Chapter 15

TBE vaccines licensed around the globe

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Key Points

- Worldwide there are 6 different TBE vaccines – two from Western Europe, three from Russia and one from China. The two western European vaccines and one of the Russian vaccines have an adult and a pediatric formulation.
- The products names are FSME IMMUN and FSME-IMMUN Junior; Encepur adults and Encepur children, Klesch-E-Vac, EnceVir and EnceVir Neo, Dry lyophilized TBE Moscow and Sen Tai Bao.
- All TBE vaccines except the one from China have similar but not identical immunization schedules with primary immunization (3 to 4 doses according to vaccine) and regular booster vaccinations. For FSME-IMMUN, Encepur and EnceVir rapid immunization schedules are also licensed. The Chinese vaccine is given with 2 primary doses 2 weeks apart followed by annual boosters.
- Both - FSME-IMMUN and Encepur are well tolerated with a well-established safety profile. TBE-Moscow and EnceVir appear to be somewhat more reactogenic.
- All vaccines induce significant immune responses. In the absence of a formal correlate of protection, the presence of neutralizing antibodies is used as a surrogate marker for protection. More recent investigations indicate that in addition to the presence of neutralizing antibodies, immunologic memory and boostability seem to play a more important role than expected at time of first licensure.
- Clinical studies show long-term seropersistence of TBE antibodies after the first and subsequent booster vaccination with the two European vaccines.
- An effectiveness of approximately 99% (years 2000–2006) and 98.7% (years 2000-2011) was calculated for regularly vaccinated persons in Austria, a country with established high vaccination uptake. Recent studies show that vaccine effectiveness (VE) increases gradually with the number of vaccinations and seems to be optimal after 4 and more doses.
- Booster immunizations every 5 or 3 years, depending on age, are licensed beyond the 4th vaccination for the European vaccines. Recent data from Germany and Switzerland provide some evidence to support extension of booster intervals (up to ten years) for certain parts of the population.
- Whereas in Western Europe post-exposure prophylaxis with immunoglobulins was discontinued in the late 1990s, due to safety and efficacy concerns, in the highly endemic regions of Russia it continues to be common practice.

Active immunization

The first generation of TBE vaccines was produced in Russia. These vaccines were based on the TBEV-FE strain Sofjin, and were mouse-brain propagated. Over several decades, formulations and growth media were adapted step-by-step to result in the currently used TBE vaccines, details of which are summarized in Table 1. The two so called 'Western vaccines' are FSME-IMMUN, which is licensed through the mutual recognition procedure (MRP) of the European Medicines Agency (EMA), and Encepur, which has several national licenses. These two vaccines are distributed mainly in Europe and Israel, while the other TBE vaccines are predominantly produced for local markets. Since 2021 FSME-IMMUN is also licensed in the USA under the name TICOVAC.

Table 1: Basic characteristics of all licensed TBE vaccines

Vaccine name/ Manufacturer	FSME-IMMUN ® Pfizer	Encepur ® Bavarian Nordic	TBE-Moscow / Klesch-E-Vac Federal state scientific institution Chumakov	EnceVir® and EnceVir®Neo NPO Microgen	Dry -lyophilized TBE-Moscow scientific institution Chumakov	Sen Tai Bao Changchun Institute of Biological Products
Antigen						
Strain	TBEV-Eu Neudörfl	TBEV-Eu K23	TBEV-Fe Sofjin	TBEV-Fe Strain 205	TBEV-Fe Sofjin	TBEV-Fe, Mori-Jang
Passages	PCEC	PCEC	PCEC	PCEC	PCEC	NK
Production	PCEC	PCEC	PCEC	PCEC	PCEC	GKMC
Amount of antigen	2.4 µg adult / 1.2 µg children	1.5 µg adult / 0.75 µg children	0.5-0.75 µg (titer ≥ 1:128)	EnceVir® -0,6-3,0 µg/ EnceVir®Neo -0,3-1.5 µg	titer ≥1:128	Not specified
Excipients						
Adjuvant	$Al(OH)_3$	$Al(OH)_3$	$Al(OH)_3$	$Al(OH)_3$	$Al(OH)_3$	$Al(OH)_3$
Preservative	no	no	no	no	no	Thiomersal
Stabilizer	HSA	Sucrose	Sucrose, HSA	Sucrose, HSA	Sucrose, HSA	HSA
Presentation						
Formulation	0.5 mL/0.25 mL liquid	0.5 mL/0.25 mL liquid	0.5 mL/0.25 mL liquid	0.5 mL/0.25 mL liquid	0.5 mL Dry	5 mL multidose vials
Packaging	prefilled syringe	prefilled syringe	in ampoules	in ampoules	in ampoules	ampoules
Shelf-life	30 months (2°-8°C)	24 months (2°-8°C)	24 months (2°-8°C)	24 months (2°-8°C)	36 months (2°-8°C)	21 months in dark storage (2-8°C)

***Abbreviations**: HSA: Human Serum Albumin; PCEC: Primary Chicken Embryonic Cells; PHKC: primary hamster kidney cells; $Al(OH)_3$: Aluminum hydroxide; GKMC: Gopher Kidney Monolayer Cells; NK: Not known*

Manufacturer and products

TBE vaccines are produced commercially by five manufacturers. Two are produced in Europe, one by Pfizer (Vienna, Austria), one by GSK Vaccines (Marburg, Germany; bought by Bavarian Nordic, Kvistgaard, Denmark end 2019); 2 in Russia: IPVE (Moscow, Russia) and Microgen (Tomsk, Russia); and one in China: Sen Tai Bao (Changchun Institute of Biological Products Co., Ltd.; CIBP). The two manufacturers in Europe use very similar manufacturing processes but different virus strains and stabilizers. Both of them have licensed formulations for adults (Pfizer: FSME-IMMUN; Bavarian Nordic: Encepur) and for children older than one year (Pfizer: FSME-IMMUN Junior; Bavarian Nordic: Encepur-Children). FSME-IMMUN Junior is licensed for children up to and including 15 years of age, whereas Encepur-Children is licensed up to and including twelve years of age. In some countries, FSME-IMMUN is marketed as TicoVac. FSME-IMMUN, Encepur as well as EnceVir have (half dose) formulations for children and the TBE-Moscow vaccine is approved for use in children age 3 years or older. Human serum albumin (HSA) is used as a stabilizer by Pfizer, IPVE, CIBP, and Microgen, whereas Bavarian Nordic uses an increased amount of sucrose for this purpose. An overview of the excipients of the European and Russian vaccines is shown in Table 1.

FSME-IMMUN

This vaccine is based on the Austrian TBE strain Neudörfl (TBEV-Eu) and was licensed first in 1976. The virus was primarily passaged in the brains of specific pathogen-free (SPF) baby mice and then propagated in primary SPF chicken embryo cells. The vaccine formulation underwent several changes over subsequent decades until 2000. The actual licensed vaccine is a formaldehyde-inactivated, whole-virus vaccine (2.4 mcg antigen per dose), adjuvanted with aluminum hydroxide and containing HSA as an essential stabilizer. Details of the actual formulation are described in Table 1. A pediatric formulation containing half of the adult dose (FSME-IMMUN Junior) was licensed in 2002. The current manufacturer of FSME-IMMUN is Pfizer.

Encepur

This vaccine is based on the European subtype virus strain K23, isolated in Karlsruhe in southern Germany and originally licensed first in Germany in 1991 as Encepur by Chiron Behring, Marburg, Germany.[1] Similar to FSME-IMMUN, the seed virus for this vaccine is grown on primary chick embryo cells. The virus is inactivated by formaldehyde, adsorbed to aluminum hydroxide, and contains 1.5 mcg of antigen. A pediatric formulation containing half the adult dose (Table 1) has been available since 1994.[2] The genomic sequence of the K23 vaccine virus in the Encepur formulation has mutations compared to the originally published sequence.[90] However, the clinical impact of the modified primary amino acid sequence is unknown. In the year end of 2019 Bavarian Nordic acquired Encepur from GSK. According to communications by GSK and Bavarian Nordic, vaccine manufacturing will be transferred over the next 5 years, sales and marketing responsibility was assumed in 2020.

