases were reported in July (> 100 cases each year from 1971–2000, > 150 from 2001–2005 and > 250 in 2006) and September (> 250 in 2006) [Source: SZÚ-CEM (ISPO and EPIDAT), by courtesy of C. Beneš, National Health of Public Health, Prague].

Estonia

Estonia has one of the highest rates of TBE in Europe. This disease has been reportable since 1949 and there has been an upward trend in new cases over the past 30 y.

In 1980, TBE was only reported in the southern regions of Estonia, but it is currently endemic throughout the country.[30] A peak incidence was noted in 1997 (27.8/100,000) and in 1998 (27.0).[30] From 2006–2010, the rate ranged from 6.7–15.0/100,000 with an average of 156 cases reported each year.[30] In 2011, the rate increased to 18.7/100,000 (250 cases in a population of 1.34 million).[17] Main drivers of the increased rate of TBE include climatic and socio-economic changes such as agricultural reforms, and increased mushroom and berry harvesting and recreational outdoor activities.

In the period 1999–2008, the highest morbidity was reported among people aged > 40 y. This is equivalent to 53.5% (lowest rate of 42.1% in 1999, highest rate of 66.5% in 2004) of the entire infected population.[30] The proportion of children aged 0–14 y in the TBE-infected population was 16.0% (lowest rate of 8.8% in 2004, highest rate of 23.5% in 2000).[30] Among children aged < 3 y, three cases of TBE were reported (0.2% of total cases).[30] Overall, the proportion of hospitalized TBE cases ranged from 75.6–96.7%.[30] During this period, a peak incidence was observed between May and September.[30]

In 2010, the highest rates of transmission were reported in the western (Pärnumaa, Läänemaa), eastern (Ida-Virumaa) and southeastern (Polvamaa, Tartumaa) regions of Estonia, and in the Western islands (Saaremaa and Hiiumaa).[17]

From 2006–2008, the proportion of ticks carrying TBEV varied, according to the region, from 0.2% in Puhtu (western Estonia) to 6.4% in Järvselja (southern Estonia).[17] Both vectors of the TBEV Western or European subtypes, *I. ricinus* and *I. persulcatus,* co-circulate in Estonia. Recently, the Far Eastern subtype was identified in western Estonia.[31] All three known subtypes have now been observed in Estonia.[31]

In 2005, the consumption of unpasteurized goat's milk contributed to nearly 30% of all nationwide TBE cases (two unrelated outbreaks with 37 cases).[1] Veterinary and Food Board investigations confirmed the presence of TBEV antibodies in the serum of goats from milk suppliers.[32] In 2009, three cases were linked to the consumption of goat's milk.

Hungary

TBE is endemic in Hungary. Approximately two-thirds of the population live in high-risk areas of the western and northern (Nógrád) regions, along the river Danube (Zala, Somogy and Vas) and around Lake Balaton.[1,15]

In 1985 over 350 cases were reported to the National Centre for Epidemiology. Up until 1996, annual rates of TBE ranged from 1.3–3.8/100,000 with 3 to 7 fatal cases/year[6,15] and from 1997–2000, rates decreased dramatically (0.67/100,000). The number of cases gradually stabilized at 50–70 cases/year in 2009 and 2010, with no fatalities during the past 3 y, possibly due to the availability of TBE vaccines.[33]

New high-risk areas are being found at high altitudes (> 1,000 m) and, in 2007, 25 TBE cases were linked to the consumption of raw goat's milk.[34] A recent cluster of four TBE cases was identified in October 2011.[35] Initial investigations revealed a possible association with consumption of unpasteurized cow's milk. Altogether 11 cases (seven confirmed and four suspected) were identified. Customers who had consumed the

unpasteurized cow's milk had more than 2-fold increased risk for TBE, however this finding was not statistically significant.

Latvia

TBE has been notifiable in Latvia since 1955.[36] Although risk areas for TBE are spread throughout the country, the highest rate was reported in 2011 near the northwest coastal regions of Talsu and Ventspils (26.4/100,000). In 2011, a rate of 97.21/100,000 was reported in Alsunga city in the Kuldīga region.[19]

Between 1990–2000, Latvia had the highest rates of TBE in the world, ranging from 8 to 53 cases/100,000 in 1993 and 1995, respectively.[6,36] After 1999, the rate decreased to 6.2/100,000 in 2005 thanks to intensive vaccination activity.[1,6] Between 2005–2009, 199 cases were reported on average each year.[19] However, since 2009, the number of cases has started to increase.

In 2010, there was a dramatic increase in TBE infections, with 494 reported cases (21.97/100,000), many (137 cases) of whom were aged > 60 y, unvaccinated, of low income and involved in berry and mushroom picking activities. The 2010 figure represents a 148% increase in TBE cases compared with that reported in previous years (2005–2010), and a 51% increase compared with 2009.[19]

In Latvia, ticks carry a higher TBEV load than in other at-risk countries. Latvia also has the highest reported rates of TBE transmitted by dairy products, mainly goat's milk, which accounts for 5% of total cases.[1] In 2010, 18 TBE cases were reported in children (0–18 y of age), which may reflect high vaccination coverage.

Both *I. ricinus* and *I. persulcatus* are present in Latvia, but each has a different seasonal activity. While *I. ricinus* has two seasonal activity peaks in western and central Latvia, *I. persulcatus* has only one spring peak and predominates in the eastern region.[36]

Lithuania

Lithuania has the highest rate of TBE of all Baltic countries[1] where it is recognized as one of the most important causes of central nervous system (CNS) diseases in adults. TBEV is highly endemic across much of the country and 3% of the population is thought to have been exposed.[6,15] In some areas, a rate of TBE as high as 100/100,000 has been reported.[6] Northern and central Lithuania account for 80% of cases reported annually.[6,15] In some of these high-risk areas—mainly the Kaunas, Panevėžys and Šiauliai counties—rates of TBE are > 40/100,000.[15] In 2003, the highest rate was reported in Panevėžys with 100/100,000.[6] In the Kaunas county, TBE infections accounted for more than 50% of all CNS infections.[37]

