Immunogenicity and safety of the tick-borne encephalitis vaccination (2009-2019): A systematic review

Rampa, John Ethan ; Askling, Helena Hervius ; Lang, Phung ; Zens, Kyra Denise ; Gültekin, Nejla ; Stanga, Zeno ; Schlagenhauf, Patricia

Abstract: BACKGROUND Tick-borne encephalitis (TBE) is increasing in Europe. We aimed to evaluate the immunogenicity and safety of TBE-vaccination. METHODS This systematic review was registered at PROSPERO (CRD42020155737) and conducted in accordance with PRISMA guidelines. We searched CINAHL, Cochrane, Embase, PubMed, and Scopus using specific terms. Original articles, case reports and research abstracts in English, French, German and Italian were included for screening and extracting (JER; PS). RESULTS Of a total of 2464 records, 49 original research publications were evaluated for immunogenicity and safety. TBE-vaccines showed adequate immunogenicity, good safety and interchangeability in adults and children with some differences in long-term protection (Seropositivity in 90.6-100% after primary vaccination; 84.9%-99.4% at 5 year follow up). Primary conventional vaccination schedule (days 0, 28, and 300) demonstrated the best immunogenic results (99-100% of seropositivity). Mixed brand primary vaccination presented adequate safety and immunogenicity with some exceptions. After booster follow-ups, accelerated conventional and rapid vaccination schedules were shown to be comparable in terms of immunogenicity and safety. First booster vaccinations five years after primary vaccination were protective in adults aged <50 years, leading to protective antibody levels from at least 5 years up to 10 years after booster vaccination. In older vaccinees, > 50 years, lower protective antibody titers were found. Allergic individuals showed an adequate response and immunosuppressed individuals a diminished response to TBE-vaccination. CONCLUSIONS The TBE-vaccination is generally safe with rare serious adverse events. Schedules should, if possible, use the same vaccine brand (non-mixed). TBE-vaccines are immunogenic in terms of antibody response but less so when vaccination is started after the age of 50 years. Age at priming is a key factor in the duration of protection.

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Review

Immunogenicity and safety of the tick-borne encephalitis vaccination (2009–2019): A systematic review

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ABSTRACT

Background: Tick-borne encephalitis (TBE) is increasing in Europe. We aimed to evaluate the immunogenicity and safety of TBE-vaccination.

Methods: This systematic review was registered at PROSPERO (#CRD42020155737) and conducted in accordance with PRISMA guidelines. We searched CINAHL, Cochrane, Embase, PubMed, and Scopus using specific terms. Original articles, case reports and research abstracts in English, French, German and Italian were included for screening and extracting (JER; PS).

Results: Of a total of 2464 records, 49 original research publications were evaluated for immunogenicity and safety. TBE-vaccines showed adequate immunogenicity, good safety and interchangeability in adults and children with some differences in long-term protection (Seropositivity in 90.6–100% after primary vaccination; 84.9%–99.4% at 5 year follow up). Primary conventional vaccination schedule (days 0, 28, and 300) demonstrated the best immunogenic results (99–100% of seropositivity). Mixed brand primary vaccination presented adequate safety and immunogenicity with some exceptions. After booster follow-ups, accelerated conventional and rapid vaccination schedules were shown to be comparable in terms of immunogenicity and safety. First booster vaccinations five years after primary vaccination were protective in adults aged <50 years, leading to protective antibody levels from at least 5 years up to 10 years after booster vaccination. In older vaccinees, > 50 years, lower protective antibody titers were found. Allergic individuals showed an adequate response and immunosuppressed individuals a diminished response to TBE-vaccination.

Conclusions: The TBE-vaccination is generally safe with rare serious adverse events. Schedules should, if possible, use the same vaccine brand (non-mixed). TBE-vaccines are immunogenic in terms of antibody response but less so when vaccination is started after the age of 50 years. Age at priming is a key factor in the duration of protection.

1. Introduction

Being endemic in 27 European countries with around 5’000–10’000 notified cases annually, tick-borne encephalitis (TBE) is one of the most important causes of viral encephalitis and the most frequent cause of viral meningitis in Europe [1–3]. TBE is geographically focused in Central and Eastern Europe, the Baltic States, the Russian Federation, and Japan, trending towards both an expansion of risk areas and an increase in incidence [2–7]. In Switzerland, incidence of TBE has increased significantly in the last few years, with more than 350 cases recorded in 2018 [8].

TBE is caused by the human pathogenic TBE virus, which is a member of the Flaviviridae family [3,4,9,10]. Three subtypes based on geographic origin and antigenic characteristics are of human importance: Far-Eastern, Siberian, and European [4,11]. Most European TBE cases are tick-transmitted by the ticks Ixodes ricinus with more than 100 species of wild and domestic animals acting as hosts reservoir [9,12,13]. Additionally, in certain areas TBE cases are transmitted from ingesting

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### 2. Aim

Using a systematic review, we aimed to evaluate safety and immunogenicity of TBE-vaccination.

### 3. Methods

We systematically reviewed original research papers addressing European TBE-vaccines’ immunogenicity and safety in accordance with PRISMA guidelines [28]. The systematic review was registered at PROSPERO: #CRD42020155737.

#### 3.1. Study eligibility and search strategy

To identify appropriate studies, the following international databases were systematically searched with specific search terms as shown in Appendix 1: CINAHL, Cochrane, Embase, PubMed, and Scopus. Inclusion criteria were papers in English, French, German or Italian language, published in the period from January 1st, 2009, to August 31st, 2019, and being original articles, case reports or research abstracts. A Cochrane systematic review, published in 2009, summarizes important earlier findings, therefore, we decided not to include studies published earlier than 2009 [17]. Exclusion criteria were papers in other languages than the above mentioned and animal studies.

#### 3.2. Data extraction

An evidence-table was created in Microsoft Word to extract the relevant data of original research (including population, intervention, control group, outcomes (PICO), study type, vaccines, laboratory analysis). To assess the methodological quality of the studies selected, we analyzed the strength of each study (original research and published abstracts) as displayed in Appendix 2.

#### 3.3. Statistical analysis

Results of immunogenicity and safety for the TBE vaccines were investigated by two researchers (JER, PS) to conclude evidence-based recommendations in a narrative form. Different available laboratory
Table 1
Evidence-table of original research investigation on TBE vaccine immunogenicity.

| Author, Year | Study Type | Original Study Title | Inv. Study Population | Vaccine(s) | Antibody methodology | Measure of seropositivity | Outcome: Immunogenicity |
|--------------|------------|----------------------|-----------------------|------------|----------------------|--------------------------|-------------------------|
| Rampa et al. | Booster co- study follow-up study | Booster vaccination against tick-borne encephalitis: 4 years follow-up indicates long-term protection | 935 adults (at 6 year follow-up) | Encepur® | Neutralisation Test titer <1:50 | 100% | In 94% and 89% of TBE vaccinated individuals aged below 50 and above 50 years, respectively, seropositivity was reported. Antibody levels were 4 fold lower in subjects above 60 years of age indicating a shorter period of protection against TBE. |
| Pierce et al. | Open-label, multicenter, booster co-host study | Long-term persistence of tick-borne encephalitis antibodies in adults 5 years after booster vaccination with Encepur® Adults | 172 adults (at 5 year follow-up) | Encepur® | Neutralisation Test titer ≥1:10 | 80% | Seropositivity was found in 99% at 5 year follow-up after first booster dose (fourth dose) of Encepur® leads to protective antibody levels for up to 5 years. |
| Winnny et al. | Break-through infection analysis | Characteristics of antibody response against tick-borne encephalitis vaccination breakthrough | 25 TBE vaccine failures | N/A | ELISA | Neutralisation Test | Good antibody response will not necessarily prevent the disease in TBE vaccinated people. Discussing, the levels of neutralizing antibodies are too low in the vaccine breakthrough, that supporting neutralizing antibodies to be the best surrogate for protection. |
| Sheld et al. | Retrospective cohort study | Serological response to tick-borne encephalitis (TBE) vaccine in the elderly - results from an observational study | 181 adults (aged ≥60 years) | FSME-Imm-Plus® | ELISA | Neutralisation Test titer ≥1:80 | Only 8% (39/152) of individuals receiving dose 2 dose TBE vaccine showed seropositivity. Therefore 18% of vaccines would have not been protected during the primary vaccination schedule. A difference of seropositivity rate reported in the two used vaccines: individuals receiving FSME-Imm-Plus® presented seropositivity in 92% (n=108/119), whereas in individuals vaccinated with Encepur® seropositivity of 88% (n=94/106) was found. |
| Nowe et al. | Open-label, phase IV, multicenter, follow-up study | Seroprevalence of tick-borne encephalitis antibodies, safety and booster response to FSME-immun® 0.5 ml in adults aged 18-67 years | 328 adults (at 3 year follow-up) | FSME-Imm-Plus® | ELISA | Neutralisation Test titer ≥1:80 | Seropositivity of the two vaccines (FSME-Imm® and Encepur®) was demonstrated by vaccination individuals with two doses of FSME-Imm® followed by either another dose of FSME-Imm® or Encepur®. This approach led to adequate antibody levels and adequate immune responses after following booster vaccination with FSME-Imm® (seropositivity rate regardless of primary vaccine vaccination: 100%). |
| Willemsen, Meil et al. | Open-label, phase IV, multicenter, booster co-host study | Long-term persistence of tick-borne encephalitis antibodies in children 5 years after first booster vaccination with Encepur® Children | 280 children (at 5 year follow-up) | Encepur® Children | Neutralisation Test titer ≥1:10 | 97% | Seropositivity at 5 year post booster in children was demonstrated to be 100% suggesting a booster interval up to 5 years in children vaccinated with Encepur® Children. |