Russian vaccines

Three TBE vaccines have been developed and are marketed in Russia (see Chapter 12b: Russia). All of them are cultured on chick embryo cells and are formalin-inactivated. EnceVir, manufactured by Microgen, Tomsk, is based on the TBEV-FE subtype strain 205.[4]

There is a vaccine for adults (EnceVir (0.5) and as of 2014 also a pediatric formulation (EnceVir Neo (0.25) for children 3-17 years). Klesch-E-Vac is based on the TBEV-Fe prototype strain Sofjin, and manufactured by the Federal State Enterprise of Chumakov Institute of Poliomyelitis and Viral Encephalitides (IPVE). It is provided as a suspension for injection.[3] Klesch-E-Vac has an adult (0.5mL) and also a pediatric formulation licensed for use as of 12 months to 16 years of age (half of the adult dose, i.e. 0.25 mL).

In addition, there is a dry-lyophilized TBE-Moscow vaccine (no specific trade name), based on the Sofjin strain.3 The producer is also the Federal State Enterprise of Chumakov Institute of Poliomyelitis and Viral Encephalitides (IPVE). The product is approved for use in patients from 3 years of age as a unified formulation.

Sen Tai Bao

The Sen Tai Bao (Changchun Institute of Biological Products Co. Ltd: CIBP; in Changchun, Jilin Province, China) TBE vaccine is manufactured by the Changchun Institute of Biological Products (CIBP) and marketed in China only.[5] There a first vaccine against TBE was developed in 1953, by propagating the TBEV on mouse brain tissue followed by inactivation. It was an inactivated TBEV grown on infected mouse brain tissues. Between 1953 and now several vaccine formulations have been developed and used. Some of the earlier vaccines were grown on chicken embryo cells.[91] The current formalin-inactivated vaccine formulation is based on the TBEV-FE Mori-Jang strain, grown on monolayer gopher kidney cells. It uses HSA as the stabilizer and aluminum hydroxide as adjuvant and thiomersal as preservative. This vaccine has been approved for use in adults and children 8 years of age or older since 2004.[6] To reduce reactogenicity, it is recommended to add 0.2 mL of sodium bisulfite solution to each 5 mL dose, which will turn the color of the product from red to yellow. The vaccine should be administered subcutaneously into the lateral deltoid muscle region. First and second injections are

Table 2: Immunization schedules for TBE vaccines according to WHO recommendations

Dose 1 considered to be given on day „0“, intervals in table below given in months unless stated otherwise.

Vaccine schedule	Primary series*				Boosters
	Dose 1	Dose 2	Dose 3	Dose 4	Following doses
FSME-IMMUN *Regular*	Day 0	1-3 months	5-12 months	3 years	5 years (<60 years old)** (3 years if ≥60 years old)
FSME-IMMUN *Rapid*		14 days	5-12 months	3 years	5 years (<60 years old)** (3 years if ≥60 years old)
ENCEPUR *Regular*		2 weeks – 3 months	9-12 months	3 years	5 years (<60 years old)** (3 years if ≥60 years old)
ENCEPUR *Rapid*		Day 7	Day 21	12 – 18 months	5 years (<60 years old)** (3 years if ≥60 years old)
TBE-Moscow *Regular*		1-7 month	12 month	3 years	3 years
TBE-Moscow (only Klesch-E-vac) *Rapid*		14 days	12 month	3 years	3 years
EnceVir *Regular*		1-7 month	12 month	3 years	3 years
EnceVir *Rapid*		14 days	12 month	3 years	3 years
SenTai Bao		7-10 days	Boosters every year***		

* *Dose 3 resp. dose 4 have to be regarded immunologically as “first booster” doses if interval to second/third vaccine dose exceeds 4 months.*

** *50 years (instead of 60 years) in Germany*

*** *annual dose before the start of the season*

administered 7-10 days apart, the third and following doses are given annually. Dosing by age is done by volume adjustment, i.e. children 2-6 years receive 0.5 mL/dose; 7-10 years 1.0 mL/dose; and 11-15 years 1.5mL/dose. Subjects 16 years and older receive 2.0 mL, 3.0 mL and 3.0 mL as dose 1, 2, and 3, respectively.

Details on the schedules for the different licensed vaccines are summarized in Table 2. In brief, the basic immunization protocol for all vaccines consists of 3 doses (except the Sen Tai Bao, which has only 2 doses), similar to conventional immunization schedules with other aluminum-adjuvanted, inactivated vaccines: the first vaccination is followed by a second dose 4-12 weeks later, and a third shot is administered 5-12 months later. However, considerable differences still exist between vaccine brands, primarily based on the schedules used in licensing studies. Extension of intervals between doses, particularly after the second dose, will not hamper successful continuation of vaccination. For Encepur and FSME-IMMUN, a rapid or accelerated immunization schedule is licensed for children and adults (Table 2). In the context of the conventional immunization schedule for any of the 4 non-Chinese vaccine brands, the first TBE booster immunization is recommended 3 years following the third vaccination of the primary series. Subsequent boosters for the European vaccines are following the licensed schedules and recommend boosters

at intervals of 5 years in persons below 50 and 60 years of age for Encepur and FSME-IMMUN, respectively, and every 3 years for persons older than 50 or 60 years of age, respectively. Booster doses for the Russian vaccines are recommended every 3 years for all age groups. Switzerland and Finland changed their national immunization schedule to subsequent boosters every 10 years, supported by newer data (see below). In February 2024, Latvian health authorities also extended the recommended booster interval after the 4th dose to 10 years. The FDA licensed FSME-IMMUN, under the name TICOVAC, for the first time in 2021 in the USA for travelers and laboratory workers.[116] A respective ACIP (Advisory Committee on Immunization Practices) recommendation was published in the MMWR in 2023. Along with a detailed exposée on the TBE virus, the disease and diagnostics, disease incidence, vaccine immunogenicity and effectiveness, vaccine safety, etc., a recommendation for a primary immunization is provided. Recommended is a 3-dose schedule for both - the adult and pediatric formulations, similar to that licensed in Europe. A booster vaccination can be administered 3 years later, in case of ongoing exposure. No ACIP recommendations are made on the need for subsequent booster doses.

Contraindications and precautions

In general, for all TBE vaccines, hypersensitivity to the active substances, any of the excipients, or production residues constitutes a contraindication to immunization (Table 1). For the four non-Chinese TBE vaccines, severe hypersensitivity to egg, chicken proteins, or latex may cause severe allergic reactions in sensitized individuals. A moderate allergy to egg proteins (defined as hives after consumption/injection) does not constitute a contraindication for TBE vaccination with either vaccine. However, patients with moderate egg allergy should be monitored for one hour after application. Therefore, persons with proven “non-severe egg allergy” can receive a TBE vaccination. In case of a moderate or severe acute illness with or without fever, TBE vaccination should be postponed.

Previous exposure to other flaviviruses or flavivirus vaccines (for example, against Yellow fever [YF], Japanese encephalitis virus [JEV], or dengue virus) has been suggested to affect the immune response to TBE vaccination. While for a long time this was not adequately studied in humans, a new study became available in 2019[101], which investigated the influence of pre-existing YF vaccine-derived immunity on the antibody response to TBE vaccination. By comparing samples from YF pre-vaccinated and flavivirus-naive individuals, it could be shown that YF immunity not only caused a significant impairment of the neutralizing antibody response to TBE vaccination but also a reduction of the specific TBE virus neutralizing activities (NT and ELISA-titer ratios). Although the clinical relevance of these findings remains unclear, in practice, an increased awareness of the possible impact of pre-existing flavivirus immunity in the assessment of flavivirus vaccines appears to be warranted. In contrast, TBE vaccination has been shown to enhance the immune response to an inactivated JEV vaccine,[7] but even though cross-reactive antibodies have been described, there is no evidence of actual cross-protection between JEV and TBE vaccines.

For both European TBE vaccines, there is no data on their use during pregnancy and lactation. As with all other inactivated vaccines, vaccine administration during pregnancy may be considered after carefully weighing risk and benefit.

Vaccine stability and storage

FSME-IMMUN is available as a pre-filled syringe without needle. The vaccine must be refrigerated at 2°C to 8°C. The shelf life is 30 months. Encepur is available as a pre-filled syringe with and without needle and must be stored at the same temperature (between 2°C and 8°C). The shelf life is 24 months. TBE-Moscow vaccine has a shelf life of 24 months and EnceVir of 36 months, both with the same temperature requirements as the European vaccines. The currently licensed Chinese vaccine has a shelf life of 21 months.