In 2003, the rate was twice that reported in the previous decade,[6,37] the highest recorded rate since notification began in 1960, and was the highest of all the Baltic countries.[6,38] This is thought to be due to the availability of improved diagnostic methods since 1993, but the high incidence in 2003 may also be linked to the high number of ticks observed in that particular year.[38] On average, 422 cases of TBE were reported in the 7-y period from 2003–2009 (range 220–763). Higher numbers of TBE cases were reported in 2008 and 2009 (605 and 612 cases, respectively) compared with the previous 5 y between 2004–2008 (range 220–462, 6.9–13.5/100,000).[6] Four fatal cases of TBE were notified in 2003[6] and none in 2011.[39]

In Lithuania, no recent seroprevalence data exist. In one study conducted in 2000, 2.9% (43 of 1488) of healthy individuals were found to be positive to TBE infection.[37]

In Lithuania, TBE affects 1.4 times as many males as females, and people from rural areas are 1.7 times more likely to be affected than those living in urban areas.[38] The latter has remained constant over the past 10 y. It has been estimated that approximately 40% of all TBE cases are among retired and unemployed adults[38] and this has remained relatively constant over recent years. One reason could be that these people are more likely to collect mushrooms and berries, which can serve as an additional source of income. The rate of TBE is approximately 2- to 3-fold higher in adults than in children (0–18 y of age).[38] Typically, 20% of all TBE cases in Lithuania are reported in people aged > 60 y and < 10% are from children. In 2003, the 40–49 age group made up nearly 20% of the total, although the increased rate of TBE affected all age groups.[38]

In Lithuania, the tick season is from late March until mid-November. In 2003, most TBE cases were reported in September and October.[38] In 2009, 447 cases were documented between August and October, and in 2010 more than 200 cases were reported in October.[39]

In Lithuania, *I. ricinus* is the only vector of TBE and the Western TBEV is the only subtype found in all districts.[37] However, the proportion of Lithuanian ticks infected with TBE is still unknown.[40] Although TBE is normally transmitted by tick bite, in 2003 22 cases of TBE from four different clusters were acquired from unpasteurized goat's milk.[6]

Poland

TBE is endemic in most of Poland with the highest rates reported in the northeastern and southwestern regions.[1,6,15] Approximately 80% of cases have been reported around Bialystock, an area located in the northwestern provinces, adjacent to Lithuania and Belarus. The districts close to the Czech Republic in the southwestern region are another important focus of the disease.[6] In 2008, new endemic foci were identified in the north-western provinces of Poland where very few cases have been reported previously (1970–2005).[6]

Since 1993, between 100–350 cases have been reported annually;[6] 339 (0.89/100,000) in 2003 and 335 (0.52/100,000) in 2009.[6,15]

Romania

In Romania, TBE is endemic and natural foci are in full territorial expansion.[41] Risk areas are focused in the Tulcea district, Transylvania, at the base of the Carpathian mountains and the Transylvanian Alps.[1,6] However, the nationwide annual rate of TBE has not been published and the relative risk of contracting this disease is unknown.

In 2001–2006, an epidemiological survey of TBEV infection was performed in 1669 individuals from 11 Transylvanian counties.[41] In the general population, the seroprevalence rate was estimated to be 0.6%, but even higher rates were found in at-risk populations: 5.8% in those living around natural foci and up to 41.5% in those with known occupational risks. A seroprevalence rate of 11.6% was reported in the domestic habitat of former patients with TBE-Central European Encephalitis.[41] TBEV was the most common cause of acute viral meningitis (14.1%).[41]

Slovakia

Most parts of Slovakia are thought to be endemic,[1] with 50–90 TBE cases reported annually. Between 1998–2007, on average, 67 (range 46–92) cases were reported annually;[1,6] 91 (1.7/100 000) in 2006 and 57 (1.1/100 000) in 2007.[20] This compares with 108 cases (2.0/100,000) in 2011.[20] In the same year, 50 cases of TBE (8.35/100,000) were reported in the northwest Trenčín region, along the river Váh near the Czech Republic.[42] New foci have been identified in eastern Slovakia, a region traditionally thought to be free of TBEV.[6] Some of the reported cases were attributed to the consumption of raw homemade goat's and sheep's milk.[6] In the Trencín region, 16 cases were reportedly caused by unpasteurised milk products between 2008–2010.[6,42,43]

Slovenia

Since 1977, notification of TBE cases and deaths has been mandatory in Slovenia.[11] TBE is endemic throughout the country.[6] Surveillance data collected over the past 20 y (1991–2011) found the highest rates of TBE in the Gorenjska and Koroska regions, with annual rates of 57.2 and 76.9/100,000, respectively.[11,44]

Between 2001–2005, the 5-y average was 261 cases,[1,6] peaking at 445 in 2006.[6] From 2000–2009, incidence rates ranged between 7.6–18.6/100,000.[11]

In Slovenia in the last decade, there has been an age distribution shift of TBE to the older age groups, resulting in the highest age-specific incidence rates in those aged 55–64 y (33.4/100,000 in 2006).[44]

I. ricinus is the main vector of TBEV in Slovenia, with a reported prevalence of 0.43% and 0.54% in 2005 and 2006, respectively.[7] Infection rates of TBEV in ticks were significantly correlated with TBE incidence rates in Slovenian patients in selected areas. The TBEV in ticks was confirmed to be genetically related to the TBEV in the Slovenian patients.[7]

Turkey

In Turkey, very limited data are available on TBE and no human cases have been officially reported; Turkey is not a TBE endemic country.[1,6,45] As in other European countries, *I. ricinus* is the most common vector, especially in the coastal regions.[46]

Although no nationwide studies have been published, two regional surveys have commented on the TBEV exposure among residents of rural areas in Sinop (a province located on the coast of the Central Black-Sea region of Turkey) and in Central/Northern Anatolia. TBEV IgG positivity was detected in 2.9% (8/273) and 1.9% (47/2454) of people in the Sinop and Anatolia regions, respectively.[45,46] In the Anatolia survey, risk factors for tick-borne infections were identified in 53% of individuals positive for TBEV. One sample from the Zonguldak province in the Black Sea region of Turkey was confirmed to possess neutralising antibodies. However, most cases should be considered as 'probable' since the majority of results obtained were not confirmed by additional testing.