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Table 2

| Author, Year | Study Type | Original Study Title | Inv. Study Population | Vaccine(s) | Antibody methodology | Measure of seropositivity | Outcome: Immunogenicity |
|--------------|------------|----------------------|-----------------------|------------|----------------------|--------------------------|-------------------------|
| Altman et al. | Randomised, controlled, single blind study | Antibody response following an immunisation of two paediatric tick-borne encephalitis vaccines using two different vaccination schedules | 544 children (aged 10 years) | Encepur® Children | Neutralisation Test titer ≥1:20 | 99% | A higher proportion of children achieved seropositivity following conventional primary vaccination schedule (3 dose Encepur®, 100%; 2 dose FSME-Imm® Junior and 1 dose Encepur®, 99%) compared to accelerated schedule (3 doses Encepur®, 100%; 2 doses FSME-Imm® Junior and 1 dose Encepur®, 99%). Results demonstrated that a primary vaccination course initiated with FSME-Imm® Junior can be completed with Encepur® Children and shows a high immunogenicity. |
| Anderson et al. | Retrospective data analysis of a Swedish cohort | Vaccine failure after active immunisation against tick-borne encephalitis | 27 TBE vaccine failures | FSME-Imm-Plus® | ELISA | Neutralisation Test titer ≥1:80 | Although vaccine failures were reported in age groups, highest incidence of vaccine failures were in individuals aged above 30 years (90% = 30/33) |
| Milhauer, Fisch et al. | Randomised, double-blind, multi-center, phase II, dose finding study | Clinical evaluation to determine the appropriate paediatric formulation of a tick-borne encephalitis vaccine | 3847 children (aged 1 year) | FSME-Imm® | ELISA | Neutralisation Test titer ≥1:26 | Investigation of 1440 children for immunogenicity demonstrated highest protective antibody response in groups with vaccine doses of 0.6 and 1.8 µg. Results demonstrate high immunogenicity in individuals aged 1-15 years. Out of 150 children vaccinated with dose of 1.8 µg (including 304 children aged 1-5 years and 208 children aged 6-15 years randomly assigned to the dose), seropositivity was reported to be 100%. |
| Milhauer, Peinova et al. | Randomised, single-blind, multi-center, phase II, comparison study | Comparison of immunogenicity and safety between two paediatric TBE vaccines | 303 children (aged 1-11 years) | FSME-Imm® Junior Encepur® Children | Neutralisation Test titer ≥1:50 | 100% | Reported data demonstrated high immunogenicity in both vaccines (FSME-Imm® Junior and Encepur® Children, Seropositivity after two dose administration was 100% and 97.8% for FSME-Imm® Junior and Encepur® Children, respectively. |
| Weiser et al. | Prospective controlled study | Decreased antibody titers and booster response in tick-borne encephalitis vaccines aged 50-90 years | 28 adults (aged 50-90 years) | FSME-Imm® | ELISA | Neutralisation Test titer ≥1:10 | Antibody concentrations of all titers were reported to be significantly lower in the older study population compared to younger populations. Close to equal low titer results were reported in the age group 50-70 compared to the age group >70 years. A booster vaccination around 5-7 years after last vaccine administration induced adequate antibody production even in the elderly. |
| Author, Year | doi or URL | Study Type | Original Study Title | Funding & Sourcing | inv or Study Population | Vaccine(s) | Antibody methodology | Measure of seropositivity | Outcome: Immunogenicity |
|--------------|------------|------------|----------------------|-------------------|--------------------------|------------|----------------------|--------------------------|--------------------------|
| J.E. Rampa et al. (2020) | 10.1016/j.triplep.2020.01.010 | open-label, follow-up study | Travel medicine and infectious disease | Funding & Sourcing: N/A | 67 adults | FSME-im-mur* Junior | Neutralization Test | 100% | Neuraminidase 100% |
| Dringer et al. (2011) | 10.3851/SV.2011.11.061 | cross-protection study | Protection of immunity in tick-borne encephalitis vaccine recipients | Funding & Sourcing: Baxter, France | 126 adults | FSME-im-mur* | ELISA | 95% | Serum positivity 95% |
| Aking et al. (2012) | 10.1016/j.triplep.2012.08.008 | open-label, booster vaccine study | Vaccine protection in children 1-11 years of age | Funding & Sourcing: Baxter | 286 children | FSME-im-mur* Junior | Neutralization Test | 100% | Neuraminidase 100% |
| Burtner et al. (2015) | 10.1046/jemmun.1302253 | age- and gender-matched immunogenicity cohort study | TBE vaccination in children | Funding & Sourcing: Baxter | 67 adults | FSME-im-mur* | Neutralization Test | 95% | Serum positivity 95% |
| Herz et al. (2013) | 10.1023/med19101.110458 | vaccination coverage and TBE incidence study | Protection of immunity in children | Funding & Sourcing: Baxter | 98 cases | FSME-im-mur* Junior | Neutralization Test | 100% | Serum positivity 100% |
| Fazekas-Koreva et al. (2012) | 10.1038/b-and-c.2013.1679 | booster follow-up study | FSME vaccination in children | Funding & Sourcing: Baxter | 583 adults | FSME-im-mur* | Neutralization Test | 95% | Serum positivity 95% |
| Becker et al. (2014) | 10.1016/j.triplep.2014.08.028 | open-label, single-centre, follow-up study | FSME vaccination in children | Funding & Sourcing: Baxter | 329 adults | FSME-im-mur* | Neutralization Test | 95% | Serum positivity 95% |
| Lottiaux et al. (2014) | 10.1371/journal.pone.0008410 | longitudinal study | FSME vaccination in children | Funding & Sourcing: Baxter | 62 and adults | FSME-im-mur* | Neutralization Test | 95% | Serum positivity 95% |
| Author, Year | Study Type | Original Study Title | Inv. Study Funding & Sourcing | Vaccine(s) | Antibody methodology Measure of seropositivity | Outcome: Immunoegenic? |
|--------------|------------|----------------------|-----------------------------|-----------|-----------------------------------------------|----------------------|
| Schierer et al. (56) 2014 | Open-label, multi-centre, booster catch-up study | Impact of tick-borne encephalitis vaccination schedules: The effect of a single catch-up vaccination with FMDV-imum* | Funding & sourcing: Baxter | FMDV-imum* | ELISA | IgG demonstrated the most important factor for long term immunogenicity being the number of previous vaccine doses regardless of time intervals between dose administration. Authors reported negative antibody titers in 4% of children after one year. Vaccine received two doses of any vaccine series to be equal had the previous vaccinations been given according to a regular schedule (every seven years) |
| Schierer et al. (48) 2014 | Swiss surveillance study | Epidemiology of tick-borne encephalitis in Switzerland, 2003 to 2011 | Funding & sourcing: N/A | FMDV-imum* | Confirmed the disease through IgG serum antibodies, IgM serum antibodies were not found. A high rate of IgG serum antibodies in period sera specimens, + TBEV genome amplification | Out of 82 TBE cases with known immunisation history, 65 individuals presented a history of at least one dose of TBE vaccine. In 28 of them a complete three-dose primary vaccination history was documented, while 13 patients received the last dose less than three years and five patients more than five years before onset of the infection. Authors were not able to calculate the rate of these TBEV-vaccine breakthroughs as they were all cases of received vaccine failures, as coverage of vaccinated people in Switzerland is not monitored. |
| Kemml et al. (42) 2013 | Controlled immunogenicity cohort study | Anti-tick-borne encephalitis (TBE) virus neutralizing antibodies dynamics in natural infections versus vaccination | Funding & sourcing: N/A | FMDV-imum* | ELISA and Neutralization test titers | In comparison to individuals which received complete three dose primary vaccination schedule, natural infected participants did not demonstrate an age-dependent decrease of neutralizing antibody levels. |
| Allermann et al. (56) 2013 | Open-label, phase IV, follow-up vaccination study | Five year follow-up after primary vaccination against tick-borne encephalitis in children | Funding & sourcing: N/A | FMDV-imum* | Neutralisation Test titers | Results demonstrated high antibody levels (131%) being converted (n=51) and accelerated (n=40) three dose primary vaccination schedule with FMDV-imum* for up to 5 years (vaccine positivity of 94-99%). Therefore, authors recommended first booster dose (fourth dose) in children vaccinated with FMDV-imum* may be extended up to 5 years. Children receiving a mixed primary immunisation series (FMDV-imum* + 3 S/4/5 (Chile)) did not present a faster decrease of antibody levels with 65-75% seropositivity at three years follow-up. |
| Ariansen et al. (57) 2015 | Open-label, uncontrolled, booster cohort study | Analysis of delayed TBE vaccine response after primary vaccination | Funding & sourcing: ViroScience GmbH Robert Koch-Institute | FMDV-imum* | Neutralisation Test titers | Results demonstrated in 10 individuals (group 2) with primary vaccination history being 3-8 years ago, seropositivity in 53% and 97% for pre-booster test and post-booster test, respectively. In 69 patients (group 2) with primary vaccination history being 3-8 years (range, eight to 27 years) aged 12-43, 54% and 85.6% showed pre- and post-booster seronegativity. Authors conclude that after 4 years after primary vaccination one booster dose of FMDV-imum* leads to protective antibody levels. |

