

Epidemiology of tick-borne encephalitis (TBE) in Europe and its prevention by available vaccines

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Abbreviations: C, capsid; CISID, the Centralized Information System for Infectious Diseases; E, envelope; ECDC, European Centre for Disease Prevention and Control; EMA, European Medicines Agency; LD₅₀, median lethal dose; M, membrane; NA, not available; NS, non-structural; RNA, ribonucleic acid; TBE, tick-borne encephalitis; TBEV, tick-borne encephalitis virus; TBEV-Eu, European subtype of the tick-borne encephalitis virus; TBEV-Fe, Far Eastern subtype of the tick-borne encephalitis virus; TBEV-Sib, Siberian subtype of the tick-borne encephalitis virus; WHO, World Health Organization; WTON, World Tourism Organization Network

Tick-borne Encephalitis (TBE), which is caused by a Flavivirus, is the most common tick-transmitted disease in Central and Eastern Europe and Russia. Today, TBE is endemic in 27 European countries, and has become an international public health problem. The epidemiology of TBE is changing owing to various factors, such as improvements in diagnosis and case reporting, increased recreational activities in areas populated by ticks, and changes in climatic conditions affecting tick habitats. Vaccination remains the most effective protective measure against TBE for people living in risk zones, occupationally exposed subjects and travelers to endemic areas. The vaccines currently in use are FSME-Immun[®], Encepur[®], EnceVir[®] and TBE vaccine Moscow[®]. The numerous studies performed on the efficacy and safety of these vaccines have shown a high level of immunogenicity and an excellent safety profile. Several studies have also shown a high level of cross-protection among strains belonging to different subtypes.

In this paper we attempted to describe the continuously changing epidemiology of TBE in European States and to overview clinical development of available vaccines paying particular attention on cross-protection elicited by the vaccines.

Introduction

In Europe, tick-borne encephalitis (TBE) has been known since 1931, when an outbreak of an “acute epidemic serous meningitis” was reported in south-eastern Austria.¹ The causative agent was first isolated in 1937 in the former Soviet Union;² subsequently, in 1949, it was isolated outside Russia.³

This zoonotic disease is endemic to a wide area, from Alsace-Lorraine and Scandinavia to North-Eastern China and Northern Japan.^{4–11} It is caused by the TBE virus (TBEV)^{2–13} belonging to

family Flaviviridae, genus Flavivirus.¹⁴ The TBEV is a member of the mammalian tick-borne Flavivirus group (the TBEV serocomplex), which includes Omsk hemorrhagic fever virus, Langat virus, Alkhurma hemorrhagic fever virus, Kyasanur Forest disease virus, Powassan virus, Royal Farm virus, Karshi virus, Gadgets Gully virus and Louping ill virus.^{15,16} TBEV has a linear positive-stranded RNA genome that consists of a single open reading frame encoding for one polyprotein, which is the precursor of three structural proteins—E (envelope), C (capsid) and M (membrane)—and seven non-structural proteins.¹⁰

TBEV can be divided into three subtypes: European (TBEV-Eu), Siberian (TBEV-Sib) and Far Eastern (TBEV-Fe).^{7,14} TBEV-Eu circulates in Western, Central, Northern and Eastern Europe; TBEV-Sib occurs mainly in the Asian parts of Russia, and TBEV-Fe is prevalent in China, Japan and eastern Russia.⁵

Moreover, on the basis of the determination of the primary structure of fragments of genes of E protein and on the basis of experiments with genotype-specific hybridization probes, the existence of a greater number of TBEV genotypes has been demonstrated.^{17,18} In particular, the strain 886–84 has its own genetic structure, which is different from the above-mentioned 3 subtypes. Likewise, the strain 178–79, which has been recently isolated in the Irkutsk Region (Siberia), presents substantial differences from the 3 subtypes.¹⁷

It is estimated that TBE is one of the most serious neurological diseases transmitted by tick bites in Central Europe, Eastern Europe and Russia, and that it has a significant impact on public health in these geographical regions.¹⁹ In the present paper, we attempted to describe the continuously changing epidemiology of TBE in European States, classified in accordance with the United Nations groupings,²⁰ and to overview the clinical development of available vaccines, with particular attention to the cross-protection elicited by these vaccines. Another aim was to point out vaccination policies in single countries, not least in the light of increased international travel.