The presence of TBEV in Sinop and the Black Sea region should be identified as these regions are located near to known TBEV endemic areas. Overall, the epidemiology of TBEV activity in Turkey needs further assessment and the benefits of vaccination for the general population, risk groups or travelers to endemic regions must be considered.

Current Available TBE Vaccines in Europe

For TBE, licensed vaccines include an Austrian vaccine (FSME–Immun® also known as TicoVac® in all Baltic and Scandinavian countries; Baxter) and a German vaccine (Encepur®; Novartis Vaccines), and which available throughout Europe.

Other licensed vaccines not available in Europe include two Russian vaccines, TBE-Moscow® (available in Russia, Kazakhstan and Ukraine) and EnceVi® (Russia only).

TBE Vaccine Immunogenicity and Effectiveness

No clinical trials have been conducted on the efficacy of TBE vaccines, but the effectiveness and safety of current vaccines has been proven in a number of observational studies.[11] In Austria, high vaccination coverage has lead to a significant decrease in TBE incidence and a protection rate over 95%.[47] TBE vaccine failure infections are reported rarely and mainly occur in older groups.[11] Very few failure cases have been reported in individuals aged < 25 y, with only two cases occurring in children.[11] A 2009 study in the Slovenian region of Gorenjska reported a higher number of TBE cases than expected among vaccinated individuals (4 patients with a history of TBE vaccination from a total of 63 TBE cases).[11] However, according to the surveillance case definition for TBE and the case classification for vaccine failures, only one of four cases previously vaccinated was reported to be a verified failure case.[11]

The Austrian and German vaccines are well tolerated and efficacious for individuals aged > 1 y,[1] and both Russian vaccines for those aged > 3 y.[1] All of the currently available vaccines appear to protect against all TBEV subtypes circulating in Europe and Asia.[2]

TBE transmitted by unpasteurised milk, such as the outbreaks in Hungary, could be effectively prevented by vaccinating people and/or dairy animals, although it is not clear yet how long the immunity against TBEV persists in animals.[48]

General Dosage and Administration Schedules

European manufacturers (Austrian and German vaccines) recommend three doses for complete priming. The second dose is given 1–3 mo after the first, and the third is given 9–12 mo after the second. The first booster is recommended 3 y after priming. For both vaccines, the manufacturer's recommended intervals and subsequent booster doses vary by age and should be given every 5 y for those aged < 60 y and every 3 y for those aged ≥ 60 y.[1]

Accelerated or rapid schedules, used in emergency situations, are based mainly on reduced intervals between the first two doses. The accelerated schedule for the Austrian vaccine recommends the first and second doses on days 0 and 14, respectively, and the third dose 5–12 mo after the second. The rapid schedule for the German vaccine recommends doses on days 0, 7 and 21, with a fourth dose 12–18 mo after the third.[1]

Vaccine Coverage in CEVAG Countries

Most CEVAG countries have not implemented a universal vaccination program for TBE, and for those that have, vaccination rates differ widely. Furthermore, in many countries, vaccine coverage is considered to be too low to effectively control the disease.[15]

In Croatia, although there are no national recommendations for TBE, vaccination of at-risk groups (mainly forestry workers in the northern Koprivnica region) has reduced the number of reported TBE cases 3-fold (304 in 1979–1988 vs. 90 in 1999–2007).[26]

In the Czech Republic, as traditional endemic areas expand, vaccination is recommended not only for residents, but also for travelers and retired persons who visit for recreational purposes.[15] In Southern Bohemia, one-third of the population is vaccinated, particularly children and younger adults.[15] Vaccination coverage fluctuates from 12 to 23% in the other parts of the Czech Republic. In Estonia in 2010, 18,000 people (10% of the population) were vaccinated, including 5561 children. In the same year, 15,274 people were reported to have been revaccinated including 2784 children aged 1–14 y, 976 adolescents aged 15–17 y and 11,514 adults.[17] In Hungary, although TBE has been recognized as an occupational hazard since the late 1990s, vaccine coverage remains low, covering only 5–15% of the total population.[15] Despite TBE being endemic across much of Poland, only 0.34% of the population were vaccinated between 1999–2007, with more than half of those living in the northeastern, highly endemic regions.[15]

Slovenia has one of the highest reported rates of TBE, but vaccination uptake remains low (only 12.4% of those aged ≥ 15 y in 2007).[49] Vaccination coverage should be improved to reduce disease burden and morbidity. This could be accomplished by offering compulsory vaccination within health insurance in addition to intensive vaccine promotion, thereby reducing the social inequality to access.[44]

In Lithuania, vaccination coverage is considered to be too low to control the disease. In Latvia, approximately 22% of children had been vaccinated by the end of 2010, most (77%) of whom were living in highly endemic areas, the cost of which is reimbursed by the state.[36] The vaccination rate for the national population was 39% in 2009 and 41% in 2010, which is the highest after Austria. This has resulted in a significant reduction of TBE cases among children living in highly endemic areas; 12.5% in 2001 to 3.6% in 2010.[19]

Existing Recommendations for TBE Vaccination

WHO recommendations. As TBE incidence varies considerably between and within geographical regions, WHO recommends that public vaccination strategies should be based on risk assessments conducted at country, regional or even district level.[1,2] Therefore, before deciding on the most appropriate preventive measures, it is important to establish adequate TBE case reporting.[2]

In areas where the disease is highly endemic (≥ 5 cases/100,000 per year), implying that there is a high individual risk of infection, WHO recommends vaccination of all age groups, including children.[50] Where the rate of TBE is moderate or low (5-y incidence of < 5/100,000 per annum), or is limited to specific areas or outdoor activities, vaccination should target individuals in the most severely-affected cohorts.[2]

The WHO also recommends TBE vaccination of travelers to rural and forested areas up to altitudes of 1,400 m.[2,50]

Although few recent cost–effectiveness evaluations exist, Austrian estimates suggest that TBE vaccination is cost effective, at least in those countries with high and widespread endemicity.[1] In Slovenia, for example, a country with high TBE incidence and low vaccine coverage, the current vaccination program against TBE was found to be cost-effective for adults from a healthcare payer's perspective.[51] Vaccination was cost saving from a societal perspective due to avoidance of costs associated with TBE infection. As TBE places a huge burden on healthcare resources (e.g., acute and long-term treatment), cost-effectiveness is expected to be strongly influenced by efficient targeting of vaccination programmes and vaccine pricing.