Induction of immunity

No clinical studies with efficacy endpoints have been conducted on any of the licensed TBE vaccines. These vaccines have been registered on the basis of immunogenicity and safety studies, which consistently show a significant rise in neutralizing antibodies after primary vaccination with the vaccine. A Cochrane Collaboration review published in 2009 summarized 11 randomized clinical trials (10 publications), conducted with 3 different TBE vaccines (IPVE, FSME-IMMUN, and Encepur) and involving 8,184 subjects (6,586 adults and 1,598 children).[8] Overall seroconversion rates exceeding 87% were observed. Studies conducted by the respective manufacturers report seroconversion rates in the range of 92%–100% for Encepur and FSME-IMMUN, as measured by a commercial enzyme-linked immunosorbent assay (ELISA) or neutralization test (NT), with seroconversion being defined as NT =1:10, or according to the recommendations of the ELISA manufacturer.[9–12] “Low responders” after TBE vaccination are seen very rarely, there is no obvious “personal constellation” (except immunosuppression) that predisposes for insufficient immune response.[112]

Correlates of protection

Neutralizing antibodies directed against the protein E represent the most important mechanism of protection

against TBEV, not only after natural infection but also after vaccination, even if antibody responses in both cases differ.[39] According to the World Health Organization (WHO), in the absence of a formal correlate of protection for TBE vaccines, these neutralizing antibodies can be used as a surrogate marker for immunity.[33] Unfortunately, there is no generally accepted, standardized neutralization test nor are there any international reference reagents. In general, a titer ≥1:10 is considered seroprotective;[40] however, in the context of some vaccine licensure studies, titers of ≥1:2 were accepted as a correlate for a significant immune response.[41] Neutralization assays as used in various studies to determine seroprotection after vaccination differed to a large extent: their sensitivity differed and different test protocols were used, which makes a comparison of results difficult. There is only one occasion of directly comparable TBE antibody test results with standardized serum samples available and even in this study different NT test results were shown. Moreover, detection of virus-neutralizing antibodies in vitro was never correlated with serum antibody concentration in vivo necessary to achieve solid protection in a subject.

ELISA results are not suitable as reliable surrogate markers for neutralizing antibodies due to cross-reactivity with other flaviviruses (specifically antibodies resulting from infection or vaccination). Moreover, the ELISA assay does not distinguish between antibodies with low and high avidity, hence determining also antibodies without neutralizing capacity. Therefore, ELISA measurements are primarily useful for screening purposes. The HI test, which has been broadly used in the past, is no longer considered state of the art.

Clinical study program with the different brands

FSME-IMMUN

The clinical development program for FSME-IMMUN included 13 studies that investigated the immunogenicity and safety of the vaccine in approximately 5,180 adults and 6,430 children. An additional 4 studies on FSME-IMMUN were identified after review and analysis of published literature.[9] The seroconversion rate in adults 16 to 65 years of age, vaccinated according to the conventional schedule, was 97% after the second dose and ranged between 99.5% and 100% after the third dose, as measured by ELISA and/or NT.[9] When the rapid immunization schedule (Table 2) was used, seroconversion rates in NT after the second vaccination were 98.0% and 89.9% in adults younger or older than age 50, respectively, and 100% and 99.3% in those 2 age groups after the third vaccination, respectively. Two pediatric studies (a dose-finding study with more than 400 children who received the later licensed pediatric dose and a large safety study with an immunogenicity subset that included approximately 370 children, all between the ages of 1 and 15 years) found seroconversion rates (ELISA) of 96% to 100% (depending on the age sub-group) after the second vaccination and almost 100% in all age subgroups after the third vaccination.[13]

Another pediatric study investigated immune response in 149 and 152 children 1–11 years of age, who were vaccinated with FSME-IMMUN Junior and Encepur Children, respectively, in the context of a primary immunization schedule. According to the NT based on the Neudörfl strain, seropositivity rates after the second vaccination in the combined age groups was 100.0% in children who received FSME-IMMUN Junior and 97.8% in those who received 2 vaccinations with Encepur Children.[14] A third vaccination with FSME-IMMUN Junior induced 100% seropositivity in both study groups.[15]

An earlier pediatric study, which investigated the immune response in 334 children to both FSME-IMMUN Junior and Encepur Children for the first 2 vaccinations, using the conventional as well as the rapid immunization schedule, found higher seropositivity rates (NT ≥10) in the Encepur-immunized group versus the group that received FSME-IMMUN Junior, using either vaccination schedule. Upon completion of the primary vaccination course, and after the third dose (given with Encepur Children), >95% of all children achieved an NT ≥10.16 Both studies confirmed the interchangeability of the 2 TBE vaccines when given as a third dose in the context of a conventional or rapid primary immunization schedule.

Encepur

Data on the immunogenicity of Encepur from 8 clinical and post-marketing studies, which included 7,500 subjects, showed 100% seroconversion or a 4-fold rise in anti-TBEV antibodies after primary immunization.[17] Similar immunogenicity was achieved with either conventional or rapid immunization schedules (see Table 2).[12]

In 3 studies, comprising a total of 3,118 subjects between the ages of 12 and 76 years, the non-inferiority of the new polygeline-free formulation to the former vaccine containing polygeline was demonstrated.[18] In addition, the rapid immunization schedule using the new formulation was investigated.[17,19,20] The new formulation was also shown to be safe and immunogenic in a review of data from clinical trials and post-marketing experience in approximately 7,500 subjects aged 1 to 77 years.[20] The immunogenicity of the vaccine and the advantages of the rapid immunization schedule were further confirmed in a number of pediatric trials that enrolled more than 3,500 children 1–11 years of age.[21,22] The immunogenicity of the rapid schedule in children, as well as the interchangeability with FSME-IMMUN when given as a third dose, was shown by Wittermann et al.[23] Seropositivity rates of 99% and 100%

were determined at 3 and 5 years, respectively, after booster doses in children 1–11 years of age.[16]

Russian vaccines

The Russian vaccines, TBE-Moscow (Klesch-E-Vac) and EnceVir, have been evaluated in 2 clinical studies, each involving 200 adults. Antibody titers ≥1:80 (hemagglutination inhibition [HI] test) were detected following 2 doses, 2 or 5 months apart, in 84% and 93% of subjects receiving TBE-Moscow vaccine and in 82% and 89% of the vaccinees who received EnceVir, respectively.[24,25]

Another study with an age-stratified analysis of 325 subjects found at least a 4-fold increase of HI-antibody titers in 96%, 93%, and 89%, respectively, for each of 3 age groups: 3–6 years, 7–14 years, and 15–18 years, after vaccination with TBE-Moscow vaccine, versus 84%, 97%, and 92%, respectively, for the same age groups after receiving the EnceVir vaccine.[23]

No significant differences regarding immunogenicity against different TBEV strains could be found between TBE-Moscow vaccine and FSME Immun Inject (FSMEV propagated in mouse brain cells).[4] After 2 doses of the TBE-Moscow vaccine given 4 months apart, 92% of children and adolescents aged 7–17 years achieved a 4-fold rise in antibody levels compared with baseline.[4] Based on these results, the vaccine was recommended first for use in children and later for use in adults.[4]

A study comparing EnceVir and TBE-Moscow vaccine (N=400) found seropositivity (HI test) in 82% and 89% of patients, respectively, after 2 doses of EnceVir given 2 or 5 months apart, whereas the seropositivity rates with the TBE-Moscow vaccine were 84% and 93%, respectively.26–28 Furthermore, the 2 vaccines were also compared in 325 children who received 2 doses of either vaccine. A 4-fold rise in HI titer was achieved in 84% to 97% of the children with EnceVir and in 96% to 98% with TBE-Moscow vaccine, respectively.[29] Twelve months after the last dose of EnceVir or TBE-Moscow vaccine, 72% and 87%, respectively, of the vaccinated individuals were still seropositive. A booster response was efficacious in all of the 131 children who received a third dose 1 year after the first 2 vaccinations.[30]

In studies comparing the available Russian TBE vaccines, seroconversion rates of 59% and 83%, after 1 and 2 doses, respectively, were achieved with TBE-Moscow vaccine, versus 75% and 85%, respectively, with EnceVir.[31] Even without randomized controlled efficacy trials, the field effectiveness of the 2 Russian vaccines has been proven in highly endemic regions, e.g., in Krasnoyarsk and Sverdlovsk.[31–33, 102]

Sen Tai Bao

According to an English-language article summarizing five clinical studies investigating the current Chinese TBE vaccine in children 8–17 years of age (N=616), in adults <60 years of age (N≈5600), and in elderly individuals >60 years of age (N=166), seropositivity rates (as measured by plaque reduction neutralization test and/or ELISA) ranged between 86.4% and 98.8% after 2 doses.[6] In the group of subjects ≥60 years old, the seropositivity rate 28 days after the second vaccination was 97.3%. In one of the studies, seropersistence rates of 86.5% and 76.9% were observed 6 and 12 months after the second vaccination, respectively.