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Virus Transmission

TBEV is transmitted by 11 tick species, but only 2 species are important vectors: *Ixodes ricinus* for TBEV-Eu and *Ixodes persulcatus* for TBEV-Sib and TBEV-Fe.^{4,5,11} *Ixodes ricinus* is found in many parts of Europe, extending as far as Turkey, Northern Iran and the Southeastern Caucasus. *Ixodes persulcatus* is widespread in Eastern Europe, Siberia and as far east as Japan and China.^{5,11,21} *Ixodes ricinus* overlaps with *Ixodes persulcatus* in an area extending from the Baltic States to the Urals.^{5,22} Consequently, in the Baltic States and Finland the three TBEV subtypes co-circulate and the genetic diversity of the virus is very complex.^{23,24}

Several animals, principally small rodents, deer, sheep and goats, act as the ticks' source of infection, whereas in the tick population TBEV is transmitted by feeding/co-feeding on the same host, trans-ovarial (transmission from infected females to their eggs) and trans-stadial (transmission from one metamorphosis phase to another: larva, nymph and adult tick) routes and, perhaps, by sexual transmission.²⁵⁻²⁷ Horizontal transmission between ticks and their vertebrate reservoir host is necessary for virus survival; an infected tick remains infected for life.^{11,25} In addition, migratory birds can carry passively infected ticks, even for great distances.^{28,29}

In majority of cases, human infections are caused by an infected tick's bite.^{5,7-9} All three tick stages can transmit the infection to humans.³⁰ In about 30% of cases, the tick bite remains unperceived.³¹ Another important route of virus transmission is through the consumption of unpasteurized dairy products from viremic livestock, mainly goat's milk.^{32,33} For instance, about 0.9% of TBE cases in the Czech Republic are linked to the alimentary route of transmission.⁵ In October 2011 in Hungary, an outbreak of 7 confirmed and 4 suspected TBE cases may have been caused by the consumption of unpasteurized cow's milk.³³ In addition, a few cases of laboratory-acquired infection through needle-prick injury or the inhalation of infected aerosol have been reported.¹¹ Vertical transmission and transmission through blood and blood products have not been described.⁵

The maximum incidence of infection in humans coincides with seasonal feeding peaks of ticks, and is closely associated with their biology and ecology. In Central Europe, where the dominant species is *Ixodes ricinus*, the peak incidence of TBE occurs between May and June and between September and October. *Ixodes persulcatus*, which is widespread in the Urals, Siberia and the Far East, has a peak feeding period only between May and June.³⁴

Epidemiology in Europe

Over the past decades, TBE has become a growing public health concern in Europe and other parts of the world. The incidence of clinical cases is reported to be between 10,000 and 15,000 per year worldwide,³⁵ though it is very probably underestimated^{36,37} because notification of the disease is not mandatory in all countries. Indeed, TBE is a notifiable disease in 17 European countries (Table 1).^{5,11,24,29,38-44} It is important to note that TBE has recently joined the diseases under surveillance in the European

Union; on 5 September 2012 it was included in the list of notifiable diseases in the European Union.⁴⁵

The incidence of TBE appears to be increasing; this could be due to several reasons: improvements in the diagnosis and reporting of TBE cases, increased recreational activities in areas inhabited by infected ticks, and changes in climatic conditions affecting tick habitats.¹¹ Some regions, such as Scandinavia, have seen an increasing trend in TBE cases.⁴⁶⁻⁴⁸

TBE is currently endemic in 27 European countries.⁴⁰ Furthermore, several new foci have recently been detected in different countries: 1 focus in Germany, 5 in the Slovak Republic, 3 in Austria and 12 in Switzerland.⁴⁹

Western Europe. Before the introduction of a massive TBE vaccination campaign in 1981, Austria had the highest recorded TBE morbidity rate in Europe, with up to 700 patients being hospitalized per year.⁵⁰ In 2010, 58 cases were diagnosed (0.7/100,000).³⁹ However, owing to the persistence of highly endemic areas in the south and east (such as Styria, Carinthia, South of Vienna, Salzburg, Burgenland, etc),⁴¹ Austria remains a high-risk country for international tourists.⁵¹

The main endemic zones in Germany include some southern parts of the country and, in particular, Bavaria (Schwandorf district) and Baden-Württemberg (Ortenaukreis district), where the incidence reaches 10.0/100,000 and 6.2/100,000, respectively.⁵² Other risk areas are the federal states of Hesse, Rhineland-Palatinate and Thuringia. However, only four federal states in the north of Germany (Schleswig-Holstein, Hamburg, Bremen, Berlin) have had no cases of TBE.⁵³