Consensus and conflicts in CEVAG country recommendations. It is evident that each CEVAG country has a different approach. Overall, vaccination is recommended for people at high risk of TBEV infection, such as those residing, working or traveling in endemic areas. Mandatory vaccination is being implemented for some of these groups in several CEVAG countries, but there is still no consensus across the region.

Existing guideline recommendations from CEVAG countries. An overview of TBE vaccine recommendations across CEVAG countries is presented in **Table 2**. There is a lot of variation from country to country and sometimes within the country. Latvia is the only CEVAG country with a national universal TBE vaccination program; most other countries in the region have programmes linked to specific conditions. Slovenia does not have a universal national program and TBE vaccination is only recommended for high-risk groups. Romania and Turkey have not implemented any national programmes, policies or recommendations for TBE.

TBE vaccination is not universally covered or reimbursed in any of the CEVAG countries. Currently, the Czech Republic,

Table 2. TBE vaccination in CEVAG countries[1-2,15-16]

Country	Available	National vaccination program	Vaccination coverage
Bulgaria	No TBE vaccine registered	No (optional) Only recommended for travelers abroad	Unknown
Croatia	Yes, Austrian and German vaccines (both registered but only Austrian currently available)	No (optional) – vaccination is on an 'individual basis' Only recommended for residents in endemic areas and those visiting endemic areas (for recreation) Forestry workers in the Koprivnica-Križevci region	Unknown
The Czech Republic	Yes, Austrian and German vaccines	No, but recommended for infants, children and adults living in or traveling to highly endemic areas As traditionally endemic areas expand, vaccination is increasingly recommended to adults/elderly living in or traveling to these endemic areas, for outdoor activities, forestry and agricultureal workers Reimbursement of the third dose of the vaccine only	2007: 16% (nationwide), 29% (Southern Bohemia), and 27% (Prague) High in children but low in elderly
Estonia	Yes, Austrian and German vaccines	No, but recommended to all individuals aged > 1 y Recommended for travelers visiting endemic areas No vaccine reimbursement is available for the general population Free for risk groups (foresters, irrigators, military personnel) – vaccination is covered by the employer	10% (nationwide) – increasing due to Health Protection Agency campaigns and pharmaceutical companies 2010: 18,000 people vaccinated (5561 children) and 15,274 revaccinated
Hungary	Yes, Austrian and German vaccines	Yes: mandatory for people with extensive exposure to ticks in rural areas (e.g., forestry workers and farmers since 1998, hikers and campers) Recommended for everyone Offered free for residents of highly endemic areas German vaccine is reimbursed (25% of cost covered by National Health Insurance)	5–15% (nationwide)
Latvia	Yes, Austrian and German vaccines	Yes, for children (since 2007) and adolescents living in endemic areas Offered free (since 2010) for orphans/children without parental care vaccination and children living in highly endemic areas Mandatory for high risk groups and/or individuals expecting to have high occupational exposure (e.g., forest workers and military personnel for whom vaccination is paid by employers) Strongly recommended for adults	Children: 22% (nationwide) and up to 77% (highly endemic areas) In highly endemic areas, vaccination has reduced child morbidity from 12.5% in 2001 to 3.6% in 2010 The vaccination rate in the whole population was 39% in 2009
Lithuania	Yes, Austrian and German vaccines	No (optional) Recommended > 1 y of age, but full cost is paid by the patient Some employers provide vaccination (e.g., forest workers) Vaccines are given on a private basis only Recommended for travelers	Vaccination rates in Lithuania are very low Approximately 20,000 doses of vaccines are used every year
Poland	Yes, Austrian and German vaccines	No national TBE vaccination policy implemented, but recommended for residents of endemic areas, particularly for military personnel, border guards, fire fighters, farmers and tourists – TBE vaccination is not universally reimbursed Mandatory for forestry workers (since 1994) – reimbursed by the employer	Not officially reported 1999: 7500 vaccine doses 2008: 30,800 vaccine doses 2011: 20,000 vaccine doses 1999-2007: 0.34% (nationwide, although more than half living in the northeastern region)
Romania	Yes, German child and adult vaccines (both registered)	No national TBE vaccination policy and/or recommendations implemented	Unknown

Table 2. TBE vaccination in CEVAG countries[1-2,15-16] (continued)

Country	Available	National vaccination program	Vaccination coverage
Slovakia	Yes, Austrian and German vaccines	National TBE vaccination policy and recommendation implemented only for high-risk occupational groups Mandatory for staff working in TBE testing laboratories Recommended for forestry workers, farmers, surveyors, geologists, mountain huts and cableway staff, police officers, military personnel and railway workers	Unknown
Slovenia	Yes, Austrian (mainly) and German vaccine	National TBE vaccination policy (follows general dosage and administration schedules from western manufacturers) and recommendation implemented only for high-risk groups Mandatory (since 1986) for high-risk workers Mandatory (since 1990) for students at high risk Recommended (since 1991) for people living in or traveling to highly endemic areas, including children aged > 1 y	12.4% (nationwide) in 2007: 3.2% (high-risk workers) 2.3% (students at high risk) 2.2% (military personnel) 4.6% (people vaccinated for 'other reasons')
Turkey	No	No	Unknown

Estonia, Hungary, Latvia, Lithuania and Poland have started to reimburse for TBE vaccination, but only for specific groups.[1]

CEVAG guidance statement. TBE vaccine should be offered to children > 10 y of age in countries with low endemic risk, and from 12 mo of age in high endemic risk countries. TBE vaccination should also be recommended to those people, regardless of age, traveling from non-endemic areas to endemic areas even where local prevelance is low (e.g., Austria and its neighboring countries have low prevalence rates due to vaccination, but the endemicity in ticks remains high). However, vaccination should be offered all year round to indivduals aged > 12 mo living in highly endemic areas. Overall, it is accepted that CEVAG countries should be free to make their own decisions based on epidemiological data and vaccination calendars, but recommendations should be made for endemic areas with outdoor activities and for those traveling to and from endemic areas.