| Author, Year | Study Type | Original Study Title | Inv. Study Funding & Sourcing | Vaccine(s) | Antibody methodology Measure of seropositivity | Outcome: Immunoegenic? |
|--------------|------------|----------------------|-----------------------------|-----------|-----------------------------------------------|----------------------|
| Bellowsky et al. (32) 2015 | Controlled study of pediatric TBE vaccine's immunogenicity | Analysis of the immunogenicity of two pediatric tick-borne encephalitis virus vaccines | Funding & sourcing: Baxter Pfizer Inc. | FMDV-imum* | Neutralisation Test titers | Both FMDV-imum* and Enervac* children presented adequate protective antibody levels towards the TBE virus strain K32 and N3.2 |
| Harth et al. (54) 2014 | Prospective, controlled, immunomodulatory phase II study | Recombinant human tumour necrosis factor aligned to tumor necrosis factor | Funding & sourcing: N/A | FMDV-imum* | Neutralisation Test titers of 100% (50% effective dose) | Seropositivity of 39% (95% CI: 24.8-51.2) was reported in the Immunomodulated group, compared to 79% (n=4/81) in the healthy control group 13 months after three dose primary vaccination schedule (n=90 weeks) and four dose primary vaccination (n=90 weeks). Authors conclude that immunomodulated individuals must be carefully informed of their low immunogenicity risk and should receive at least one extra dose of TBE vaccination regardless of age. |
| Ito et al. (33) 2018 | Observational cohort study | Comparison immune responsiveness but increased reactogenicity after subcutaneous versus intramuscular administration of tick-borne encephalitis (TBE) vaccine | Funding & sourcing: Pfizer Vaccine | FMDV-imum* | Neutralisation Test | Both intramuscular (51%) and subcutaneous (46%) TBE vaccine administration presented adequate immune response in both genders for booster vaccination. No statement can be done about administration route efficacy in primary vaccination as participants have had a vaccination history. |
| Author(s) | Year | Study Type | Original Study Title | Funding & Sourcing | Inv. Study Population | Vaccine(s) | Antibody methodology | Measure of seropositivity | Outcome: Immunogenicity |
|----------|------|------------|----------------------|-------------------|----------------------|------------|----------------------|--------------------------|--------------------------|
| Almeida et al. | 2017 | prospective, follow-up cohort study | Travel Medicine and Infectious Disease 37 (2020) 101876 | Travel Medicine and Infectious Disease 37 (2020) 101876 | J.E. Rampa et al. | Travel Medicine and Infectious Disease 37 (2020) 101876 | J.E. Rampa et al. | Travel Medicine and Infectious Disease 37 (2020) 101876 | J.E. Rampa et al. | Travel Medicine and Infectious Disease 37 (2020) 101876 |
| J.E. Rampa et al. | 2017 | retrospective & gender-matched comparison study | Tick-borne encephalitis in patients vaccinated for the disease | Funding & sourcing: - Finnish Travel Health Service - Tick-borne encephalitis vaccine (TBEV) | 153 adults (aged 21-70 years) | TBE vacccine failures (TBEV) | Conformation of the disease through IgG and IgM seroconversion in intracutaneous antibodies | Travel Medicine and Infectious Disease 37 (2020) 101876 | J.E. Rampa et al. | Travel Medicine and Infectious Disease 37 (2020) 101876 |
| Devor et al. | 2018 | immunogenicity cross-sectional study | Effectiveness of primary vaccination against tick-borne encephalitis in employees of the armed forces | Funding & sourcing: - Israeli Research Agency - Vaccine grants | 151 adults (aged 22-49 years) | TBEV | Conformation of the disease through IgG and IgM seroconversion in intracutaneous antibodies | Travel Medicine and Infectious Disease 37 (2020) 101876 | J.E. Rampa et al. | Travel Medicine and Infectious Disease 37 (2020) 101876 |
| Goren-Sigal et al. | 2019 | open-label, phase IIa, controlled cohort study | Tick-borne encephalitis vaccine failures following different primary vaccination schedules demonstrated at 10 years after vaccination | Funding & sourcing: - Israeli Research Agency - Vaccine grants | 21 patients with specific immunotherapy | 49 patients (21 patients with specific immunotherapy) | Conformation of the disease through IgG and IgM seroconversion in intracutaneous antibodies | Travel Medicine and Infectious Disease 37 (2020) 101876 | J.E. Rampa et al. | Travel Medicine and Infectious Disease 37 (2020) 101876 |

| Author(s) | Year | Study Type | Original Study Title | Funding & Sourcing | Inv. Study Population | Vaccine(s) | Antibody methodology | Measure of seropositivity | Outcome: Immunogenicity |
|----------|------|------------|----------------------|-------------------|----------------------|------------|----------------------|--------------------------|--------------------------|
| Benvenuti et al. | 2020 | open-label, phase IIa, follow-up cohort study | Second five-year follow-up after a booster vaccination against tick-borne encephalitis vaccine | Funding & sourcing: - Italian Research Agency - Vaccine grants | 206 individuals | Doseup* | Conformation of the disease through IgG and IgM seroconversion in intracutaneous antibodies | Travel Medicine and Infectious Disease 37 (2020) 101876 | J.E. Rampa et al. | Travel Medicine and Infectious Disease 37 (2020) 101876 |
| Hassan et al. | 2019 | retrospective data analysis of region | Tick-borne encephalitis vaccine failures following the rationale for adding or removing dose in individuals starting at age 50 years | Funding & sourcing: - Italian Research Agency - Vaccine grants | 51 vaccine failures | unspecified | Conformation of the disease through TBE specific IgM and IgG in sera or specific IgM in cerebrospinal fluid, seroconversion in paired sera over time, or detection of TBE RNA in a clinical specimen | Travel Medicine and Infectious Disease 37 (2020) 101876 | J.E. Rampa et al. | Travel Medicine and Infectious Disease 37 (2020) 101876 |

* Representative data from a study with a specific focus on tick-borne encephalitis vaccine failures following different primary vaccination schedules demonstrated at 10 years after vaccination.
tests are used to quantify a vaccine’s immunogenicity but this leads to difficulties in comparing study results. Therefore, in this systematic review a study’s laboratory test methodology is elaborated in Table 1 and Table 2. If available, the results acquired by an NT were used for interpretation.