In Switzerland, natural TBE foci have been found throughout the country.⁵¹ Like other countries, Switzerland has seen a marked increase in reported cases, which rose by 81% from 2005 to 2006.^{54,55}

In France, the first case was diagnosed in 1968; since then, 5–10 cases have occurred annually, mainly in Alsace-Lorraine, in the northeastern part of the country. Moreover, some cases have been observed in the French Alpine region—probably caused by the consumption of goat's milk cheese—and at least one case in Aquitaine, in southwestern France.^{56,57}

Northern Europe. All Baltic states are highly endemic and all three TBEV subtypes co-circulate.^{23,58} TBE is currently endemic throughout Latvia, the highest incidences (47–55/100,000) occurring mainly in the central regions of the country.⁵⁹ In Estonia, the incidence fell from 27.8/100,000 in 1997 to 6.7/100,000 in 2008. In this period, the areas at highest risk were the north (Harju region), northeast (Ida-Viru region) and a group of islands off the west coast of the country; however, TBE foci are found nationwide.⁶⁰ In Lithuania, as in Latvia, TBE occurs throughout the country, especially the central regions. The incidence of TBE has increased since the 1990s, and during the period 2000–2011 a total of 4,814 cases of TBE were reported.⁶¹

In Finland, approximately 20–40 new cases of TBE per year are currently being recorded; about two thirds of these occur in the Åland Islands, where the incidence of TBE ranged from 7 to 93 new cases per 100,000 inhabitants in 1990–2010. However, owing to active vaccination in Åland, which has reached about

65% coverage, the geographical distribution of TBE cases has changed, and nowadays most cases occur in mainland Finland (Kokkola, Lappeenranta).^{41,62}

Norwegian endemic foci are concentrated along the southern coast. Since the first case, which occurred in 1998, more than 50 cases have been registered to date.⁶³

The incidence of TBE has seen a rapid increase in Sweden, reaching 1.7/100,000 nationwide. However, TBE is restricted to a few zones (Baltic coastal regions, around lakes in southern Sweden and on the west coast), where a rate of 9.3/100,000 (in Södermanland) has been recorded.⁴²

In Denmark, TBE occurs on the island of Bornholm in the Baltic sea, where the annual incidence reaches 4.0/100,000. However, in 2009, two laboratory-confirmed cases of TBE were registered outside Bornholm, thus confirming the spread of TBEV in Scandinavia.^{64,65}

Southern Europe. Slovenia is endemic for TBE, its incidence is high and vaccination coverage is low. TBE cases occur in all regions, but the most seriously affected are situated in the north and northwest, in particular Gorenjska (57.2/100,000) and Koroska (76.9/100,000).⁶⁶

TBE is endemic in the Italian Northeast: in the Provinces of Trento, Bolzano, Belluno, Pordenone, Udine, Treviso and Vicenza. The mean annual incidence of TBE in these seven provinces increased from 0.06/100,000 in 1992 to 0.88/100,000 in 2006. Most cases were registered in 2000–2006 (151 cases out of 198, or 76.3%).^{67,68}

In Romania, TBE is endemic in the Transylvania Region (Mures and Sibiu) in the North West; seroepidemiological investigations have revealed the prevalence of historical TBE infection, which was estimated to be 0.6%.^{41,69,70}

From only one focus located in the northern Croatia, TBE has recently spread along the Adriatic coast and to the islands;⁵ the incidence peaked at 1.0/100,000 in 2009.³⁹

Some cases of TBE have been detected in Serbia (Belgrade area and Adriatic coast) and Bosnia-Herzegovina (in the north) and some of these have been linked to alimentary infection.⁵ Southern Albanian areas are also endemic (districts of Permet and Gjirocaster).⁵ It has been shown that, in northern Greece, a flavivirus of the TBEV serocomplex circulates; this has caused isolated clinical cases in the Thessaloniki Region.^{5,71}

Eastern Europe. A high incidence (6.19/100,000) was registered in the Czech Republic in 2000–2009. While natural foci are disseminated in almost all parts of the country, the greatest numbers of cases occur in highland areas. In this country, the alimentary route of transmission is important and accounts for approximately 0.9% of cases, with 64 clinical cases from 1997 to 2008.^{5,72}

In the Slovak Republic, TBE is endemic in western and north-western areas. Moreover, there are several foci in the center and the east of the country.⁴¹ From 1998–2007, the mean annual number of TBE cases was 67 (ranging from 46 to 92).⁵⁵