Discussion

In most CEVAG countries, there is no clear perception of the risk of TBE. Since TBE incidence varies considerably between geographical areas, vaccination strategies should be based on the specific risk of each country, appropriate to the local endemic level. Therefore, an epidemiological survey is paramount before deciding on the most appropriate vaccination policy. A standardised case definition of TBE is essential to ensure that epidemiological data are gathered correctly, regardless of whether or not the disease is highly prevalent.[16] European consensus is also necessary to guarantee the comparability of cases and vaccine failures.[11] Furthermore, establishing surveillance at the national and European level is fundamental for the monitoring and evaluation of disease burden, the impact of vaccination, vaccine effectiveness and an early warning to change the vaccination schedule when necessary.[11]

TBE vaccination programmes are not implemented universally by any of the governments of CEVAG countries however, there are various recommendations or mandatory programmes for high risk groups, endemic exposure and other specific conditions. In many countries, vaccination strategies are based on local endemic situations, provincial budgets and financial resources.[3]

Recommendations for TBE vaccination have existed for many years in various European countries. However, these recommendations are not generally followed, including in endemic CEVAG countries. Better compliance with these recommendations could be achieved through encouraging national TBE awareness campaigns and distribution of educational materials and resources for the general public. Increasing the awareness of TBE among all physicians and healthcare workers is vital, so that they can remind patients to get vaccinated if they either live in an endemic area, or are traveling to one.[15]

TBE is not fully reimbursed by national healthcare systems in any of the CEVAG countries except for some specific population subgroups (e.g., in Latvia, it is offered free for all orphans and children living in highly endemic areas). In highly endemic areas, vaccination should be available for all age groups, as recommended by the WHO, leading to some form of reimbursement. In the Czech Republic, little or no direct support is available from state institutions for vaccinations in highly endemic areas and in children and adolescents nationwide (e.g., reimbursement of one dose by larger healthcare insurance companies), and this may have contributed to the rising incidence of TBE.[29]

Vaccine coverage has a major influence on disease incidence. Although TBE cannot be completely eliminated from endemic areas, in Austria, large-scale vaccination campaigns have proven highly effective in reducing disease burden. Latvia is the only CEVAG country to have a large-scale vaccination campaign for all age groups.[52]

Furthermore, data on vaccination coverage are based solely on the number of vaccination doses sold annually and do not reflect the percentage of the population vaccinated.[16] In this situation, therefore, vaccine coverage should be compared carefully with incidence rates.

Currently, there is no cure for TBE and treatment is symptomatic with the use of antipyretic and anti-inflammatory medication.[1] Patients with severe neurologic manifestations have to be closely monitored.[1] Vaccination or other prophylactic measures are not recommended after a tick bite.[1] Since TBE has a relatively short incubation period, starting vaccination after a tick bite may not provide sufficiently high levels of neutralising antibody to protect the individual.[1] Very limited clinical data exist supporting the use of active postexposure prophylaxis (PEP) using anti-TBEV immunoglobulins. There is the theoretical concern that PEP could result in antibody-dependent enhancement of the disease, resulting in higher morbidity.[1] Although application of PEP was withdrawn from the European market in the late 1990s, it is still being used in Russia.[53]

An important target for vaccination should be the older age groups, as the disease tends to be more serious in those aged ≥ 50 y. Many studies have shown that both Western vaccines show effective immune responses in children and adults, but none have been conducted on the primary response in those aged ≥ 50 y. In the elderly population, however, both Western vaccines show relatively good boosting responses[54,55] with relatively low breakthrough rates.[56,57] Nevertheless, older persons (aged > 60 y) face the risk of becoming seronegative earlier because of the lower antibody titer achieved immediately after the booster.[1] For example, in the Czech Republic, the increase of recreational outdoor activities in newly high-risk areas has resulted in more TBE cases being detected among the elderly, in whom the disease course is more serious.[15] Despite this, vaccination rates among older age groups (≥ 50 y) remain low in the Czech Republic.[15]

TBE is becoming all the more important because it is now being reported in previously non-endemic areas. In recent years, drivers for increased incidence include climatic (warmer climates where ticks live all year round) and socio-economic changes (recreational activities in endemic areas and changes in land use).[58-61] This is true in Lithuania where new TBE cases are being reported in previously non-endemic areas. In Latvia, the marked decrease in TBE morbidity among children in 2010 was significantly correlated with the implementation of a TBE vaccination program in high-risk areas in 1994.

Both the Austrian and the German TBE vaccines seem to be interchangeable for boosting or for completion of previous vaccination series.[62,63] Recent clinical data show that they may also be conditionally interchangeable during primary vaccination with conventional schedules.[64] However, data are still lacking and thus, a change of vaccines is only acceptable after careful consideration and then only in specific cases, e.g., vaccine shortage.[65]

To our knowledge, no clinical studies have been published indicating that neonates or infants (< 6 mo) are passively protected against TBEV infection by neutralizing antibodies from previously infected mothers, but this protection has been demonstrated with other flaviviruses, such as the dengue virus.[66]

TBE burden in CEVAG countries can only be reduced if there is a standardised European case definition for the disease. Only then can epidemiological data be collected and vaccine effectiveness evaluated in highly endemic countries.