4. Results

After removing duplicates and screening, 55 papers were selected for full-text assessment from the investigated databases. Three additional publications were identified for full-text assessment through checking the included papers’ reference lists. Title-, abstract-, and full-text screening was conducted by two researchers (JER, PS). Of the 58 full-text assessed papers, 49 publications (40 pieces of original articles, five research abstracts of poster/oral sessions, three case reports and one case series) were investigated for immunogenicity and safety. Of the 40 original abstracts 26 showed external funding and/or sourcing, 17 excluded for qualitative analysis after full-text assessment and were used for background information if relevant: Three systematic reviews were published original articles were included into two comprehensive tables including 20 with connections to vaccine companies. Relevant data of 37 investigated original articles reported immunogenicity data. Fully vaccinated individuals regardless of the route of vaccination or delays in booster intervals were found to have an adequate immune response [18,38,4]. More severe illness, occurring more often in elderly individuals aged ≥50 years but failures also occurred in younger individuals [2,45]. Further, individuals ≥60 years with an extra priming dose reported no TBE-vaccine failure [2].

The elderly have lower antibody levels with a diminishing immune response starting in individuals aged ≥60 years and even in individuals aged ≥50 years [9,22,44]. Most investigated vaccine failures occurred in individuals aged ≥50 years but failures also occurred in younger individuals [2,45]. Further, individuals ≥60 years with an extra priming dose reported no TBE-vaccine failure [2].

In children, aged 1–15 years, the vaccine formulas of Encepur® and FSME-Immun® Junior lead to high immunogenicity after primary vaccination of 95.6% up to 100% and high long-term seropositivity up to 5 years after primary vaccination [16,19,36,46–48]. There seems to be no age-related differences in the avidity and functional activity of antibodies induced by vaccination [2,49].

4.1. Booster-interval

In children, long term seropositivity for vaccine Encepur® Children and FSME-Immun® Junior were reported for up to 5 years, or 10 years, respectively after primary vaccination [38,50]. In adults both primary vaccination with Encepur® or FSME-Immun® lead to high long term seropositivity (77.3%–94% at ten year follow-up; 91.8% at a median of 15 year of follow-up) [10,22,44,51,52]. However, age groups >60 years showed a faster decline in seropositivity levels [38,44,53].

4.1.2. Interchangeability of TBE vaccines

For both adults and children TBE vaccines can be largely interchanged for primary and booster vaccination [18,37,38,46]. However, one study demonstrated a faster decrease in seropositivity in children receiving a mixed primary vaccination schedule (two doses of FSME-Immun® Junior followed by one dose Encepur® Children) [16].

4.1.3. Special groups

Seropositivity was found to be lower in 66 immunosuppressed patients compared to healthy individuals at 13 months follow-up after primary vaccination schedule [54]. In 17 thymectomized patients no significant differences in antibody levels compared to healthy controls was presented [55]. We found no papers on TBE vaccination in pregnant women. Allergic individuals with or without specific immunotherapy showed adequate immunogenicity [56]. Furthermore, Hepatitis-B vaccine failure showed no correlation to TBE-vaccine failure, as patients with Hepatitis-B vaccine failure were able to gain adequate TBE-vaccine immunogenicity [1]. We found no gender specific data on immunogenicity.
Table 2
Evidence-table of original research investigation on TBE vaccine safety.

| Author, Year doi: | Study Type | Original Study Title | Vaccine(s) | Antibody methodology | Measure of seropositivity | Outcome: Safety |
|-------------------|------------|----------------------|------------|----------------------|--------------------------|----------------|
| Loew-Baselli et al. [38] 2009 [10.4161/hv.5.8.18571] | open label, phase IV, multi-center, follow-up study | Seropersistence of tick-borne encephalitis antibodies, safety and booster response to FSME-Immun® 0.5 ml in adults aged 18-67 years | FSME-Immun® | Neutralization Test titers | ≥1:10 | Safety assessed in 328 individuals |
| Wittermann, Schindorf et al. [46] 2009 https://doi.org/10.1016/j.vaccine.2008.10.003 | randomized, controlled, single blind study | Antibody response following administration of two paediatric tick-borne encephalitis vaccines using two different vaccination schedules | Encepur® Children, FSME-Immun® Junior | Neutralization Test titers | ≥1:10 | 334 children assessed for safety |
| Pollabauer, Fritsch et al. [47] 2010 https://doi.org/10.1016/j.vaccine.2010.04.075 | randomized, double-blind, multi-center dose finding study | Clinical evaluation to determine the appropriate paediatric formulation of a tick-borne encephalitis vaccine | FSME-Immun® | ELISA | >126 VIEU/ml | Safety analysis in 2417 children |
| Pollabauer, Pavlova et al. [19] 2010 https://doi.org/10.1016/j.vaccine.2010.04.047 | randomized, single blind, multi center, phase III comparison study | Comparison of immunogenicity and safety between two paediatric TBE vaccines | FSME-Immun® Junior, Encepur® Children | Neutralization Test titers | ≥1:10 | Safety assessed in 302 individuals |
| Schumacher et al. [59] 2010 https://doi.org/10.1016/j.vaccine.2010.04.002 | retrospective data analysis of Swiss data bases | Surveillance for adverse events following immunization (AEFI) in Switzerland-1991-2001 | unspecified | N/A | | 73 reported TBE-vaccine adverse events between 1991 – 2001 were investigated |

(continued on next page)
Table 2 (continued)

| Author, Year doi: | Study Type | Original Study Title | Vaccine(s) | Antibody methodology | Outcome: |
|-------------------|------------|----------------------|------------|----------------------|---------|
| Madar et al. [82] 2011 | retrospective data analysis of diabetic patients | Vaccination of patients with diabetes mellitus – a retrospective study | FSME-Immun® Encepur® | N/A | TBE-vaccination was performed using Encepur® (n=6) and FSME-Immun® (n=223) without increasing the risk of serious adverse events. |
| Askling et al. [37] 2012 | open-label, booster vaccine study | Immunogenicity of delayed TBE-vaccine booster | FSME-Immun® | Neutralization Test titers of ED50 (50% effective dose) ≥5 | Total of 260 individuals assessed for safety. AE at injection site pain: n=22/260 (8.5%), mild AE: n=25/260 (10%), serious adverse events: n=0/260 (0%). |
| Prymula et al. [18] 2012 | randomized, single blind, multi center, phase III protectivity study | Antibody persistence after two vaccinations with either FSME-IMMUN® Junior or ENCEPUR® | FSME-Immun® Junior Encepur® Children® | Neutralization Test titers ≥1:10 | 298 children were assessed for adverse events (106 systemic reactions, 11.1% fever 4.0%, 0.0% local reactions, 2.0% serious adverse events). |
| Paulke-Korinek et al. [22] 2013 | booster follow-up study | Factors associated with seroimmunity against tick borne encephalitis virus 10 years after booster vaccination | FSME-Immun® | Neutralization Test titers ≥1:10 | In adults suffering of allergies (including atopy and anaphylactic allergies) significant higher antibody levels were found compared to individuals without allergy. |
| Beran et al. [40] 2014 | open-label, single centre, follow-up study | Five-year follow-up after a first booster vaccination against tick-borne encephalitis following different primary vaccination schedules demonstrates long-term antibody persistence and safety | Encepur® | Neutralization Test titers ≥1:10 | 278 adults were analyzed for adverse events. Pain 55%, swelling 6%, erythema 8%, myalgia 17%, malaise 7%, headache 14%, nausea 4%, arthralgia 5%, fever 1%, serious adverse events 1.1%. |
| Aerssens et al. [57] 2016 | open-label, uncontrolled, booster cohort study | Analysis of delayed TBE-vaccine booster after primary vaccination | FSME-Immun® | Neutralization Test titers ≥1:10 | Total of 88 individuals were analyzed for safety. Total adverse events n=7/88 (8%), mild adverse events n=22/88 (2.3%), Systemic reactions n=5/88 (5.7%), fever and/or malaise n=3/88 (2.3%). |
| Hertzel et al. [54] 2016 | prospective, controlled, immunosuppressive immunogenicity study | Tick-borne encephalitis (TBE) vaccine to medically immunosuppressed patients with rheumatoid arthritis: A prospective, open label multi-centre study | FSME-Immun® Encepur® | Neutralization Test titers of ED50 (50% effective dose) ≥5 | Safety investigation included 122 individuals. One immunosuppressed individual suffered of gastroenteritis two days after first dose vaccination. There were no Serious adverse drug reactions reported. |
| Hopf et al. [35] 2016 | non-randomized, controlled, administration route study | Comparable immune responsiveness but increased reactogenicity after subcutaneous versus intramuscular administration of tick-borne encephalitis (TBE) vaccine | FSME-Immun® | Neutralization Test titers | 116 adults were assessed for safety analysis local reactogenicity (SC / IM) n=54/58 (93.2%) / n=26/58 (50%), local pain (SC / IM) n=44/58 (75.9%) / n=26/58 (44.8%), fever (SC / IM) n=0/58 (0%) / n=2/58 (3.4%). |