Hungarian endemic zones are mostly located in the north and west of the country.⁷² In recent years, several clinical cases have been associated with the consumption of raw goat and cow milk.³³

In Poland, infection occurs in all parts of the country, though the areas mostly affected are the North-East (Podlaskie and Warminsko-Mazurskie provinces) and South-West (Opolskie province). In these provinces, the average 5-y incidence in 2004–2008 was 9.3, 5.4 and 0.8 per 100,000 inhabitants, respectively.⁷³

TBEV circulation in Belarus has been detected in almost the entire country, the maximum incidence of 9.1/100,000 being recorded in 2006. The most intensive natural foci have been found in the western areas (Brest and Grodno Oblasts).⁷⁴

In Ukraine, at least 3 endemic zones have been detected: Crimea and Zaporizhia Oblast in the south and Volyn Oblast in the north west.^{5,43}

Russia used to be a high-risk area, with about 10,000 cases being reported in 1996 and 1999.⁵⁵ TBE is endemic in at least 44 of the 83 federal subjects; these are located in both European and Asian areas, and some display a particularly high risk of infection. Indeed, the incidence of TBE reaches 72.5/100,000 inhabitants in the Tomsk Region and 53.5/100,000 in the Udmurt Republic.^{5,75}

Finally, in the United Kingdom, Ireland, Belgium, the Netherlands, Luxembourg, Spain, Portugal and Malta no autochthonous TBE cases have been registered to date.⁵²

Table 1 summarizes epidemiological data from 17 European countries and reports information on TBE notification and vaccination policies.

It is important to underline that TBE has become an international public health problem, owing to the rise in travel to risk areas. According to the World Tourism Organization Network (WTON), Europe is the most popular travel destination in the world; indeed, international tourist arrivals in Europe are estimated to have exceeded 500 million in 2011 and are expected to increase by a further 2–4% in 2012.⁷⁶ It has been estimated that, in Austria alone, 60 overnight visitors may be infected every summer. Furthermore, the risk of TBEV infection among unvaccinated travelers to a highly endemic region is calculated to be 1/10,000.⁷⁷ The American Morbidity and Mortality Weekly Report describes five cases of TBE in international travelers who visited endemic areas between 2000 and 2009; 2 cases were recorded in Russia, 1 case in China, 1 in the Czech Republic and 1 in Sweden.⁷⁸

Currently Available TBE Vaccines

The vaccines currently in use are FSME-Immun® (Baxter, Austria), Encepur® (Novartis Vaccines, Germany), EnceVir® (Scientific Production Association Microgen, Russia) and TBE vaccine Moscow® (Federal State Enterprise of Chumakov Institute of Poliomyelitis and Viral Encephalitides, Russian Academy of Medical Sciences, Russia).¹⁹ FSME-Immun® and Encepur® are available in the European Union and have been authorized by the European Medicines Agency (EMA).⁷⁹

The protective properties of these four killed whole vaccines are associated mostly with virions, particularly with the envelope protein E, which is responsible for important biological functions, such as virion assembly, membrane fusion and binding to receptors. The development of inactivated vaccines has focused

Table 1. Annual number of cases of TBE in the decade 2001–2010, TBE notification and vaccination program by country