Comparative studies

There is only one study in which the immunogenicity of TBE-Moscow, EnceVir, FSME-IMMUN, and Encepur Adults was directly compared by using the Far-Eastern virus strain P-73 in adults.[34] All vaccines induced neutralizing antibodies against the tested strain with TBE-Moscow; neutralizing antibodies were detected in 100% and 94% of the vaccinees after 2–5 months and 2 years, respectively. With EnceVir, neutralizing antibody detection rates were 88% and 84%; with FSME-IMMUN, 88.2% and 78.1%; and with Encepur, 100% and 100%, respectively.

Irregular vaccination

Even irregular vaccination schedules confer good protection for the vaccinee. An investigation of the field effectiveness of TBE vaccination in Austria – a country in which 88% of the total population is vaccinated against TBE at least once and 58% is regularly vaccinated according to the recommended schedule – found an overall effectiveness in regularly vaccinated persons of about 99%, and 95% in subjects with a record of irregular vaccination.[35,36] A later investigation of the effectiveness of two or > 3 doses of a TBE vaccine found consistently high VE across both groups (94.5% and 97.4%, respectively).[103] These findings are especially important for travelers with insufficient time to complete the primary immunization schedule. Nevertheless, according to the ACIP recommendation for US travelers, the 3rd dose of the primary series should be completed at least one week before potential exposure. For persons who cannot complete the 3-dose primary series, a reference is made to immunogenicity and effectiveness after incomplete primary series (1 or 2 Doses) in Adults and Children.[116]

Furthermore, in a cohort study of more than 1,100 persons whose vaccination deviated from the recommended schedule, a single booster immunization with FSME-IMMUN was administered up to 20 years after 1, 2, or 3 primary vaccinations.[37] The results of this study demonstrated that, independent of the interval since last vaccination and the age of the vaccinee, a sufficient booster response was

induced if at least 2 or 3 primary vaccinations were previously administered.[37,38] In addition, similar results have been seen with Encepur, given as a catch-up vaccination after primary or primary + booster vaccination.[51] Altogether study results suggest that even initial irregular vaccination schedules do not implicate a complete "restart" of vaccination series, regular completion of vaccination course is sufficient to induce an adequate immune response.

Cell mediated immunity

Until recently little was known about the cellular immune response after TBE vaccination. Immunization with inactivated TBE vaccine has been reported to induce primarily a CD4+ T-cell response with a very low induction of CD8+ cells.[60,61] More recent investigations of TBE 'low-responders' after vaccination showed a positive correlation with humoral and cellular immune responses upon booster vaccination: high or low TBE titers were associated with sufficient or lack of Ag-specific T-cell proliferation, respectively.[62]

Research published in 2016 reported on the cellular immune response after a booster vaccination of FSME-IMMUN, administered by subcutaneous and intramuscular routes, revealing that interleukin-2 (IL-2), interferon (IFN) gamma, and interleukin-10 (IL-10) levels, produced upon antigen re-stimulation of peripheral blood mononuclear cells (PBMCs), were already elevated prior to vaccination.[63] This observation is in line with the fact that all study subjects had received multiple TBE vaccinations in the past and therefore had high numbers of TBE-specific effector memory T cells. Quantification of different T-cell subpopulations (naïve, memory, and suppressor T cells) before and 1 week after booster vaccination showed a relative decrease in regulatory T cells after vaccination. This is most likely due to an effector T-cell expansion induced by the booster vaccination and not the result of a decrease in the total number of regulatory T cells.[63] Moreover, the investigators observed an increase in the percentage of CD4+ T cells combined with a slight relative decrease of CD8+ T cells after intramuscular vaccination and a relative decrease of effector memory CD4+ T cells after subcutaneous vaccination. However, the observed changes in the CD4+ and CD8+ T-cell sub-populations were very small and had no influence on neutralizing antibody titers.[63] Whereas all these data were obtained after TBE booster immunization in previously vaccinated individuals, data are lacking on the cellular immune response in the context of TBE primary vaccination.

In order to provide an answer to this question the age-related differences in the humoral and cellular immune response after primary immunization was investigated using another flavivirus vaccine – an inactivated, adjuvanted Japanese Encephalitis vaccine.[109] Both, humoral and cellular immune responses were analyzed in elderly (mean age 69y) and younger (mean age 24y) subjects according to age and cytomegalovirus (CMV) seropositivity. A reduced humoral immune response was found in the elderly group. This was paralleled by a reduced cytokine production, such as Interferon gamma in vitro, as well as higher frequencies of late differentiated effector and effector memory cells and T regulatory cells. The described cellular changes combined with lower humoral responses were in particular prominent in CMV seropositive elderly people. The finding of this study, although based on results after JE-vaccination, once more confirms the importance of maintaining the existing booster intervals for individuals who were primed after the age of 60 years in order to ensure sufficient long-lasting protection.

Vaccine interchangeability and cross-protection

In general, it is preferred that the same vaccine brand is used for the complete primary immunization series. However, in order not to interrupt a vaccination series in case of unavailability of a certain vaccine, the immunization series can be completed with a different brand of TBE vaccine. Several studies confirmed that FSME-IMMUN and Encepur can be safely interchanged for the third vaccination in the context of the conventional primary immunization of adults and children, as well as for subsequent booster vaccinations.[11,15,23] In two studies – one in adults and one in children aged 12 years and younger - FSME-IMMUN was administered as the 3rd dose of the primary schedule after two doses of Encepur;[11,15] in a third pediatric study Encepur was given for the 3rd dose after two doses of FSME-IMMUN.[23]

A review describing 3 studies in which Encepur was given as a booster after a complete primary immunization with FSME-IMMUN (with or without booster) and further 3 studies in which Encepur or FSME-IMMUN was given for the third vaccination after two doses of the respective other brand in the context of the conventional schedule come to the same conclusion, irrespective of the somewhat differing immunogenicity results.[92] These differences, as mentioned several times throughout this chapter, are primarily due to the different test systems used – utilizing a homologous or heterologous TBE virus strain.

A switch from Encepur to FSME-IMMUN for the 3rd vaccination of the rapid immunization schedule (1-7-21), as well as a switch between first and second vaccination in the conventional schedule for FSME- IMMUN as well as for Encepur should be considered only under exceptional

circumstances, as these schedules are not licensed.

Evidence exists that TBE vaccines protect not only against the homologous subtype, but also against heterologous subtypes (European, Siberian, and Far-Eastern TBEV subtypes). In vitro and in vivo studies have shown broad cross-neutralizing capacity of vaccine-induced antibodies by either vaccine.[24,25,34,42,43] Moreover, a systematic review[44] published a few years ago supports robust cross-neutralization with the exception of 1 strain (TBEV-Fe P-69), for which a significantly lower level of neutralization was determined. In contrast, there is no evidence from human studies (except against Omsk HF)[43] that vaccine-induced TBEV antibodies provide cross-protection against other flaviviruses.