(continued on next page)
| Author, Year doi: | Study Type | Original Study Title | Vaccine(s) | Antibody methodology Measure of seropositivity | Outcome: Safety |
|------------------|------------|----------------------|------------|-----------------------------------------------|----------------|
| Oberle et al. [69] 2016 doi: 10.1097/INF.0000000001073 | retrospective analysis of German pediatric database ESPED\(^1\) | Anaphylaxis after immunization of children and adolescents in Germany Funding & sourcing: N/A | 1 unspecified 1 strain K23 (probably Encepur®) | N/A | systemic reactions (SC / IM) n=20/58 (34.5%) / n=24/58 (41.4%) SAE n=0/116 (0%) 2 of 22 post-immunization anaphylactic incidences in Germany between June 01, 2008 and May 31, 2010 occurred after TBE-vaccination. Based on 3’125.546 administered doses of TBE vaccine in Germany, the incidence was calculated at 0.69 (0.67 – 1.2) [1.0 (0.99 – 1.4)] (Point Estimate and 95% confidence interval) per million TBE doses administered.\(^{14}\) |
| Konior et al. [53] 2017 https://doi.org/10.1016/j.vaccine.2017.03.059 | prospective, follow-up cohort study | Seropersistence of TBE virus antibodies 10 years after first booster vaccination and response to a second booster vaccination with FSME-IMMUN 0.5 mL in adults Funding & sourcing: Pfizer | FSME-Immum® Neutralization Test titers ≥1:10 | 47 individuals were assessed for Safety data mild adverse events: (fatigue, injection pain, malaise) Serious adverse events: n=0/47 (0%) |
| Garner-Spitzer et al. [56] 2018 https://doi.org/10.1016/j.vaccine.2018.03.076 | open-label, phase IV, controlled cohort study | Allergic patients with and without allergen-specific immunotherapy mount protective immune responses to tick-borne encephalitis vaccination in absence of enhanced side effects or propagation of their Th2 bias Funding & sourcing: Pfizer, UCB Pharma, MSD, Baxter, Sanofi | FSME-Immum® Neutralization Test titers ≥1:10 | 119 individuals (70 allergic, 49 controls) were investigated for safety data. There was found no risk increase for exacerbations and for difference in adverse events rate of the allergic groups in comparison to the non-allergic group.\(^{15}\) local reactions: n (%) allergic no SIT\(^{13}\) group males: 22/49 (50%) females: 0/19 (0%) | |
| Pollabauer et al. [21] 2019 https://doi.org/10.1016/j.vaccine.2019.03.032 | prospective, open-label, phase IV, follow-up cohort study | Seropersistence and booster response following vaccination with FSME-Immum in children, adolescents, and young adults Funding & sourcing: Pfizer | FSME-Immum® Junior Neutralization Test titers ≥1:10 | 119 individuals (70 allergic, 49 controls) were investigated for safety data. There was found no risk increase for exacerbations and for difference in adverse events rate of the allergic groups in comparison to the non-allergic group.\(^{15}\) local reactions: n (%) allergic no SIT\(^{13}\) group males: 22/49 (50%) females: 0/19 (0%) allergic + SIT\(^{13}\) group males: 12/21 (57.1%) females: 5/9 (56%) control group males: 27/49 (55.1%) females: 6/19 (32%) systemic reactions: n (%) allergic groups 31/70 (44.3%) control group 23/49 (46.9%) In 231 children assessed for adverse events, no vaccine-related serious adverse events or deaths were reported. |

\(^{1}\) Digital Object Identifier; \(^{2} \) SAE = Serious adverse events; LR = Local reactions; SR = Systemic reactions; Systemic reactions were considered not to be related to the vaccination; \(^{3} \) E.C. = Encepur® Children; F-I.J. = FSME-Immum® Junior; \(^{4} \) Dose-finding study of FSME-Immum® Junior; \(^{5} \) Fever at 2nd dose only reported being much lower than 1st dose. Fever showed age dependency; \(^{6} \) FSME-I.J. = FSME-Immum® Junior; Ence. C. = Encepur® Children; SAE = Serious adverse events; Both vaccines present well tolerance in children 1–11 years of age. A significant lower rate of injection site reaction was reported after vaccination with FSME-Immun® Junior compared to Encepur® Children. Close to equal were both vaccines in terms of systemic reactions and fever. Fever was reported more often in children aged 1–2 years compared to other age groups and injection site reaction was showing lowest rate in this age group; \(^{7} \) based on all reports received by the Swiss Federal Office of Public Health or the National Drug Pharmacovigilance Center (“Schweizerische Arzneimittel- benurkungszentrale”);\(^{8} \) In a passive reporting system, such as the ones investigated, milder events tend to be reported at a lower rate making numbers of SAE overrepresented. Incidence of serious adverse events reported to be 2.3 (95%CI: 1.4–3.5) per 100’000 distributed TBE-vaccine doses. Incidence of any adverse drug reactions for any kind of vaccine was described to be 2.7 per 100’000 distributed vaccine doses; \(^{9} \) AE = adverse events; SAE = serious adverse events; \(^{10} \) 298 children assessed for adverse events within seven days of third vaccination dose. No statistically significant differences between Encepur® Children and FSME-Immum® Junior for first and second vaccination reported; \(^{11} \) SAE = serious adverse events; SAE were considered unrelated to the study vaccine by the authors and happened during the long follow-up time. Elective surgeries were not considered as SAE. During the study period four deaths occurred (two grade IV glioblastomas, one myocardial infarction and one suicide). As the suicide did not receive intervention it was not included into the safety analysis, therefore, only three deaths are included into SAE; \(^{12} \) SC = subcutaneous; IM = Intramuscularly; SAE = serious adverse events; There was a significant lower local adverse event rate of redness, swelling and local pain in the intramuscular route compared to the subcutaneous; \(^{13} \) ESPEED – Erhebungseinheit für seltene pädiatrische Erkrankungen in Deutschland (German pediatric surveillance unit); \(^{14} \) Half the anaphylaxis cases following unspecified vaccinations occurred after the first dose. Authors conclude that either another component in the vaccine was the origin of the anaphylaxis or another molecular pathway without need of sensitization started the anaphylaxis; \(^{15} \) SIT = specific immunotherapy; In the group with specific immunotherapy females showed an equal frequency on adverse events compared to males, whereas females in the group without specific immunotherapy and in the healthy control group showed higher adverse events rate than men in the same groups. |
4.2. Safety (Table 2)

17 original articles reported safety data. Local reactions/mild adverse events such as pain at the injection site, tenderness or local swelling were described in 24.8% (4.3–54%) of study participants [18, 19, 35–37, 38–40, 46, 53–56, 57]. Systemic reactions were reported in about 30% (0.6–45.9%) of vaccinees [18, 35, 38, 40, 46, 47]. Fever was reported in 3.4% (0–9.7%) of vaccinees [18, 19, 35–37, 38, 40, 46, 47]. Systemic reactions were reported to be lower after the 2nd dose compared to the first dose administration [19]. Higher rates of local and systemic reactions were reported in 7–11 year old children compared to 1–2 and 3–6 year old age groups [18]. In adults, no age pattern of adverse events was found. Furthermore, the application route led to differences in adverse event reporting: A significantly lower local adverse event rate of redness, swelling and local pain in the intramuscular administration group compared to the subcutaneous group was reported. Systemic reactions were reported to be increased in the intramuscular group, however, this was not statistically significant [35].