Country	Number of cases per year										Notification ^{5,11,41,44}	Vaccination program
	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010		
Albania	0*	0*	0*	0*	n.a.	n.a.	0*	n.a.	n.a.	23*	n.a.	n.a.
Austria	23*	36*	44*	54 [^]	59*	51*	45 [^]	86 [^]	79 [^]	58*	Mandatory	Yes [×]
Belarus	61*	18*	53*	44*	n.a.	108*	82*	n.a.	88*	86*	n.a.	n.a.
Bosnia and Herzegovina	n.a.	1*	0*	0*	0*	0*	n.a.	n.a.	n.a.	2*	Not mandatory or takes part of a general meningitis or encephalitis surveillance	n.a.
Croatia	27*	30*	36*	38*	28*	20*	11*	20*	44*	36*	n.a.	n.a.
Czech Republic	633*	647*	606*	507*	643*	1029*	546*	631*	816 [^]	589*	Mandatory	Recommended [×]
Denmark	1 [^]	1 [^]	4 [^]	8 [^]	4 [^]	2 [§]	2 [^]	1 [^]	1 [^]	0*	Not mandatory	Optional [×]
Estonia	215*	90*	237*	182*	164*	171*	140*	90*	179*	201*	Mandatory	Recommended [×]
Finland	33*	38*	16*	29*	16*	17*	20*	23*	26 [^]	44*	Mandatory	Yes for Åland and recommended for other Regions [×]
France	0 [^]	2 [^]	6 [^]	7 [^]	0 [^]	6 [^]	7*	10 [^]	n.a.	10*	Not mandatory	Optional [×]
Germany	255*	239*	278*	274 [^]	431*	547*	238*	285 [^]	313*	n.a.	Mandatory	Yes [×]
Greece	n.a.	n.a.	n.a.	n.a.	0*	n.a.	0*	0*	n.a.	n.a.	Mandatory (as arboviral encephalitis)	Optional [×]
Hungary	55*	60*	73*	76*	53*	57*	69*	77*	70*	n.a.	Mandatory	Yes, for occupationally exposed people [×]
Italy	19 [^]	6 [^]	14 [^]	23 [^]	22 [^]	14 [^]	4 [^]	34 [^]	32 [^]	23 [§]	Not mandatory	Yes, in endemic Regions and professionally exposed people ^{××}
Latvia	303*	153*	365*	251*	142*	170*	171*	184*	328 [^]	494*	Mandatory	Yes for children and recommended for adults [×]
Lithuania	298*	168*	763*	425*	243*	462*	234*	220*	617 [^]	612*	Mandatory	Optional [×]
Norway	1*	2*	1*	5*	2*	5*	13*	11*	8 [^]	11*	Mandatory	Optional [×]
Poland	210*	126*	339*	262*	262*	317*	233*	202 [^]	351*	294*	Mandatory	Recommended for high risk groups [×]
Republic of Moldova	n.a.	n.a.	n.a.	n.a.	0*	0*	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
Romania	0*	n.a.	1*	n.a.	n.a.	n.a.	67 [†]	8*	4 [§]	3*	Mandatory	n.a.
Russia	6,528*	5,150 [^]	4,770 [^]	4,156*	4,566*	3,494*	3,138*	2,796*	3,720*	3,094*	Mandatory	Yes, in endemic Regions [×]
Serbia	n.a.	n.a.	n.a.	1*	6*	1*	0*	n.a.	n.a.	n.a.	n.a.	n.a.
Slovak Republic	75*	62*	74*	70*	50*	91*	57*	85*	71 [^]	90*	Mandatory	Optional [×]
Slovenia	260*	262*	282*	204*	297*	373*	199*	251*	306*	166*	Mandatory	Yes [×]

Notes: *Centralized Information System for Infectious Diseases (CISID) – WHO: incidence of tick-borne encephalitis.³⁹ [^]Süss J. Tick-borne encephalitis 2010: Epidemiology, risk areas, and virus strains in Europe and Asia - An overview. *Ticks Tick Borne Dis* 2011; 2:2–15.⁵ [§]European Centre for Disease Prevention and Control. Epidemiological situation of tick-borne encephalitis in the European Union and European Free Trade Association countries. Stockholm: ECDC; 2012.⁴⁰ [†]VENICE II. Tick-borne encephalitis surveillance systems and vaccination recommendations in UE/EEA, 2009.⁴¹ ^{††}Lundkvist A, Wallensten A, Vene S, Hjertqvist M. Tick-borne encephalitis increasing in Sweden, 2011. *Euro Surveill* 2011; 16:pii = 19981.⁴² ^{§§}Incidence of Infectious and Parasitic Diseases in Ukraine in 2003. State Sanitary and Epidemiological Service of Ukraine.⁴³ [×] Donoso Mantke O, Escadafal C, Niedrig M, Pfeiffer M, on behalf of the Working group for Tick-borne encephalitis virus. Tick-borne encephalitis in Europe, 2007 to 2009. *Euro Surveill* 2011; 16:pii:19979.⁴⁴ ^{××} Italian Ministry of Health. National Vaccine Plan 2012–2014.³⁸

Table 1. Annual number of cases of TBE in the decade 2001–2010, TBE notification and vaccination program by country (continued)

Country	Number of cases per year										Notification ^{5,11,41,44}	Vaccination program
	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010		
Sweden	117*	105 [^]	107*	175*	131*	163*	182*	224*	211 [^]	174 ^{††}	Mandatory	Optional [×]
Switzerland	108*	53*	116*	137*	202*	252*	106*	121*	117*	90*	Mandatory	Yes [×]
Ukraine	n.a.	12 ^{§§}	28*	n.a.	n.a.	n.a.	n.a.	7*	n.a.	3*	n.a.	n.a.