To overcome the problem of missing comparability data between immune responses to different TBEV strains, due to a poorly standardized methodology, a novel test system that uses hybrid viruses was developed; this system allows an unbiased head-to-head comparison of the humoral responses against different TBEVs from all 3 subtypes. Studies using this new technique have found comparable vaccine-induced neutralizing titers against TBEVs of all subtypes, in sera of subjects who received 2 doses of FSME IMMUN Junior, and somewhat reduced, but still protective, neutralization capacity against Omsk hemorrhagic fever virus (OHFV).[43] Another study found differences in the ability of 2 European pediatric TBE vaccines to induce antibodies capable of neutralizing heterologous TBEV strains.[45]

While it has been shown that an immunization with Encepur in subjects living in regions with Far Eastern TBEV circulation induced higher immune responses in originally seropositive as compared to seronegative individuals, similar data with vaccines based on the Far Eastern TBEV strains are limited.[94]

A recently published study found statistically significant differences in the immune response in subjects with pre-existing immunity to the TBEV FE strain Sofjin or Siberian strain Ekaterinburg-27-11-06 as compared to seronegative individuals, only after the first vaccination with one of the two Russian TBE vaccines (Tick-E-Vac based on FE strain Sofjin and EnceVir based on FE strain 205). After the second dose, the difference was insignificant.[95]

Antibody persistence and boosting properties

Up to the year 2004, 3-year booster intervals were recommended for the 2 European TBE vaccines. However, in 2004 and 2006 data suggesting a longer seropersistence became available.[38,46] Since then, studies investigating the seropersistence after primary and booster vaccinations with both European vaccines have been conducted.[16,19,47–49]

The seropersistence of TBEV antibodies in 347 adults between the ages of 18 and 67 years was evaluated 2 and 3 years after completion of the primary vaccination, with the first 2 doses being either FSME-IMMUN or Encepur. The third dose consisted of FSME-IMMUN for all study subjects.[50] Seropositivity rates of 96.8% and 95.4% were determined using NT 2 and 3 years after the third dose of the primary series, respectively. All subjects (100%) achieved seropositivity after the subsequently administered first booster vaccination.

A subsequent long-term investigation of seropersistence after an Encepur booster vaccine was initiated,47,48,52 and seropositive rates (SPR) were evaluated from 2 to 10 years after the booster was given. After 2, 3, and 4 years, SPR of 95.9%, 96.7%, and 93.8% were found. In subjects 50–60 and >60 years of age, SPR dropped after 4 years to 93.0% and 91.7% for the 2 age groups, respectively. After 5 and 6 years, SPR in subjects below age 60 dropped to 96% and 94%, while for subjects age 60 years and older, rates of 89% and 86% were detected, respectively. Geometric mean titers (GMTs) were also lower not only in subjects age 60 years and older, but also in subjects older than 50 years. At the end of the study, 8 and 10 years after the booster, SPR were 86.8% and 77.3%, with a pronounced age correlation, while in subjects younger than 50 years of age, seropositivity rates of 83.9% could be detected after 10 years. In the age group older than 50 years, only 66% of these subjects remained seropositive.[47] Similar to observations in young adults, seropersistence over a 5-year period was shown for adolescents who received their primary immunization according to different immunization schedules.[16,53]

A prospective investigation of seropersistence of TBE antibodies was published by Konior et al.[88] The study – a follow-up study of the one described above in 347 adults, investigated the seropersistence of TBE antibodies up to 10

years after a primary immunization and first booster with FSME-IMMUN. The necessity for a booster vaccination was evaluated on the basis of yearly NT determinations. As expected, the decrease in seropositivity was more pronounced in elderly as compared to younger individuals - the proportion of subjects left potentially unprotected by prolonging the booster interval beyond 5 years was 7% in the 18–49 years age group and 18% in the 50–60 years age group. By 10 years, these proportions increased to 11% and 26% in the 18–49 years and 50–60 years age groups, respectively. Nevertheless, overall, a total of only 47 subjects (14.9%) received the second booster dose over the follow-up period, and 84.9% of the study subjects were still seropositive after 10 years. Seropositivity rates were even higher (88.6%) in subjects below 50 years of age.

In a phase IV follow-up study published by Beran et al.[89] adults and adolescents who had received 3 different primary vaccination schedules (rapid, conventional and accelerated conventional) in a predecessor study and a booster dose 12-18 months or 3 years after the primary series were followed for the persistence of their TBE antibodies by yearly NT determinations. Overall, ≥97% of the study subjects in the per protocol set were seropositive (NT titers ≥10) across all timepoints, regardless of the primary vaccination schedule; however, older age groups showed overall lower GMTs.

Long-lasting seropersistence of TBEV antibodies after the first booster was confirmed also by a another published study98 investigating the antibody persistence in children, adolescents and young adults who received their primary immunization with FSME-IMMUN Junior when they were aged 1-15 years and an age-appropriate booster with either FSME-IMMUN or FSME-IMMUN Junior 4-5 years after the primary schedule. Seropositivity rates as determined by NT were 99.4% after 5 years and 90.3% after 10 years.

Furthermore, seropersistence of TBE antibodies after the 3rd dose of the primary immunization has been investigated 2 and 3 years thereafter: 50 subjects aged 18-50 years showed higher seropositivity rates (88.7% and 92.3%, after 2 and 3 years, respectively) than those aged 51 -67 years (65.5% and 70.9% after 2 and 3 years, respectively), thus confirming the still existing manufacturer recommendation for the administration of the first booster dose 3 years after completion of the primary series.

The seropersistence studies with both European vaccines show long-term anti-TBEV antibody persistence after the first booster vaccination, especially in the population below 50-60 years of age, as well as excellent boostability in all age groups, indicating the establishment of a strong immune memory. It is not clear if permanent presence of neutralizing antibodies is a prerequisite for protection against clinical disease, as rapid recall of immune memory after vaccination may contribute as well to protection. However, there is no substantial evidence that immune memory alone will protect the patient from TBE in case of infection, particularly in the elderly and in immunocompromised persons.

More recent investigations in Germany and Latvia found high vaccine effectiveness after 2, 3 and > 4 doses not only for subjects vaccinated according to the licensed schedules, but also for those immunized outside the regular schedule, whereby delayed boostering did not cause significant differences in VE.

There is no data on long-term seropersistence for the 2 Russian and the Chinese vaccines. Twelve months after primary immunization, seropositivity rates of 72%, 87%, and 77% were determined for EnceVir, TBE-Moscow, and the Chinese Vaccine, respectively.[6]

Even before results on long term seropersistence became available, a recommendation for a 10-year booster interval starting directly after the 3rd vaccination of the primary series was introduced in 2006 in Switzerland. Meanwhile Finland, and very recently, in 2024, also Latvia adopted a 10 -year booster interval recommendation, however, after the 4th dose. The primary goal of the change in Switzerland was to increase the vaccine coverage, which was achieved only to a moderate extent in some Swiss cantons in the years thereafter.[89] However, according to a more recent survey, a public health benefit resulting from an increased acceptability of TBE vaccination, was noted. [105]Nationwide, a coverage of 41.7% was found for 1 dose and 32.9% for a complete primary series. According to the authors 135 TBE cases were prevented in 2018 due to vaccination. A TBE incidence rate of 6.83/100,000 among the unvaccinated population was calculated and a VE of 91.5% was estimated. Furthermore, a retrospective analysis of surveillance data, collected between the years 2000 and 2019, which compared breakthrough infections and the breakthrough rate 0-3 years and >3-10 years after the 3rd dose across time periods and age groups, found no indication that

Table 3: Safety and Reactogenicity of FSME-IMMUN and Encepur (source: SMPCs)