Disclosures of Potential Conflicts of interest

D.Z. has received lecture fees from GlaxoSmithKline (GSK), sanofi pasteur and Abbott and has received sponsorship from GSK to attend scientific meetings. I.A. has been the principal investigator in clinical studies supported by GSK, Apogepha and Ferring. She has also been a scientific consultant to GSK, Wyeth Lederle, Teva, AstraZeneca and Nestlé, and has received sponsorship from GSK, Wyeth and Nestlé to attend scientific meetings. M.B. has received sponsorship for scientific meetings from GSK, Wyeth Lederle, sanofi aventis, and Merck Sharp and Dohme (MSD). R.C. has received lecture fees and sponsorship to attend scientific meetings from GSK, sanofi pasteur and Pfizer, has been principal investigator in clinical trial sponsored by GSK. M.C. is a member of GSK advisory boards on vaccines and has received honoraria for lectures on vaccine use from GSK, Pfizer and MSD. I.I. has been a scientific consultant to Baxter, GSK, Merck and Pfizer and has received sponsorship from these companies to attend scientific meetings. A.M. has been a scientific consultant to Wyeth, GSK, Aventis Pasteur, Pfizer, Danone and Solvay Pharma and has received sponsorship from these companies to attend scientific meetings. Z.M. is a consultant to Wyeth, GSK, MSD, sanofi pasteur, Novartis and Baxter on vaccination issues and has also received travel grants. M.P. has received lecture fees from GSK Slovenia, speaker fees from GSK and has received sponsorship from GSK and PharmaSwiss Slovenia to attend scientific meetings. R.P. is a member of advisory boards for GSK, MSD, Wyeth, Baxter and Aventis Pasteur and has received research grants and honoraria from GSK, Wyeth, Baxter, Aventis Pasteur and Novartis. D.R. has received honoraria for lectures on vaccines and respiratory drugs from GSK Croatia, MSD Idea Inc. Croatia, Pfizer and Medoka (representing Sanofi Pasteur). P.S. has received consulting fees and lecture fees from GSK, Wyeth and MSD. E.T. has received sponsorship from GSK and PharmaSwiss to attend scientific meetings. G.T. has received sponsorship from GSK, MSD, PharmaSwiss, Wyeth and Pfizer to attend scientific meetings. I.U. has been a scientific consultant to GSK and Pfizer and has received lecture fees from GSK, Pfizer, MSD, Novartis and has received sponsorship from GSK, Pfizer and Sanofi Pasteur to attend scientific meetings. V.U. is has been the principal investigator in clinical studies supported by GSK, Novartis, and Pfizer. He has also been a scientific consultant to Aventis Pasteur, Baxter, GSK, Merck, and Pfizer, and has received sponsorship from these companies to attend scientific meetings. F.A. and N.S. have no competing interests.