Notes: *Centralized Information System for Infectious Diseases (CISID) – WHO: incidence of tick-borne encephalitis.³⁹ [^]Süss J. Tick-borne encephalitis 2010: Epidemiology, risk areas, and virus strains in Europe and Asia - An overview. *Ticks Tick Borne Dis* 2011; 2:2–15.⁵ [§]European Centre for Disease Prevention and Control. Epidemiological situation of tick-borne encephalitis in the European Union and European Free Trade Association countries. Stockholm: ECDC; 2012.⁴⁰ [†]VENICE II. Tick-borne encephalitis surveillance systems and vaccination recommendations in UE/EEA, 2009.⁴¹ ^{††}Lundkvist A, Wallensten A, Vene S, Hjertqvist M. Tick-borne encephalitis increasing in Sweden, 2011. *Euro Surveill* 2011; 16:pii = 19981.⁴² ^{§§}Incidence of Infectious and Parasitic Diseases in Ukraine in 2003. State Sanitary and Epidemiological Service of Ukraine.⁴³ [×] Donoso Mantke O, Escadafal C, Niedrig M, Pfeffer M, on behalf of the Working group for Tick-borne encephalitis virus. Tick-borne encephalitis in Europe, 2007 to 2009. *Euro Surveill* 2011; 16:pii:19979.⁴⁴ [×] Italian Ministry of Health. National Vaccine Plan 2012–2014.³⁸

on improving immunogenicity and reducing allergic reactions; this has been achieved by concentrating and purifying the virions.^{11,80}

FSME-Immun[®]. FSME-Immun[®], which is based on the Neudoerfl strain, has been approved for the vaccination of risk groups since 1976.⁸¹ In recent decades, the production process of the vaccine has undergone several modifications: the virus master bank has been changed from mouse brain to primary cells; excipients, especially stabilizers and preservatives, have been improved, and formulations for children have been developed.⁸² FSME-Immun[®] contains human albumin as a stabilizer.¹¹ The conventional schedule of the primary vaccination course consists of 3 doses, administered intramuscularly (0.5 ml for adults and 0.25 ml for children aged 1–15 y). The recommended interval between the first and second dose is 1–3 mo, and between the second and the third dose 5–12 mo. Accelerated schedules can be implemented in emergency situations (vaccination on days 0 and 14, followed by a third dose 5–12 mo after the second). The primary 3-dose schedule may be followed by booster doses every 3–5 y.^{11,19,83,84}

Several studies have been conducted on the immunogenicity of FSME-Immun[®] in both adults and children on a conventional schedule.^{85–89} In adults (16–65 y), the seroconversion rates were close to 100% after the third vaccination.^{85,86} Similarly, an excellent immunogenicity profile has been seen in the pediatric population aged up to 15 y, with seroconversion rates reaching 100% after completion of the primary immunization course.^{87–89} The rapid immunization schedule, which induces an early immune response, has been demonstrated to be suitable, as no difference in the level of antibody titers has been found after the third dose.⁹⁰ However, the rapid schedule elicits a less marked immune response than the conventional schedule after the second dose,⁸⁸ and antibodies have been seen to decline more rapidly.⁹¹

The persistence of immunity following the complete primary vaccination has been shown to be long-lasting in both adults (antibodies titers of 95% after 3 y)⁸³ and children (antibodies titers of 98% after 3 y).⁸⁹

The results of numerous clinical trials have shown a good safety and tolerability profile of both FSME-Immun[®] formulations; systemic reactions have been observed mostly among children and were mild and transient.^{85–89} Postmarketing

pharmacovigilance has reported a rate of severe adverse events of 1.6 per 100,000 doses.⁹²

Encepur[®]. The Encepur[®] vaccine is produced by using strain K23, which belongs to TBEV-Eu.^{11,19}

The adult formulation of Encepur[®] was licensed in Germany in 1991 and contained a polygeline stabilizer;¹¹ the first licensed TBE vaccine for children was licensed in 1994 (Encepur[®] K).⁹³ Since 2001, the vaccine has not contained preservatives, protein-derived stabilizers or human serum albumin. The current formulations of the German vaccine are: Encepur[®] Adults (for subjects over 12 y of age) and Encepur[®] Children (for children aged 1–11 y). The conventional primary vaccination schedule is the same as for FSME-Immun[®] (on day 0, after 1–3 mo and after 9–12 mo); a rapid vaccination schedule consists of 3 doses on days 0, 7 and 21, and a first booster after 12–18 mo. Subsequent boosters can be administered every 3–5 y.^{11,19,94}

Like the Austrian vaccine, Encepur[®] was found to be highly immunogenic, with close to 100% seroconversion rates after concluding the primary conventional or rapid schedule in adults and children.^{91,93,95} Interestingly, an advantage of the rapid schedule in children has been described, in that it provides rapid protection that lasts at least 300 d.⁹⁶

Rendi-Wagner et al.⁹⁷ reported the persistence of high antibody titers 3–5 y after the last vaccination dose in 96–100% of subjects.