Ten studies in our analysis comprising 4455 vaccinees reported no serious adverse events (SAE) [18, 19, 21, 35, 37, 38, 46, 47, 53, 54]. Three studies described SAE: One Encepur® booster five-year follow-up study reported an incidence rate of 5% in 278 adults. These SAE were considered by the authors to be “life events” during the long follow-up and not related to the vaccination (including two grade IV glioblastomas and one myocardial infarction), the possibility of an etiologic link was suggested by Strojnik in 2017 describing neurotropic viral genome in glioblastoma cells [40, 58]. The second study reporting SAE was a surveillance study in a passive Swiss reporting system and it described 19 SAE after unspecified TBE-vaccine administration, leading to a calculation of an incidence rate of 2.3 SAE in 100’000 distributed doses of vaccine [59]. The third publication, a retrospective analysis of a German pediatric surveillance database, presented two cases of anaphylactic shocks after TBE vaccination (one unspecified vaccine, one based on K23 – probably Encepur®). Based on TBE vaccines...
administration numbers in Germany, the incidence was calculated at 0.69 (0.67–1.2) [1.0 (0.99–1.4)] (Point Estimate and 95% confidence interval) per million TBE-doses administered [60].

Based on the data it wasn’t possible to identify sex patterns of adverse events. Although one paper showed adverse events to be reported at a higher rate in healthy females and in allergic females without specific immunotherapy compared to healthy men and allergic men without specific immunotherapy [56]. Further data about safety is displayed in Table 2.

4.3. Research abstracts and case reports/series

4.3.1. Immunogenicity and safety data

Four research abstracts of poster-/oral sessions and one case series reported data on immunogenicity in thymectomized children (presented in 2009) or juvenile idiopathic arthritis (JIA) patients (presented in 2015) [61,62]. An adequate response was achieved in these groups after full vaccination. In a cohort study of 33 adults a lower antibody response was found in individuals aged 60–80 years compared to age group 21–31 years (presented in 2012) [63]. Another controlled cohort study demonstrated an adequate protective antibody level after primary TBE vaccination in elderly [64]. One case-series described four reported vaccine failures; one patient was deemed not to be a vaccine failure case (no second booster vaccination), two individuals to be probable vaccine failures and one case to be a confirmed vaccine failure [24].

Three case reports and one case series reported safety data. Jiménez et al. described the use of a statistical measure, the Information Compound (IC) measure of association. An IC score of 3.0 was found for TBE vaccines suggesting a statistical association between TBE vaccine and facial paralysis, compared to an IC score of 3.1 for a H1N1 influenza pandemic vaccine, an IC score of 3.0 for a hepatitis b/a vaccine or an IC score of 2.3 for a yellow fever vaccine [65]. Another case report described the reactivation of immune thrombocytopenic purpura by a TBE vaccination (FSME-Immun®) with subsequent recovery [66]. A 3-case series investigated excessive daytime sleepiness and narcolepsy-cataplexy starting a few weeks, one month, and two months after TBE vaccination (vaccine unspecified) [67]. In an expert opinion forum, a case of a 2 year old-child with facial paralysis presenting two years after TD with FSME-I. J.® was reduced and studies point to reduced long-term protection in older age groups [68].

### Table 3

| Author | Years after TD | Seropositivity |
|--------|----------------|----------------|
| Loew-Baseli et al. [38] | 3 years after TD with F&E | 97.1% |
| Prymula et al. [18] | 28 days after TD with 2x Ence. C.® + 1x FSME-I. J.® | 100% |
| Beran et al. [40] | 5 years after TD with Encepur® | 100% |
| Aerssens et al. [57] | ≥8 years after TD with FSME-I. J.® | 51% |
| Polfa-bearing et al. [21] | 4 years after TD with FSME-I. J.® | 90.9% |

a TD = third dose.
b Seropositivity = NT titers ≥ 1:10.
c F&E = FSME-Immun® and Encepur®.
d Ence. C. = Encepur®. Children.
e FSME I.J. = FSME-Immun®. Junior.
f Demonstrated in per-protocol set, whereas in all-screened set at five-year follow-up: conventional schedule = 94%, rapid schedule = 90%, accelerated schedule = 93%.
g Demonstrated in 69 patients.
h Median with a range of 0.5–34 months.

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|--------|----------------|----------------|
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a TD = third dose.
b Seropositivity = NT titers ≥ 1:10.
c F&E = FSME-Immun® and Encepur®.
d Ence. C. = Encepur®. Children.
e FSME I.J. = FSME-Immun®. Junior.
f Demonstrated in per-protocol set, whereas in all-screened set at five-year follow-up: conventional schedule = 94%, rapid schedule = 90%, accelerated schedule = 93%.
g Demonstrated in 69 patients.
h Median with a range of 0.5–34 months.

### Table 4

| Recommendations | Switzerland [83] | Germany [72] | Austria [74] | Sweden [73] |
|-----------------|------------------|--------------|--------------|------------|
| Age recommendations | 6 years | no specific age | 1 year (6 months: 3 doses) | Depending on risk of exposure |
| Primary schedule in months | 3 doses | 3 doses | 3 doses | 3 doses <50 years |
| | 0, 1, 6 | 0, 1-3, 5-12 after 2nd | 0, 1-3, 5-12 after 2nd | 0, 1-3, 5-12 after 2nd |
| | Encepur® | 0, 1, 10 | 0, 1-3, 9-12 after 2nd | 0, 1-3, 5-12 after 2nd |
| | >50 years | 0, 1, 3 after 2nd, 5-12 after 3rd dose |
| | Accelerated/Rapid schedules | | | | |
| | FSME-Immun® | 0, 14 days, 5-12 months | 0, 14 days, 5-12 months | N/A |
| | | 0, 1-3, 5-12 after 2nd | 0, 1-3, 5-12 after 2nd | N/A |
| | Encepur® | 0, 7, 21 days | 0, 7, 21 days | N/A |
| | First booster interval | | | | |
| | primary schedule | 10 years | 3 years | 3 years | 3 years |
| | Rapid schedule | N/A | 12-18 months | 12-18 months | N/A |
| | 2nd and following Booster intervals: | | | | |
| | ≥50 years | 10 years | 5 years | 5 years | 5 years |
| | 50-59 years | 10 years | 3 years | 5 years | 5 years |
| | 40-60 years | 3 years | 3 years | 3 years | 5 years |

a Below six years individual risk-benefit estimation.
b Individuals below 3 years of age should be taken into consideration.
c Swiss government vaccine advice documents only described rapid schedules as being available. Exact timing was taken according to the manufacturer’s package insert.
d Rapid schedule described as available but not to prefer if possible.
e After regular primary schedule or after primary rapid schedule with the vaccine Encepur® used.
In adults, terms of safety, the European, licensed vaccines were found to be well tolerated in both children (aged 1–17 years) and in adults, with local injection site reactions in 24.8% (4.3–54%) and systematic reactions in 30% (6.4–45.9%) of vaccinees. Vaccine related serious adverse events (SAE) were rare.

The conventional TBE vaccination schedule (0,28, 300 days) was superior to other schedules in the short-term only [31,46]. Studies show that long-term immunogenicity, after several booster vaccinations, was comparable regardless of the primary vaccination schedule [29,40]. Nevertheless, rapid vaccination schedules should be administered only in individuals requiring protection within a short timespan (such as travellers).