Probability	≥1/10	≥1/100 <1/10	≥1/1000 <1/100	≥1/10.000 <1/1000	Not known
FSME-Immun 1st vaccination: n=3512 2nd vaccination: n=3477 3rd vaccination: n=3277	Local reaction at injection site: e.g., Injection-site pain	Headache, nausea, myalgia arthralgia, malaise, fatigue.	Lymphadeno-pathy, vomiting, fever (only exceptionally >39°C), injection-site hemorrhage.	Acute allergic reactions, somnolence, diarrhea, abdominal pain, vertigo, local reaction at injection site: redness, swelling, induration, pruritus, paraesthesia, inflammation	Herpes Zoster (in pre-exposed individuals), aggravation of autoimmune disease, anaphylactic reaction, visual impairment, photophobia, eye pain, demyelinating disorders, meningismus, encephalitis, neuritis, neuralgia, tachycardia, tinnitus, dyspnea, urticaria, rash, pruritus, dermatitis, erythema, hyperhidrosis, back pain, joint swelling, neck pain, musculoskeletal stiffness, pain in extremity, gait disturbance, chills, flu-like symptoms, weakness, edema
Encepur *(Pooled data from clinical studies and post-marketing surveillance)*	Transient pain at injection site, general malaise, myalgia, headache	Redness, swelling at injection site, flu-like symptoms, fever ≥38°, nausea, arthralgia	Arthralgia and myalgia (neck), vomiting	Granuloma at injection site, diarrhea, arthralgia and myalgia in the neck region, lymphadenopathy, neuritis-like symptoms, systemic allergic reactions - like urticaria, dyspnea, bronchospasm, hypotension, transient thrombocytopenia	Extremely rare: Guillain-Barre Syndrome

extended booster intervals resulted in higher rate of breakthrough infections. Moreover, a marked public health benefit was observed with respect to increased acceptability of TBE vaccination.[107] Nevertheless, due to the increased endemicity of TBE in Switzerland and the overall still low vaccine coverage, in 2019 vaccination recommendations were geographically extended to the entire country except the cantons of Geneva and Ticino.[97]

A systematic literature review[106] suggests that seropersistence alone does not explain the high effectiveness of TBE vaccination irrespective of the time since the last vaccine dose. While in >90% of younger subjects seropositivity persisted for more than 10 years, only 37.5% of subjects over 60 years of age were still seropositive, which is in contrast to the high VE, even in irregularly vaccinated individuals. The authors believe that Immunological memory is an alternative mechanism of action for protection against TBE, however, there is no proof for this assumption so far.

Vaccine effectiveness

Austria is a highly endemic country for TBE with a very long history of TBE immunization. Vaccination coverage has increased steadily since the 1970s, when the first TBE vaccine – FSME-Immun – was initially licensed. According to an investigation of the field effectiveness of TBE vaccines in Austria during the years 2000–2006, 88% of the Austrian population has a history of TBE vaccination, and 58% were

vaccinated according to the licensed schedule.[35] For the above-mentioned period, when FSME-IMMUN comprised 90% to 95% of the TBE vaccines administered in Austria, an effectiveness of approximately 99% was calculated for regularly vaccinated persons, with no statistically significant difference between age groups.[35] Not a single case of TBE was recorded within the first year after a documented history of 2 vaccinations, thus achieving a vaccine effectiveness of 100% after 2 vaccinations. A later investigation of vaccine effectiveness for the years 2000-2011[36] showed a slight decrease of vaccination coverage to 85% in 2011. Nevertheless, similarly high rates of effectiveness were seen: 98.7% and 96.3% for regularly vaccinated subjects under best- and worst-case assumptions, respectively, and 92.5% and 91.3% for irregularly vaccinated subjects under best- and worst-case scenarios, respectively. These findings highlight the importance of adhering to the recommended vaccination schedule in high-risk regions, as there is a considerably higher risk of acquiring TBE in irregularly vaccinated subjects. As a result of the high vaccination uptake in Austria, an estimated 4,000 TBE cases and 20 deaths were prevented between 2000 and 2011.35,36 During the same time, neighboring countries including the Czech Republic and Slovenia, which are also highly endemic for TBE but with very low vaccination coverage (16% in 2009 and 12% in 2008, respectively),[36,64] experienced an increase in disease incidence.

A recent survey conducted in Southern Germany and Latvia revealed a VE of 97.2%, 95.0% and 95.4% after 2, 3 and > 4 doses, respectively for Germany and 98.1%, 99.4% and 98.8%, respectively, for Latvia, among subjects vaccinated on schedule.[104] Only marginal differences in VE was observed for subjects vaccinated outside the regular schedule. According to the authors of this survey delayed timing after the 4th vaccination did not result in significant differences in VE for any age group.

As presented above, more recent investigations in Germany and Latvia found high vaccine effectiveness after 2, 3 and > 4 doses not only for subjects vaccinated according to the licensed schedules, but also for those immunized outside the regular schedule, whereby delayed boostering did not

Table 4: Post-exposure prophylaxis according to vaccination status

Vaccination history (written documentation)	Interval between last immunization and tick sting	Interval between tick sting and physicians visit[b]	Recommendation
Unvaccinated or unknown	Not applicable	<4 weeks	Wait until ≥4 weeks after sting, then initiate immunization series
1 dose	≤ 14 days	Not relevant	Wait until ≥4 weeks after sting, then administer 2nd dose
	15 days - 1 year	<48 hours	Administer 2nd dose immediately
		≥48 h	Wait until ≥4 weeks after sting, then administer 2nd dose[a]
	≥1 year	<48 h	Administer 2nd dose immediately[a]
		≥ 48 h	Wait until ≥4 weeks after sting, then administer 2nd dose[a]
≥2			Additional vaccination according to regular schedule

Austrian Immunization Plan 2017[79] (http://www.bmgf.gv.at/cms/home/attachments/2/8/1/CH1100/CMS1452867487477/impfplan.pdf)

[a] *Testing of antibody response recommended. If not possible, count this vaccination as the first one in basic immunization schedule*

[b] *If time elapsed is not to be determined, use schedule: >48 h after tick bite*

cause significant differences in VE.

A systematic literature review of the effectiveness of tick-borne encephalitis vaccines in Europe identified a total of 13 studies, conducted in Austria, the Czech Republic, Latvia, Germany and Switzerland, published between 2003 and 2023. TBE vaccine effectiveness was estimated >92% against TBEV infection in all age groups. Studies in Austria, the Czech Republic, Latvia, and Switzerland estimated that TBE vaccines prevented >1,000 TBE cases a year.[114] An Abstract Disposition Report from Boston, Massachusetts, October, 2023, on effectiveness of vaccination in the Czech Republic between 2018 and 2022 concluded that TBE vaccination averted an estimated 1,020 TBE cases in the Czech Republic in the investigated time period.[115]

Based on the meanwhile accumulating amount of vaccine effectiveness data, a prolongation of the booster intervals appears feasible, especially for younger and fully immunocompetent persons. Primarily in countries with very low vaccination coverage this could have a positive effect. A potential negative effect for countries with very well-established vaccination programs and high vaccination uptake should be avoided through appropriate national recommendations. Such recommendations have however, to take carefully into account individual risk factors as well as the local epidemiological situation. Important points to consider in this regard are immunocompetence and age. Therefore, a general prolongation of booster intervals seems well reasonable only after the 4th dose, especially for subjects who received their primary vaccination after the age of 60 years, as the formation of immune memory is impaired with increasing age.[111] This is supported by a Swedish study on vaccination failures (see below), which indicates that additional vaccinations in the elderly might overcome the problem of an age-related impaired immune response[99].

Impaired immune response

Most of the studies conducted in elderly individuals have shown consistently lower antibody concentrations compared with younger age groups.[54-57] A cross-sectional study from the highly endemic Åland Islands found that age of the individual and number of vaccine doses were the 2 most important factors for determining the immune response to vaccination.[50,55] The majority of these studies included subjects who received their primary vaccination series below the age of 50 years, which might have influenced the duration of seropositivity and B-cell memory.[47,53] This is well in accordance with data on vaccine failures, which are significantly more often seen in older persons. Unfortunately, few data exist on primary vaccination in individuals of more advanced age and eventual immunological consequences.

An observational study with FSME-IMMUN and Encepur administered to previously unvaccinated elderly subjects reported seropositivity rates of 95% and 80%, respectively, for subjects vaccinated with FSME-IMMUN (as measured by the Immunozym and Enzygnost ELISA Kits) and 65% and 80%, respectively, for subjects vaccinated with Encepur (as measured by the Immunozym and Enzygnost ELISA Kits).[56] This study illustrates not only the reduced immune response after TBE vaccination seen in the elderly population, but it also gives evidence for the dependence of serologic results on the commercial ELISA test systems. Unfortunately, NT was not evaluated in the context of this study. Another study, which compared the primary immune response in older and younger subjects, showed that those primed after the age of 50 years achieve not only lower titers but also experience a more rapid decline of neutralizing antibodies as compared to subjects primed at a younger age. Of note, almost no difference in the booster response was found between the 3 older age groups: 50–59 years, 60–69 years, and >69 years of age, indicating that responsiveness to vaccination is impaired already by the age of 50.[54]

The immune response to a conventional primary immunization schedule with FSME-IMMUN in previously unvaccinated subjects >70 years of age was investigated in another study.[58] Four weeks after the second and third vaccinations, 98.5% and 99.3% of subjects were seropositive (≥10) by NT, even if GMTs were generally lower. Although antibody concentrations are lower in the elderly, booster doses have been shown to increase sufficiently the antibody levels, indicating an adequate immune memory response in the elderly population as well. Moreover, the quality of antibodies as measured by antibody avidity were shown to be intact despite the lower antibody titers.[59]

Due to the concern of waning immune response with age, a Swedish study investigated the immunogenicity in subjects > 50 years of age using the standard 3-dose primary

schedule and alternatively two different 4-dose schedules (0-7-21-360 or 0-30-90-360).[108] Immune response was measured by NT at days 0-60, 120, 360 and 400. The 0-7-21-360 schedule showed higher titers in the older age group than the standard 3-dose schedule for all investigated timepoints. The second 4-dose schedule did not show such differences on day 400.