The German vaccine is safe and well-tolerated, the rate of severe adverse events being 1.9 per 100,000 administered doses on postmarketing surveillance.⁹²

Regarding the two above-mentioned vaccines, a dose of either one may be successfully followed by a dose of the other, as shown by Prymula et al.⁹⁸ Thus, subjects who received either FSME-Immun[®] Junior or Encepur[®] Children vaccine for the first two vaccinations and FSME-Immun[®] Junior for the third showed a comparably strong immune response, regardless of the previous TBE vaccine administered.⁹⁸

Although regular booster TBE vaccinations every 3–5 y are recommended, recent data from clinical studies suggest that TBE antibodies persist at high levels for longer than the currently recommended intervals.⁹⁴

Russian vaccines. EnceVir[®] and TBE vaccine Moscow[®] are used only in the Russian Federation and some post-Soviet

Republics.¹⁹ EnceVir[®] is based on TBEV-Fe strain 205, and TBE vaccine Moscow[®] is based on the Sofjin strain (TBEV-Fe). Both vaccines contain human albumin as a stabilizer. A pediatric formulation is available only for TBE vaccine Moscow[®]. The conventional vaccination schedule is the same for both vaccines: the second dose is administered 5–7 mo after the first one, and a third dose 6–12 mo thereafter completes the primary series. Boosters are given at intervals of three years.⁹⁹ However, the two Russian vaccines have not undergone randomized, controlled clinical trials of their efficacy and effectiveness.¹¹

Cross-Protection

All three TBEV subtypes are closely related at the genetic level,¹⁰⁰ and can co-circulate, as in Baltic countries.^{23,58} Surface viral protein E induces the production of neutralizing antibodies, which play an important role in establishing a protective immune response in the host.^{10,101} Furthermore, a role of protective immunity has been associated with the NS protein (NS1), one of the seven non-structural proteins.¹⁰² However, neutralizing cross-reactive antibodies mostly recognize protein E epitopes.^{10,101} No data are available on cellular responses.¹⁰² It is important to note that the glycoprotein E can vary by about 2% in the same subtype and by about 5% between different subtypes.¹⁰⁰ These data suggest that vaccines based on TBEV-Eu may also be effective against other subtypes, and vice versa. The question of whether a vaccine based on TBEV-Eu may be protective toward TBEV-Sib and TBEV-Fe is of great importance in view of the increase in international travel and the spread of non-European subtypes. Indeed, TBEV-Sib, which is widespread in Asia, has been found in Finland.²⁴

Preclinical studies on the immunization of animals have revealed a high level of cross-protection between strains belonging to different subtypes. Holzmann et al. found no statistically significant difference in the degree of protection when mice were immunized with a European prototype vaccine virus and subsequently challenged with three selected Asian isolates and one isolate from the European part of the former Soviet Union.¹⁰³

Chiba et al. demonstrated a high level of survival of mice after vaccination with 2 doses of a European TBE vaccine (FSME-Immun[®]) and subsequent challenge with 100 median lethal doses (LD₅₀) of three different TBEV strains (Oshima 5–10 – TBEV-Fe, Hochosterwitz – TBEV-Eu and Sofjin – TBEV-Fe). The percentage of survival was 80% among mice challenged with Oshima 5–10 and Hochosterwitz strains, and 100% among those challenged with the Sofjin strain.¹⁰⁴

A recent study by Fritz et al. on a mouse model revealed that the cross-protective responses elicited by FSME-Immun[®] and two Russian vaccines against heterologous strains were similar to those induced against the respective homologous vaccine strains.¹⁰⁵

Hayasaka et al. demonstrated that the European vaccine (FSME-Immun[®]) induced efficient NT antibodies in humans and protective immune responses in mice against various isolates of TBEV found in eastern Siberian and Far-Eastern regions of Russia, and that the European vaccine could prevent TBE in humans in those regions.¹⁰⁶