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References

1. Kollaritsch H, Krasilnikov V, Holzmann H, Karganova G, Barrett A, Süss J, et al. Background document on vaccines and vaccination against tick–borne encephalitis. Geneva, WHO Strategic Advisory Group of Experts on Immunization. Available at: http://www.who.int/immunization/sage/6_TBE_backgr_18_Mar_net_apr_2011.pdf (last accessed May 2012).
2. World Health Organization (WHO). Vaccines against tick-borne encephalitis: WHO position paper. Wkly Epidemiol Rec 2011; 86:241-56; PMID:21661276.
3. Donoso-Mantke O, Schädler R, Niedrig M. A survey on cases of tick-borne encephalitis in European countries. Euro Surveill 2008; 13:pii=18848. Available at: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=18848 (last accessed October 2012).
4. Centers for Disease Control and Prevention (CDC). Tick-borne encephalitis among U.S. travelers to Europe and Asia 2000–2009. JAMA 2010; 303:2132-5.
5. Süss J. Tick-borne encephalitis 2010: epidemiology, risk areas, and virus strains in Europe and Asia-an overview. Ticks Tick Borne Dis 2011; 2:2-15; PMID:21771531; http://dx.doi.org/10.1016/j.ttbdis.2010.10.007.
6. Süss J. Tick-borne encephalitis in Europe and beyond – the epidemiological situation as of 2007. Euro Surveill 2008; 13:pii=18916. Available at: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=18916 (last accessed October 2012).
7. Durmiši E, Knap N, Saksida A, Trilar T, Duh D, Avšic-Županc T. Prevalence and molecular characterization of tick-borne encephalitis virus in Ixodes ricinus ticks collected in Slovenia. Vector Borne Zoonotic Dis 2011; 11:659-64; PMID:21028962; http://dx.doi.org/10.1089/vbz.2010.0054.
8. Knap N, Korva M, Dolinšek V, Sekirnik M, Trilar T, Avšic-Županc T. Patterns of tick-borne encephalitis virus infection in rodents in Slovenia. Vector Borne Zoonotic Dis 2012; 12:236-42; PMID:22022821; http://dx.doi.org/10.1089/vbz.2011.0728.
9. Gritsun TS, Lashkevich VA, Gould EA. Tick-borne encephalitis. Antiviral Res 2003; 57:129-46; PMID:12615309; http://dx.doi.org/10.1016/S0166-3542(02)00206-1.
10. Haglund M, Günther G. Tick-borne encephalitis--pathogenesis, clinical course and long-term follow-up. Vaccine 2003; 21(Suppl 1):S11-8; PMID:12628810; http://dx.doi.org/10.1016/S0264-410X(02)00811-3.
11. Grgić-Vitek M, Avšic-Županc T, Klavs I. Tick-borne encephalitis after vaccination: vaccine failure or misdiagnosis. Vaccine 2010; 28:7396-400; PMID:20854899; http://dx.doi.org/10.1016/j.vaccine.2010.09.003.
12. Lindquist L, Vapalahti O. Tick-borne encephalitis. Lancet 2008; 371:1861-71; PMID:18514730; http://dx.doi.org/10.1016/S0140-6736(08)60800-4.
13. Kaiser R. Tick-borne encephalitis. Infect Dis Clin North Am 2008; 22:561-75, x; PMID:18755391; http://dx.doi.org/10.1016/j.idc.2008.03.013.
14. Dumpis U, Crook D, Oksi J. Tick-borne encephalitis. Clin Infect Dis 1999; 28:882-90; PMID:10825054; http://dx.doi.org/10.1086/515195.
15. Kollaritsch H, Chmelík V, Dontsenko I, Grzeszczuk A, Kondrusik M, Usonis V, et al. The current perspective on tick-borne encephalitis awareness and prevention in six Central and Eastern European countries: report from a meeting of experts convened to discuss TBE in their region. Vaccine 2011; 29:4556-64; PMID:21549781; http://dx.doi.org/10.1016/j.vaccine.2011.04.061.
16. Donoso-Mantke O, Escadafal C, Niedrig M, Pfeffer M. on behalf of the Working group for Tick-borne encephalitis virus. Tick-borned encephalitis in Europe, 2007 to 2009. Euro Surveill 2011; 16:pii=19976. Available at: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=19976 (last accessed May 2012).
17. Estonian Health Board. http://www.terviseamet.ee/fileadmin/dok/Nakkushaigused/statistika/2010/Epid_ulevaade_2010.pdf (last accessed April 2012).
18. European Centre for Disease Prevention and Control (ECDC). TBE situation in individual European countries. Available at: http://ecdc.europa.eu/en/healthtopics/spotlight/spotlight_tickborne/pages/situation_in_european_countries.aspx (last accessed April 2012).
19. Epidemiological Safety and Public Health Department of Infectology. Available at: http://www.lic.gov.lv/docs/268/2009-dok/12_09_II.pdf (last accessed March 2012).
20. Public Health Authority of the Slovak Republic. Available at: http://www.uvzsr.sk (last accessed April 2012).
21. Hristova I, Dikov I, Andonova L, Taseva E, Kalvachev N, Popal S, et al. Four cases of Tick-borne encephalitis in Bulgaria. Science Infectology Parasitology Number 1 2011:43-6.
22. Aleraj B. Infectious diseases in Croatia in 2009. Croatian Journal of Infection 2010; 30:167-75.
23. Borčić B, Kaić B, Gardašević-Morić L. Tick-borne meningoencephalitis in Gorski Kotar--new findings. Lijec Vjesn 2001; 123:163-4; PMID:11729608.
24. Borčić B, Kaić B, Kralj V. Some epidemiological data on TBE and Lyme borreliosis in Croatia. Zentralbl Bakteriol 1999; 289:540-7; PMID:10652720; http://dx.doi.org/10.1016/S0934-8840(99)80007-3.
25. Miletić-Medved M, Đaković-Rode O, Cvetko-Krajinović L, Markotić A. Tick-borne meningoencephalitis in central Posavina, Croatia: seroepidemiological survey among forest workers. Infektološki glasnik 2011; 31:87-94.
26. Mišić-Majerus Lj, Zaninović K, Cmrk-Kadija V, Đaković-Rodé O. Global warming, climate change and the effect on ticks and tick borne pathogens. Infektološki glasnik 2008; 28:61-8.
27. Anic K, Soldo I, Peric Lj, Karner I, Barac B. Tick-borne encephalitis in eastern Croatia. Scand Infect Dis J 1998; 30.
28. Mišić-Majerus Lj, Đaković-Rode O, Ružić Sabljić E. Post-encephalitic syndrome in patients with tick-borne encephalitis. Acta Med Croatica 2009; 63:269-78; PMID:20034327.
29. Beran J. Tickborne encephalitis in the Czech Republic. Euro Surveill 2004; 8:pii=2493. Available at: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=2493 (last accessed October 2012).
30. Epstein E, Kutsar K. Epidemological trends of tick-borne encephalitis in Estonia. EpiNorth 2009; 10:58-62.
31. Golovljova I, Vene S, Sjölander KB, Vasilenko V, Plyusnin A, Lundkvist A. Characterization of tick-borne encephalitis virus from Estonia. J Med Virol 2004; 74:580-8; PMID:15484275; http://dx.doi.org/10.1002/jmv.20224.
32. Kerbo N, Donchenko I, Kutsar K, Vasilenko V. Tickborne encephalitis outbreak in Estonia linked to raw goat milk, May-June 2005. Euro Surveill 2005; 10:pii=2740. Available at: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=2740 (last accessed October 2012).
33. Hungarian National Centre for Epidemiology (OEK). Epinfo - Weekly Epidemiological Information Sheet. 2011;26-27. Available at: http://www.oek.hu (last accessed July 2012).
34. Balogh Z, Ferenczi E, Szeles K, Stefanoff P, Gut W, Szomor KN, et al. Tick-borne encephalitis outbreak in Hungary due to consumption of raw goat milk. J Virol Methods 2010; 163:481-5; PMID:19836419; http://dx.doi.org/10.1016/j.jviromet.2009.10.003.
35. Caini S, Szomor K, Ferenczi E, Szekelyne Gaspar A, Csohan A, Krisztalovics K, et al. Tick-borne encephalitis transmitted by unpasteurised cow milk in western Hungary, September to October 2011. Euro Surveill 2012; 17:pii=20128. Available at: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=20128 (last accessed October 2012).
36. Lucenko I, Jansone I, Velicko I, Pujate E. Tickborne encephalitis in Latvia. Euro Surveill 2004; 8:pii=2495. Available at: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=2495 (last accessed October 2012).
37. Mickiene A, Laiskonis A, Günther G, Vene S, Lundkvist A, Lindquist L. Tickborne encephalitis in an area of high endemicity in lithuania: disease severity and long-term prognosis. Clin Infect Dis 2002; 35:650-8; PMID:12203160; http://dx.doi.org/10.1086/342059.
38. Asokliene L. Tickborn encephalitis in Lithuania. Euro Surveill 2004; 8:pii=2494. Available at: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=2494 (last accessed October 2012).
39. Infectious Diseases and AIDS Center. Available at: http://www.ulac.lt/ (last accessed April 2012).
40. European Centre for Disease Prevention and Control. Available at: http://ecdc.europa.eu/ (last accessed January 2012).
41. Molnár GB, Perseca T, Feder A, Pacuraru D, Marialaki E, Cojan A. [Epidemiological assessment of morbidity and natural foci of TBE-CEE virus infection in Transylvania]. Rev Med Chir Soc Med Nat Iasi 2008; 112:471-7; PMID:19295022.
42. Epidemiological Information System. Available at: http://www.epis.sk/ (last accessed July 2012).
43. Litvová S, Orlovská K. Alimentárny prenos klieštovej encefalitídy v endemickom ohnisku na Považí. Pediatria(Bratisl) 2011; 6:S 25.
44. Grgić-Vitek M, Klavs I. High burden of tick-borne encephalitis in Slovenia--challenge for vaccination policy. Vaccine 2011; 29:5178-83; PMID:21620916; http://dx.doi.org/10.1016/j.vaccine.2011.05.033.
45. Ergünay K, Saygan MB, Aydogan S, Litzba N, Sener B, Lederer S, et al. Confirmed exposure to tick-borne encephalitis virus and probable human cases of tick-borne encephalitis in Central/Northern Anatolia, Turkey. Zoonoses Public Health 2011; 58:220-7; PMID:20604912; http://dx.doi.org/10.1111/j.1863-2378.2010.01342.x.
46. Günes T, Poyraz O, Atas M, Alim A. Seroprevalence of tick-borne encephalitis virus (TBEV) among the residents of rural areas in Sinop, central Black-Sea region, Turkey. Mikrobiyol Bul 2010; 44:585-91; PMID:21063971.
47. Kunz C. TBE vaccination and the Austrian experience. Vaccine 2003; 21(Suppl 1):S50-5; PMID:12628814; http://dx.doi.org/10.1016/S0264-410X(02)00813-7.
48. Balogh Z, Egyed L, Ferenczi E, Bán E, Szomor KN, Takács M, et al. Experimental infection of goats with tick-borne encephalitis virus and the possibilities to prevent virus transmission by raw goat milk. Intervirology 2012; 55:194-200; PMID:21325791; http://dx.doi.org/10.1159/000324023.
49. Grgić-Vitek M, Klavs I. Low coverage and predictors of vaccination uptake against tick-borne encephalitis in Slovenia. Eur J Public Health 2012; 22:182-6; PMID:21398380; http://dx.doi.org/10.1093/eurpub/ckr018.
50. WHO. International Travel and Health, Chapter 6. Available at: http://www.who.int/ith/ITH2010.pdf (last accessed February 2012).
51. Smit R. Cost-effectiveness of tick-borne encephalitis vaccination in Slovenian adults. Vaccine 2012; 30:6301-6; PMID:22885012; http://dx.doi.org/10.1016/j.vaccine.2012.07.083.
52. Latvian journal of the legislation forums. Available at: http://www.likumi.lv/ (last accessed March 2012).
53. Onischenko GG, Fedorov YM, Paksina ND. Surveillance of tick-borne encephalitis and activity for its prophylactic in Russian Federation. Vopr Virusol 2007; 52:8-10.
54. Loew-Baselli A, Poellabauer EM, Pavlova BG, Fritsch S, Koska M, Bobrovsky R, et al. Seropersistence of tick-borne encephalitis antibodies, safety and booster response to FSME-IMMUN 0.5 ml in adults aged 18-67 years. Hum Vaccin 2009; 5:551-6; PMID:19430202; http://dx.doi.org/10.4161/hv.5.8.8571.