All findings described above underscore the importance of establishing well differentiated and personalized vaccination recommendations, which allow safe extension of booster intervals in order to simplify immunization schedules and improve vaccine coverage in affected geographies on the one hand, but, on the other hand, not increasing the risk of being insufficiently protected for immunocompromised groups of the population or subjects who received their primary immunization after the age of 60 years. Furthermore, if prolonged booster intervals should be applied, additional data are also needed for children, particularly when the primary vaccination course is applied at a very young age.[113] In these children an additional dose, for instance at school entry, could be considered, assuming that an interval of at least 3 years since the primary vaccination has passed.

In the context of a mass immunization program that started in 1996 in the highly endemic region of Sverdlovsk in Russia, an impressive decrease in TBE incidence could be achieved – from 42.1/100,000 in 1996 to 9.7/100,000 in 2000 to 5.1/100,000 in 2006. The vaccines used were TBE-Moscow (market share 80%); EnceVir (market share 6%); FSME-IMMUN (market share 12%); and Encepur (market share 2%). Based on these data, an overall vaccine effectiveness of 62% and 89% was estimated for the years 2000 and 2006, respectively.[31] Nevertheless, rare cases of TBE breakthrough disease, primarily in subjects older than 50 years of age, have been reported after primary TBE vaccination but not after booster immunization.[65-68]

No effectiveness data are available for the Chinese vaccine. There is only a single report, from the Center for Disease Control and Prevention, of the Hailar Railway, which showed that since the use of the current generation TBE vaccine, no TBE cases had been reported in 2009 and 2010.[6] However, details of the vaccination program (vaccination schedule, type of surveillance, etc.) are largely unknown.

Vaccine failures

Vaccine failures have been reported only occasionally. A retrospective investigation of breakthrough cases over a period of 8 years was conducted in Sweden.[65] During this period, 19 verified and 8 probable cases of TBE vaccine failures were reported. No accepted and plausible rationale exists to explain the immunological mechanisms leading to a vaccination failure. Therefore, it is not clear whether primary low-level responsiveness after regular TBE vaccination may be a risk factor for vaccine breakthrough. In contrast to unvaccinated subjects, most patients with breakthrough disease already had high antibody avidity and strong neutralizing antibodies in the first sample taken after hospitalization. When combined with an observed delayed immunoglobulin M (IgM) antibody response, and therefore presenting the features of an anamnestic response, this immune profile was obviously not sufficient to prevent the disease.[68] In 2019 a second retrospective study[99] on vaccine breakthroughs in Sweden was published and identified particularly i) older age (over 50 years of age), ii) immunocompromising comorbidities and iii) number of preceding vaccinations as key parameters for a higher risk of vaccine failures. The authors recommend for those persons, who start with their primary immunization series after the age of 50 an “extra” priming dose to reduce this risk. In addition, this study could for the first time define the probability of vaccine failures with 5% in a vaccinated population. While the Swedish study found there is an indication for more severe disease courses in older age, a retrospective study on clinical severity of vaccine breakthroughs from Germany,[100] however, could not identify a higher risk of more severe clinical disease in these patients.

A more recent retrospective case-control study investigated the occurrence of severe and mild TBE in hospitalized vaccinated and unvaccinated patients in Austria from 2000 to 2018. Of 1,545 hospitalized patients, 206 were vaccinated; in those, a higher proportion of severe disease course was observed, especially in children.[110] According to the authors the higher proportion of severe courses is not the result of an increased risk associated with vaccination, but rather can be explained by the lower field effectiveness against severe than against mild disease. This difference is especially pronounced in children (Field Effectiveness of 82.7% for severe vs 94.7% for mild disease). Impressively, this study found that in Austria vaccinated patients with

TBE were significantly younger than non-vaccinated; the proportion of patients below the age of 16 years was 2-fold higher in the group of vaccinated than in unvaccinated patients. A potential explanation of this striking finding could be the pediatric dose (half of the adult dose). In this regard the authors examined records of TBE in vaccinated children before the introduction of the pediatric dose and found only 2 cases among vaccinated children between 1979 and 2003. Taking into account increased awareness and improved diagnostics, which could have influenced this difference over time, this finding should result in a special vigilance when considering prolongations of booster intervals for children. On the contrary, the authors of this study suggest adding an additional priming dose for children in order to confer protection against severe disease.

Safety and tolerability

The currently available European TBE vaccines have a well-established safety record.[8,33] Safety and tolerability have been investigated in a number of clinical studies conducted in children and adults. Broad experience also comes from the field, with extensive pharmacovigilance over many years. Over the past decades, TBE vaccine formulations have been refined, thereby significantly reducing reactogenicity. In contrast, little published data are available on the safety of the 2 Russian vaccines and almost no data are available on the Chinese vaccine.[69] Frequently reported reactions after TBE vaccination basically do not differ from those occurring after vaccination with other aluminum-adjuvanted vaccines, e.g., local pain, redness, and swelling at the injection site, as well as headache, fatigue, malaise, muscle pain, joint pain, and fever.

Safety has been investigated in the context of many clinical studies with FSME-IMMUN, involving more than 13,800 children and adults.[9-11,13,14,50] All adverse reactions observed during clinical studies and relevant reports to the pharmacovigilance departments of the manufacturers are summarized in the Summary of Product Characteristics, Table 3. The most frequently reported reactions to the vaccination are local pain (≥1/10), headache, fatigue, malaise, myalgia, and arthralgia (1/100 and <1/10), whereas the frequency of fever was uncommon (≥1/1,000 and <1/100). Adverse reactions to vaccination seen in children are similar to those observed in adults. However, children more frequently experience fever, especially young children after the first vaccination. In addition, young children commonly react to vaccination with irritability, appetite loss, and disturbed sleep.

Similarly, at least 4 clinical trials have established the safety profile of Encepur in children and adults[12,18,20,22] (Table 3). Similar to FSME-IMMUN, the most frequently reported reactions to vaccination with Encepur are local pain, malaise, myalgia, and headache (>10% of vaccinees), whereas local redness, swelling, flu-like symptoms, nausea, arthralgia, and fever (primarily after the first vaccination) were observed in 1–10% of the vaccinees.

As of 2002, 2 TBE pediatric vaccines, FSME-IMMUN Junior (Baxter) and Encepur Children (Novartis/GSK), were marketed and at that time a post-marketing sentinel study was carried out in Austria. The study was conducted by the Institute for Vaccine Safety of the Austrian Green Cross and included 500 selected pediatricians and general practitioners who generated data on more than 25,000 vaccinations (85% with FSME-IMMUN). A total of 107 adverse events (AEs) were reported, with 69 (64.5%) of these occurring in children below the age of 2 years; also, 75.8% of the AEs were reported in association with the first vaccination. Fever was reported in 63 cases; 45 of these cases were mild, 15 moderate, and 3 severe (fever >39.5° C).[70]

Data derived from spontaneous reporting to the pharmacovigilance departments of manufacturers of both vaccines (FSME-IMMUN, for the period between 2001 and 2009, and Encepur, for the period between 2002 and 2009) indicate comparable rates of serious AEs (1.57 per 100,000 doses administered).[41] According to safety grading, as published in a WHO position paper in 2011, currently available TBE vaccines are not causally associated with serious adverse vaccine reactions.[71] Finally, although the safety sections of the SMPCs for FSME IMMUN and Encepur show some differences, it can be concluded that both vaccines have a similar safety and reactogenicity profile.