A Russian study has shown that Encepur[®] induces a marked humoral immune response toward heterogeneous strains of TBEV-Fe (P-69, P-202 and P-73). Specifically, the percentages of adult volunteers who had neutralizing antibodies against the three different strains after triple immunization were: 63.9% for P-69, 95.5% for P-73 and 97.6% for P-202.¹⁰¹

In 2009, Leonova et al. compared the immunogenicity of TBE vaccine Moscow[®], EnceVir[®], FSME-Immun[®] and Encepur[®] in adults. Immunogenicity was measured 2–5 mo and 2 y after the administration of 3 doses of the respective vaccines. All vaccines induced neutralizing antibodies against the P-73 strain of TBEV-Fe. In the case of TBE vaccine Moscow[®], antibodies were detected in 100% and 94% of vaccinees after 2–5 mo and 2 y, respectively. With EnceVir[®], the corresponding figures were 88% and 84%; with FSME-Immun[®], 88.2% and 78.1%, and with Encepur[®] 100% and 100%.¹⁰⁷

Orlinger et al. quantified neutralizing antibodies against prototype TBEV strains of all subtypes (Neudoerfl - TBEV-Eu, K23 - TBEV-Eu, Sofjin HO - TBEV-Fe, Oshima 5–10 - TBEV-Fe, and Vasilchenko - TBEV-Sib) and Omsk hemorrhagic fever virus by using hybrid viruses encoding their respective surface proteins. Seropositivity rates were 100% against the hybrids Neudoerfl, K23, Sofjin HO, Oshima 5–10 and Vasilchenko, and 98% against the hybrid Omsk hemorrhagic fever virus. The authors concluded that FSME-Immun[®] protects fully against all TBEV subtypes, and less potently against the more distantly related Omsk hemorrhagic fever virus.¹⁰⁸

Concluding Remarks

Vaccination is the most effective protective measure against TBE.¹⁹ The WHO and the European Centre for Disease Prevention and Control (ECDC) recommend TBE vaccination for people who live in TBE risk areas or who frequently visit forests and grasslands in TBE risk areas.^{19,109} Where the mean 5-y incidence of disease is moderate/low, i.e., less than 5 cases per 100,000, or limited to certain areas, immunization should be provided for high-risk groups.¹⁹

TBE vaccination is currently included (under certain conditions) in official government vaccination programs in several European countries (Table 1). In Austria, where the vaccination program has been implemented, a good coverage rate has been achieved, with 88% of the total population having received at least one dose of the vaccine and 58% being within the officially recommended vaccination schedule.¹¹⁰ This has led to a marked reduction in the annual number of clinical cases and proves that vaccination is an effective means of preventing TBE.¹¹¹ Indeed, in the period 2000–2011, about 4,000 cases were prevented.¹¹² Furthermore, immunization against TBE has also proved cost-effective.^{113,114} By contrast, other highly endemic countries have insufficient vaccine coverage rates: Latvia 39% (2008), Estonia 20% (2008), Lithuania 19% (2008), Switzerland 17% (2007), the Czech Republic 16% (2009), Slovenia 13% (2009) and Sweden 13% (2008).¹¹⁵

Vaccination policies are in continuous evolution in different European countries. For example, the recent 2012–2014 Italian

National Vaccine Plan for the first time recommends TBE vaccination for people living in high risk areas and for professionally exposed persons.³⁸

Travelers to endemic areas should also be vaccinated, especially if their visits include outdoor activities. Since the incidence of TBE varies widely among geographic regions, public health vaccination strategies should be based on careful analysis of the effectiveness of the vaccine and the cost-effectiveness of immunization regimens.¹¹⁶

As we have seen, both conventional and rapid schedules enable optimal protection to be achieved after completion of a course. However, while the rapid schedule elicits an earlier response than the conventional schedule, the duration of this response is shorter.

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Therefore, the rapid scheme could be implemented, for example, for short-term travelers, while the conventional one is more suitable for people exposed to TBE for the whole tick-season.⁹¹

In conclusion, given the availability of safe and effective vaccines, it is advisable to increase vaccination coverage not only among people living in regions considered at risk of TBE, but also among travelers who plan to spend some time in countries where TBE is endemic.

Disclosure of Potential Conflicts of Interest

D.A., A.D., D.P., P.L.L., M.L.C. and R.G. declare that they have no competing interests. U.A. is an employee of Baxter S.p.A.

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