55. Rendi-Wagner P, Kundi M, Zent O, Banzhoff A, Jaehnig P, Stemberger R, et al. Immunogenicity and safety of a booster vaccination against tick-borne encephalitis more than 3 years following the last immunisation. Vaccine 2004; 23:427-34; PMID:15530690; http://dx.doi.org/10.1016/j.vaccine.2004.07.002.
56. Andersson CR, Vene S, Insulander M, Lindquist L, Lundkvist A, Günther G. Vaccine failures after active immunisation against tick-borne encephalitis. Vaccine 2010; 28:2827-31; PMID:20167301; http://dx.doi.org/10.1016/j.vaccine.2010.02.001.
57. Heinz FX, Holzmann H, Essl A, Kundi M. Field effectiveness of vaccination against tick-borne encephalitis. Vaccine 2007; 25:7559-67; PMID:17869389; http://dx.doi.org/10.1016/j.vaccine.2007.08.024.
58. Randolph SE. on behalf of the EDEN-TBD subproject team. Human activities predominate in determining changing incidence of tick-borne encephalitis in Europe. Euro Surveill 2010; 15:pii=19606. Available at: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=19606 (last accessed October 2012).
59. Randolph SE. To what extent has climate change contributed to the recent epidemiology of tick-borne diseases? Vet Parasitol 2010; 167:92-4; PMID:19833440; http://dx.doi.org/10.1016/j.vetpar.2009.09.011.
60. Kriz B, Benes C, Danielová V, Daniel M. Socio-economic conditions and other anthropogenic factors influencing tick-borne encephalitis incidence in the Czech Republic. Int J Med Microbiol 2004; 293(Suppl 37):63-8; PMID:15146986.
61. Sumilo D, Asokliene L, Bormane A, Vasilenko V, Golovljova I, Randolph SE. Climate change cannot explain the upsurge of tick-borne encephalitis in the Baltics. PLoS One 2007; 2:e500; PMID:17551580; http://dx.doi.org/10.1371/journal.pone.0000500.
62. Wittermann Ch, Nicolay U, Hilbert A, Schondorf I. TBE vaccines: schedule to optimize protection. Int J Med Microbiol 2008; 298(Suppl.1):S301-4; http://dx.doi.org/10.1016/j.ijmm.2008.01.002.
63. Prymula R, Pöllabauer EM, Pavlova BG, Löw-Baselli A, Fritsch S, Angermayr R, et al. Antibody persistence after two vaccinations with either FSME-IMMUN® Junior or ENCEPUR® Children followed by third vaccination with FSME-IMMUN® Junior. Hum Vaccin Immunother 2012; 8:736-42; PMID:22699436; http://dx.doi.org/10.4161/hv.20058.
64. Bröker M, Schöndorf I. Are tick-borne encephalitis vaccines interchangeable? Expert Rev Vaccines 2006; 5:461-6; PMID:16989626; http://dx.doi.org/10.1586/14760584.5.4.461.
65. Banzhoff A, Bröker M, Zent O. Protection against tick-borne encephalitis (TBE) for people living in and travelling to TBE-endemic areas. Travel Med Infect Dis 2008; 6:331-41; PMID:18984477; http://dx.doi.org/10.1016/j.tmaid.2008.06.011.
66. Murphy BR, Whitehead SS. Immune response to dengue virus and prospects for a vaccine. Annu Rev Immunol 2011; 29:587-619; PMID:21219187; http://dx.doi.org/10.1146/annurev-immunol-031210-101315.