According to the Russian National Regulatory Authority, both Russian vaccines – TBE-Moscow and EnceVir – are safe and well tolerated,[33,41] and their manufacturing process fulfills WHO standards. However, no official documentation of quality control exists and no published data from large, controlled safety trials are available. Small-scale observational studies with TBE-Moscow and EnceVir have suggested a moderate reactogenicity profile with no

significant differences between the 2 vaccines. Post-marketing surveillance data did not identify any serious AEs.[26,32,72]

A study in children between 7 and 17 years of age comparing TBE-Moscow vaccine and FSME-Immun (old formulation; adult dose used also for children) found that fever was reported more frequently with TBE-Moscow vaccine; however, the differences were not significant.[4]

A passive, post-marketing surveillance review of EnceVir did not reveal any serious AEs up to 2010.[72] In 2010 and 2011, some lots of EnceVir were associated with a high incidence of fever and allergic reactions, particularly in children and adolescents. As a result, these lots were withdrawn from the market and the vaccine indication was restricted to adults above the age of 17 years.[73]

No published safety data are available for the Chinese TBE vaccine.

Passive Immunization and post-exposure prophylaxis

For many years, passive immunization as well as post-exposure prophylaxis with TBEV IgG preparations (immune globulin concentrate) was a state of the art treatment following a tick bite in unvaccinated subjects in Europe and Russia. Administration of an immunoglobulin concentrate for passive immunization was expected to protect against disease. However, passive immunization was blamed for antibody-mediated enhancement (ADE) of TBE infection in children,[74] like ADE phenomena in Dengue infections. In the late 1990s, the use of these immunoglobulins after tick exposure in a TBE-endemic area was discontinued even if the enhancement of TBEV infection could not be proven, either in humans or in a mouse model.[75,76] In Russia, especially in the highly endemic regions, post-exposure prophylaxis with immunoglobulins continues to be common practice. Russian studies report that timely administration of specific immunoglobulin after a tick bite can prevent clinical disease in about 80% of cases. The recommended dose is 0.05 mL/kg body weight of TBE immunoglobulin, whereby the antibody titer should not be less than 1:80.[77,78] However, investigations of the TBE-specific neutralizing antibody titers in IVIG (intravenous immunoglobulin) preparations from different geographic regions showed significantly lower TBEV neutralization titers in Russian-IVIG preparations compared with European IVIG preparations.[78]

Post-exposure prophylaxis with TBE vaccines in persons with a tick bite has to take into account the vaccination status and the incubation period of the disease. An accepted approach is summarized in Table 4.[79]

TBE vaccination in special patient groups

Underlying medical conditions can influence the outcome of vaccination by reducing the immune response. Alternatively, vaccination can theoretically cause a deterioration or exacerbation of the underlying condition. Therefore, the decision to vaccinate or not in subjects with serious medical conditions must be based on a careful risk/benefit analysis. Several studies have investigated immune response effects or influence on the course of the disease in the context of TBE immunization.

A controlled trial on TBE vaccination in patients with multiple sclerosis found no association between the vaccination and disease activity (as detected by magnetic resonance imaging [MRI]), clinical relapse, or disease progression.[80]

Another study investigated the effect of TBE vaccination in medically immunosuppressed patients with rheumatoid arthritis.[81] The patients (N=66) received a TBE primary immunization series while they were on regular treatment with a tumor necrosis factor inhibitor (TNFi) and/or methotrexate (MTX) for at least 1 year. One month after the third dose, 39% (26/66) of the patients and 79% (44/56) of the healthy controls had seroprotective NT levels. The relatively low SPR observed in the control group may be attributed to the fact that 37 and 35 of the patients and controls, respectively, were 60 years of age and older. Interestingly, the group of patients receiving a combined treatment (TNFi + MTX) had a significantly lower protection rate compared with healthy controls (36% vs 87%), while rates in patients treated with only a single medication did not differ from those seen in healthy controls. The significant difference in SPR remained even when an additional priming dose was given to all patients and healthy controls who were ≥60 years old: 31% (9/29) in the patient group compared with 81% (17/21) in the control group. In addition, this study demonstrated that in older patients (>60 years of age) immunosenescence apparently added to the treatment effects, leading to seroconversion rates of only around 30% after 4 doses of TBE vaccine in patients with combined immunosuppressive treatments.

The effect of TBE vaccination using an abbreviated

immunization schedule was also compared in 31 heart transplant recipients, under cyclosporine-based immunosuppression, and 29 controls.[82] Immune response (seroconversion rates [SCRs] and GMTs) were markedly reduced in the transplant recipients as compared with the control group. Even though the vaccine used in this study is no longer on the market (previous generation of Encepur, stabilized with polygeline), the findings are consistent with more recent investigations.

Public health considerations

While no formal vaccine efficacy study has been conducted with any TBE vaccine, effectiveness and pharmacoeconomic studies have been conducted, and the evidence for the public health impact of TBE immunization is indisputable. The most impressive example can be obtained from Austria, a country with a longstanding tradition of TBE immunization and reliable epidemiological data since the early 1970s. Since that time, vaccination coverage has increased steadily with currently 85% to 88% of the population having received at least 1 dose of TBE vaccine.[36] As a result, disease incidence dropped from approximately 700 to fewer than 100 cases per year, while in neighboring countries, with low vaccine coverage, the disease incidence has increased (see chapter on epidemiology).

As TBE disease was believed to be less severe in children, some countries had recommendations for adults only. More recent publications on severe disease courses and underestimation of long-term sequelae in children have led to adaptations of the vaccination recommendations for children in some countries. For instance, in Sweden, the age cut-off was reduced in 2012 from 7 years to 3 years of age and in 2013 from 3 years to 1 year of age.

In 2011, the WHO published a position paper on TBE vaccination33 recommending vaccination of all age groups in areas of high pre-vaccination disease incidence, defined as an incidence of ≥5/100,000 population per year, while in regions with lower incidence, vaccination recommendations should be confined to groups of the population exposed to a particular risk. Furthermore, the WHO also recommends vaccination of travelers planning outdoor activities in endemic areas during the active tick season.[84] In 2012, TBE became notifiable on the European level at the European Centre for Disease Prevention and Control (ECDC), which is a further, important step towards comprehensive and continuous assessment of the disease epidemiology across Europe.

Based on the newly arising vaccine effectiveness data it appears strategically correct to prolong the booster intervals up to 10 years after the 4th dose for certain parts of the population. This would partly align the booster intervals with those of other routinely administered vaccines, leading to a simplification of immunization schedules for the TBE vaccine, but also in general, with the goal of improving vaccine uptake and coverage. For immunocompromised individuals and those who received their primary immunization after the age of 60 years the currently licensed intervals should remain valid. Due to the fact that respective data for children are still missing, the current intervals should remain valid for the pediatric population as well. Moreover, as recent retrospective investigations provide some indications that the pediatric dose might be insufficient to confer long-lasting protection against severe disease.

Little information is published on the economic burden of TBE disease. Based on the finding that the Austrian TBE vaccination campaigns for the period 1981–1990 led to a reduction of more than 50% of clinical TBE cases, a benefit of €24 million was calculated versus the pre-vaccination era. Using a linear trend prognostic model for the further decline of TBE cases while vaccination coverage reached 85% by 2000, the author concluded that for the period 1991 to 2000, a total cost saving of €60 million can be estimated.[83] Epidemiological trends and progress in vaccination coverage have confirmed these assumptions.36 The majority of endemic countries in Europe, as well as Russia, have TBE vaccination recommendations in place, targeting primarily at-risk groups. More recently, recommendations for travelers to endemic regions were issued in many countries (see Chapter 12b).

More recently, in 2018, a cost/benefit analysis became available for Sweden. In the highly endemic area of Stockholm, where the number of cases is increasing despite the increased uptake of TBE vaccines, earlier studies showed that low-income households have lower vaccination coverage even when they are at high risk. The newly performed analysis showed again in cost per QALY (Quality-adjusted Life Years) of a free vaccinations program for the Stockholm County, especially for children of 3 years old, below generally acceptable cost-effectiveness thresholds in Sweden.[96]

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