The interchangeability of the two European vaccines was shown in several publications except one from Wittermann et al. which showed a faster decline of antibody levels after a mixed primary vaccination [16,18,37,38,46]. It appears that a mixed vaccine approach can be considered but is not optimal.

Many countries consider that the primary vaccination schedule protects for at least 3 years (Austria, Germany, Sweden), whereas in Switzerland the recommended first booster dose is ten years after the primary schedule [69]. The evidence from this systematic review supports an earlier first booster dose at 3–5 years in children and adults [16,21,51,52,76].

Subsequent booster intervals of at least 5 years in healthy adults were recommended in five studies and, indeed, adequate post-booster protection from 5 years up to ten years for adults and/or children was confirmed [2,10,21,37,40,50]. Our results show a safe immunogenicity of TBE-vaccines for up to ten years after booster vaccination in healthy children (seropositivity at ten year follow-up: 90.3%) and adults below 60 years (seropositivity at ten year follow-up: 77.3%–94%) although lower immunogenicity was observed in adults >50 years of age. Older individuals who have had a 4-dose primary schedule show longer duration of seropositivity after booster doses [2]. Therefore, to ensure protection of older people, recommendations should include a fourth vaccination during the primary schedule and shorter booster intervals [2,25,54].

Evidence on immunogenicity and safety of TBE vaccination in special risk groups remains scant. In a cohort of 70 allergic individuals an immune response after TBE-vaccination was comparable to healthy controls [56]. In studies with limited numbers, immunosuppressed patients showed a lower immune response compared to healthy individuals [54,71]. For thymectomized individuals the evidence shows only an early decreased immune response later approaching levels comparable to healthy controls [55,61]. Immunosuppressed groups must be informed of their high-risk status and should receive an extra dose of TBE-vaccine for primary vaccination regardless of age. There are research gaps: We found no studies documenting incidental TBE vaccine use in pregnant or breastfeeding women. There are few data on use of the vaccine in diabetic patients. Study results were rarely stratified by age and sex, although there are some indications that this is important.

TBE vaccines have both shown to be well tolerated in children and adults with a lower rate of injection site reactions reported with FSME-Immun® Junior compared to Encepur® Children [17–19]. In 10 out of 13 investigated studies analyzing SAE in 4455 individuals no SAE were recorded [18,19,21,35,37,38,46,47,53,54]. In a 5-year follow up study, an incidence rate of 5% SAE was reported for 313 investigated individuals. These SAE were considered “life events” unrelated to the vaccine [40]. In a Swiss surveillance study of 73 adverse events in the years 1991–2001 following TBE-vaccination 19 presented to be SAE corresponding to a rate of 2.3 SAE per 100,000 distributed doses. This time span includes the application of the old mouse-brain derived TBE vaccines [59]. Another study of a German pediatric surveillance database described anaphylactic shock after TBE-vaccination and showed an SAE incidence of 0.69 (0.67–1.2) [1.0 (0.99–1.4)] per million TBE doses administered [60]. In summary, SAE associated with TBE vaccination are rare.

The issue of the timing and the frequency of booster doses is important: Swiss vaccine recommendations, issued by the Federal Office of Public Health, recommend administration of TBE-vaccine to all healthy individuals (>6 years old) in all areas except the cantons of Geneva and Ticino. The primary vaccination schedule should be administered, depending on the vaccine used, at months 0, 1 and 5–12. Thereafter booster vaccinations are recommended every 10 years in all age groups [8]. Swiss recommendations for booster vaccines differ from other countries’ guidelines where boosters are recommended at earlier intervals [72–74] (Table 4).

Vaccination coverage of TBE vaccination is not actively monitored in Switzerland and therefore it is not possible to describe actual coverage, amount of used vaccines or field effectiveness of TBE-vaccines in the Swiss population. An unpublished report suggests a national TBE vaccination coverage of 9.5% for four TBE doses (personal communication Vasiliki B). In Austria Heinz et al. described a field effectiveness for regularly TBE-vaccinated individuals estimated to be around 99% under best case scenario and 96% under worst-case assumptions [34]. To increase coverage, Switzerland’s rules for vaccination availability were adapted in 2015: certain cantons allowed community pharmacists with vaccination certification to administer specific vaccines, such as TBE-vaccine without prescription [75]. To expand coverage of TBE-vaccine, the Swiss army recommended voluntary TBE-vaccinations in young recruits, since 2007 [76]. Because service is only mandatory for Swiss men, there needs to be found another way to reach Swiss females and those who are not of Swiss nationality.

A strength of this Systematic Review is that it was conducted in accordance with PRISMA guidelines [28]. Five online databases were searched to include all the important publications and to summarize most important evidence for the European TBE-vaccines and the main results are highlighted in Table 5. Limitations of this systematic review were the different approaches of the included and investigated studies making outcomes hard to compare. Per example different laboratory tests used like Enzyme-linked Immunosorbtent Assay (ELISA) and NT may not always be comparable. With regard to capturing SAE, most of the vaccine studies investigated, had a small sample size and were not powered to detect rare or SAE. Surveillance systems did identify SAE
research must be done on sex differences in TBE vaccine response and to allow finetuning of risk assessment. Additionally, more research must be done on sex differences in TBE vaccine response and booster intervals for individuals 50–59 years of age, impact of age at priming and on vaccine response in the immunocompromised. To further evaluate TBE vaccine recommendations, it is essential to continuously follow up all previously vaccinated TBE cases with respect to the number of doses and the time of vaccination. This information should be collated in a vaccination register to avoid memory or reporting biases.

In conclusion, TBE vaccination is generally safe with rare serious adverse events. Schedules should, if possible, use the same vaccine brand (non-mixed) and be age adjusted. TBE vaccines are immunogenic in terms of antibody response but less so when vaccination is started later than the age of 50 years. Age at priming is a key factor in the duration of protection.

Conflicts of interest

None of the authors have relevant conflicts of interest to declare.

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Appendix

Appendix 1

Detailed search strategy and keywords in the five databases CINAHL, Cochrane, Embase, PubMed, and Scopus

| Search Step | CINAHL | Cochrane | Embase | PubMed | Scopus
|-------------|--------|----------|--------|--------|-------|
| 1 | tick borne disease | tick-borne encephalitis | ‘tick borne encephalitis’/exp | Encephalitis, Tick-Borne | tick AND borne AND encephalitis
| 2 | encephalitis, tick borne | Publication Year > 2009 | ‘tick borne encephalitis’ | Encephalitis | tick-borne AND encephalitis
| 3 | tick-borne encephalitis | Date added to database < August 31, 2019 | ‘tick-borne’ AND ‘encephalitis’ | tick-borne | fene
| 4 | encephalitis, tick-borne | ‘fene’ | tick-borne encephalitis | tick-borne encephalitis | 1 OR 2 OR 3
| 5 | fene | Combine 1–4 with OR | ‘adverse’ AND (‘reactions’ OR ‘events’) | adverse | side and effects
| 6 | Combine 1–4 with OR | ‘adverse’ | Combine 1–6 with OR | side AND effects | gender AND effects
| 7 | adjuvant | ‘adverse’ AND (‘reactions’ OR ‘events’) | Viral Vaccines | adverse AND events | gender
| 8 | adverse (reactions AND events) | ‘side’ AND ‘effects’ | Drug-Related Side Effects | adverse AND side | effects
| 9 | side AND effects | ‘pediatric’ | ‘gender’ | adverse AND reactions | Reaction
| 10 | gender AND effects | ‘child’ OR ‘children’ | ‘child’ OR ‘children’ | gender | Adjuvant
| 11 | pediatric | ‘elderly’ | ‘elderly’ | Pediatric OR Child OR | OR
| 12 | child OR children | ‘immunosenescence’ | ‘immunosenescence’ | side AND effects | Older children
| 13 | Elderly | ‘gender’ | ‘gender’ | side AND effects | Elderly
| 14 | immunosenescence | ‘sex’ | ‘immunocompromised’ | Immunocompromised | sex
| 15 | gender OR sex | ‘immuno compromised’ | ‘immunocompromised’ | Immunocompromised | gender AND effect
| 16 | immunocompromised | ‘viral’ AND (‘vaccines’ OR ‘vaccination’) | ‘viral’ AND (‘vaccines’ OR ‘vaccination’) | viral AND vaccines | immunocompromised
| 17 | viral AND (vaccines OR vaccination) | ‘virus’ AND (‘vaccines’ OR ‘vaccination’) | ‘vaccine’ AND (‘vaccines’ OR ‘vaccination’) | viral AND vaccination | virus AND vaccines
| 18 | virus AND (vaccines OR vaccination) | ‘protect’ OR ‘protection’ | ‘protect’ OR ‘protection’ | Elderly | virus AND vaccination
| 19 | safety AND (vaccines OR vaccination) | ‘dosage’ OR ‘dose’ | ‘dosage’ OR ‘dose’ | immunosenescence | immunosenescence
| 20 | protect OR protection | Combine 6–19 with OR | Protect OR protection | Protect OR protection | vaccines AND safety
| 21 | dosage OR dose | Protection Date | Protect OR protection | Protect OR protection | vaccines AND safety
| 22 | Combine 7–21 with OR | Date added to database between January 01, 2009 and 31/08/2019 | viral AND (vaccines OR vaccination) | vaccination AND safety | vaccination AND safety
| 23 | Publication time between January 2009 and August 2019 | 5 AND 20 AND 21 AND 22 | virus AND (vaccines and vaccination) | dosage OR dose | dosage OR dose
| 24 | 6 AND 22 AND 23 | 5 AND 20 AND 21 AND 22 | safety AND (vaccine OR vaccination) | Combine 5–23 with OR | vaccines AND safety
| 25 | | | | |
| 26 | | | | |
| 27 | | | | |
| 28 | | | | |

Search type for Scopus: Title-Abs-Key (‘…’)[Mesh]; Search type: ‘…’ [All Fields]; Original search: (2009:py OR 2010:py OR 2011:py OR 2012: py OR 2013:py OR 2014:py OR 2015:py OR 2016:py OR 2017:py OR 2018:py OR 2019:py); (“2009/01/01”[PDAT] OR “2019/08/31”[PDAT]); [1-1-2009]/sd NOT
Appendix 2
Strength of original research assessment table

| Author, Year       | Randomized | Concealed allocation | Controlled | Blinding       | Inclusion of >90% patients in analysis | Dropouts described | comments                                      |
|--------------------|------------|----------------------|------------|----------------|-----------------------------------------|--------------------|-----------------------------------------------|
| Jílková [79] 2009 | NO         | –                    | YES        | open-label     | NO (75.5% included in final analysis)   | Adequate           | 1/3 of study population in rapid schedule excluded |
| Loew-Baselli [38] 2009 | NO      | –                    | YES        | open-label     | Immun: NO (60.7% at 3yfu\(^1\))       | appropriate only from follow-up time point |
| Paulke-Korinek [44] 2009 | NO      | –                    | NO         | open-label     | Immun: YES                             | Adequate           |
| Plentz [51] 2009  | NO         | –                    | NO         | open-label     | Immun: YES                             | Adequate           |
| Stiasny [41] 2009 | NO         | –                    | YES        | N/A            | YES                                     | No dropouts        | retrospective analysis of vaccine failures    |
| Wittermann [20] 2009 | YES    | –                    | YES        | single-blind   | Immun: YES                             | No dropouts        |
| Wittermann [50] 2009 | NO      | –                    | NO         | open-label     | NO                                      | Adequate           |
| Andersson [45] 2010 | NO       | –                    | NO         | –              | YES                                     | No dropouts        | retrospective analysis of vaccine failures    |
| Pollabauer [47] 2010 | Immune assessment: YES | N/A             | IMMUN: YES  | double-blind   | IMMUN: YES                             | Numbers provided – |
|                     | Safety assessment: NO | open-label     | SAFETY: YES | N/A            | SAFETY: YES                            | reasons not described |
| Pollabauer [19] 2010 | YES      | N/A                  | YES        | single-blind   | YES                                     | Yes                |
| Schumacher [59] 2010 | NO       | –                    | NO         | –              | YES                                     | N/A                | retrospective safety data analysis            |
| Weinberger [9] 2010 | NO        | –                    | YES        | N/A            | YES                                     | NO                 |
| Zlamy [55] 2010    | NO         | –                    | YES        | open-label     | N/A                                     | N/A                |
| Madzar [82] 2011   | NO         | –                    | NO         | open-label     | YES                                     | N/A                | retrospective data analysis                  |
| Orlinger [4] 2011  | NO         | –                    | NO         | –              | YES                                     | N/A                |
| Askling [57] 2012  | NO         | –                    | NO         | open-label     | NO                                      | YES                | 313 included, 53 lost to follow-up           |
| Baldwin [70] 2012  | NO         | –                    | YES        | N/A            | YES                                     | No dropouts        |
| Prymula [18] 2012  | YES        | YES                  | YES        | single-blind   | YES                                     | NO                 |
| Garner-Spitzer [1] 2013 | YES   | –                    | N/A        | YES            | N/A                                     | N/A                |
| Heinz [34] 2013    | –          | –                    | –          | –              | YES                                     | N/A                | vaccination coverage and TBE incidence study |
| Paulke-Korinek [22] 2013 | NO      | –                    | NO         | open-label     | NO                                      | appropriate        | follow up study                              |
| Bern [40] 2014     | NO         | –                    | YES        | NO             | Immun: YES                             | No dropouts        | appropriate Follow-up Study                  |
| Lindblom [80] 2014 | NO         | –                    | NO         | N/A            | YES                                     | No dropouts        |
| Remoli [81] 2014   | No         | –                    | YES        | open-label     | YES                                     | N/A                |
| Schoser [56] 2014  | NO         | –                    | NO         | open-label     | NO                                      | appropriate        | 2915 enrolled subjects and 1240 (42.6%) included for analysis Surveillance study |
| Schulter [43] 2014 | NO         | –                    | NO         | open-label     | N/A                                     | N/A                |
| Wittermann [14] 2015 | YES     | –                    | YES        | open-label     | After 3 years group of 111 discontinued | appropriate        | follow-up study                              |
| Aernsens [57] 2016 | NO         | –                    | NO         | open-label     | YES                                     | No dropouts        |
| Beck [48] 2016     | YES        | Unknown              | Unknown    | YES            | No Dropouts                            | All tested sera included into analysis |
| Běsková [53] 2016  | NO         | –                    | NO         | N/A            | YES                                     | appropriate        |
| Hertzell [52] 2016 | NO         | –                    | YES        | open-label     | YES                                     | No Dropouts        |

(continued on next page)
Appendix 2 (continued)

| Author, Year | Randomized | Concealed allocation | Controlled | Blinding | Inclusion of ≥90% patients in analysis | Dropouts described | comments |
|--------------|------------|----------------------|------------|---------|--------------------------------------|-------------------|---------|
| [54] 2016    | Hopf       | NO                   | NO         | N/A     | YES No Dropouts                      |                   |         |
| [53] 2016    | Oberle     | NO                   | NO         | N/A     | YES No Dropouts                      |                   |         |
| [52] 2016    | Konior     | NO                   | NO         | open-label | YES appropriate                      |                   |         |
| [51] 2017    | Lotrícia-Furlan | NO | open-label | YES | No Dropouts | TBE-breakthrough data analysis (no intervention) |
| [50] 2018    | Dorko      | NO                   | open-label | NO | (51.5% at 10yfu) | No Dropouts | retrospective database analysis |
| [49] 2019    | Garner-Spitzer | NO | open-label | NO | (87% at 10yfu) | No Dropouts |         |
| [48] 2019    | Beran      | NO                   | YES open-label | NO | Retrospective surveillance study     |                   |         |
| [47] 2019    | Hansen     | NO                   | NO         | open-label | No Dropouts | No Dropouts |         |
| [46] 2019    | Pollabauer | NO                   | NO         | open-label | NO (87% at 10yfu) | 179 enrolled into 10yfu from 205 receiving 2nd booster dose (87%) and 358 from earlier study |

1) yfu = years of follow-up.

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