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[Intervention Review]

Vaccines for preventing tick-borne encephalitis

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ABSTRACT

Background

Tick-borne encephalitis (TBE) is a disease of the central nervous system caused by a tick-borne viral infection. TBE can lead to severe neurological syndromes such as meningitis, meningoencephalitis, and meningoencephalomyelitis, which can result in death. There is no treatment, and prevention with the vaccine is the only intervention currently available.

Objectives

To evaluate vaccines for preventing TBE in terms of effectiveness and adverse effects.

Search methods

In June 2008, we searched the Cochrane Infectious Diseases Group Specialized Register, CENTRAL (*The Cochrane Library* 2008, Issue 2), MEDLINE, EMBASE, LILACS, and *m*RCT. We also checked reference lists of articles.

Selection criteria

Randomized and quasi-randomized controlled trials comparing TBE vaccines against placebo, control vaccines, no intervention, or a different dose or schedule of the intervention vaccine.

Data collection and analysis

Two authors applied the inclusion criteria, extracted data, and assessed each trial's risk of bias. We could not combine the included trials in a meta-analysis because of differences in comparisons and outcomes.

Main results

Eleven trials (corresponding to 10 papers) involving 8184 participants (6586 adults and 1598 children) were included. Different versions of three types of TBE vaccines were tested (IPVE, FSME-IMMUN, and Encepur); out of which only three (Encepur children, Encepur Adults, and FSME-IMMUN "new") are currently licensed. No trials reported on cases of clinical TBE, but all reported on antibody titre (seroconversion). All the vaccines gave seroconversion rates of over 87%. Systemic and local adverse effects were common; none were severe or life threatening.

Authors' conclusions

Tick-borne encephalitis vaccines appear to be highly immunogenic, but the relationship between seroconversion and clinical protection has not been established. Although adverse effects were commonly reported, none were serious or life threatening.

23 April 2019

No update planned

Other

This is not a current research question.

PLAIN LANGUAGE SUMMARY

Vaccines for preventing tick-borne encephalitis

Tick-borne encephalitis (TBE) is a disease of the central nervous system caused by a tick-borne viral infection. TBE can lead to severe neurological syndromes, which can result in death. Many species of wild and domestic animals act as hosts of ticks; transmission to humans occurs often in woodland areas, especially during the summer, which is the time of greatest human outdoor activity. TBE is particularly prevalent in Central and Eastern Europe.

Although personal protective measures to avoid tick bites (such as insect repellents, avoidance of tick-infested areas, and use of protective clothing) are recommended, there is no effective treatment for TBE, and vaccination is the only preventive measure currently available.

This review evaluates the effectiveness and adverse events induced by current vaccines for preventing TBE. The authors identified 11 trials involving 8184 participants, which assessed different versions of three types of tick-borne encephalitis vaccines. No trials reported on cases of clinical TBE, but all tested vaccines were highly immunogenic. Adverse effects were commonly reported, none were serious or life threatening.

The authors recommend further trials or well-conducted observational studies with clinical outcomes (ie TBE cases) to better estimate vaccine effectiveness and the duration of vaccine protection, as well as long-term adverse events.

BACKGROUND

Tick-borne encephalitis (TBE) is a disease of the central nervous system caused by a tick-borne viral infection, which comes from a family of viruses known as *Flaviviridae* (Barret 1999). There are three subtypes of TBE: European (transmitted by *Ixodes ricinus*), Far Eastern, and Siberian (both transmitted mainly by *I. persulcatus*) (Ecker 1999; Süss 2003).

The European subtype occurs throughout Central and Eastern Europe, with the highest incidence in the summer months – the time of greatest human outdoor activity (see country profiles in Appendix 1). TBE is particularly prevalent in Southern Germany, Austria, Slovenia, Czech Republic, Croatia, and areas in Slovakia (the Vojvodina and around Bratislava) (Süss 2003). Other countries with endemic foci of the European subtype of TBE virus include Italy, France, Switzerland, Russia, Lithuania, Estonia, Latvia, and Poland.

The Far Eastern subtype is found in China and the Asian and European regions of the former Soviet Union, where it co-exists with the European subtype. The Siberian subtype, closely related to the Far Eastern subtype, was identified more recently and has natural foci in Siberia and Far-Eastern Russia (Ecker 1999; Hayasaka 2001).

Transmission

More than 100 species of wild animal including foxes, voles, and deer, and domestic animals (eg dogs, sheep, and horses) act as a reservoir hosts. Transmission to humans is common in ecological transition areas such as forest fringes, glades, and riverside meadows.

Symptoms

About a quarter of TBE infections result in significant clinical symptoms. A third of these may go on to develop a more serious neurological syndrome that can result in serious disability or death. The incubation period of the virus ranges from two to 28 days (mean 11 days, median 8 days) (Barret 1999). This is followed by an initial viraemic phase, which begins with up to eight days of a febrile illness accompanied by non-specific signs and symptoms (headache, malaise, and myalgia). After an afebrile period of around seven days (range one to 21 days) (Barret 1999), a second more serious phase may develop in which the virus infects the brain (encephalitis), the lining of the brain (meningitis), the spinal cord (myelitis), the peripheral nerves (radiculitis), or any combination of these.

Of people entering the second phase, about half develop meningitis, a third develop meningoencephalitis, and 10% develop meningoencephalomyelitis. Between 10% and 20% of people with meningoencephalitis or meningoencephalomyelitis have long-lasting or permanent weakness, central deafness, or neuropsychiatric sequelae, and about 2% of meningoencephalomyelitis cases are fatal. The disease is less severe in children than in adults (Haglund 2003; Kaiser 2007).

Diagnosis

A diagnosis of TBE requires the use of serological tests due to the non-specific nature of the clinical symptoms. Isolation of TBE virus from blood is possible only during the initial viraemic phase of the disease using a reverse transcriptase polymerase chain reaction (RT-PCR). Most admissions to hospital occur during the second phase of the illness when the neurological syndromes develop; at this point the virus is often no longer detectable in blood or cerebrospinal fluid due to the initiation of an immune response by the body.

Three serological tests are used to diagnose TBE: enzyme-linked immunosorbent assay (ELISA), neutralization test, and haemagglutination inhibition test. ELISA is the simplest test, while the most definitive test is likely to be the neutralization test. Levels of viral titre that correspond to immunity have not yet been determined even for the neutralization test (Holzmann 2003). It has been shown that high anti-TBE ELISA and haemagglutination inhibition test titres may be generated in people previously immunized or exposed to different flaviviruses (yellow fever and dengue) (Clement 1996; Holzmann 1996). There is little information on how antibody levels, as assessed by the different tests, relate to either exposure to or protection from the disease. Thus extreme caution in interpretation of TBE serology is required because there are no international standards for TBE diagnosis (Holzmann 2003).

Vaccines

Vaccination is a the most important preventive measure against TBE infection. Prevention through personal measures such as insect repellents, avoidance of tick-infested areas, and use of protective clothing is unreliable (Kunze 2004). Post-exposure immunoprophylaxis is dangerous and often not available, and no effective treatment currently exists.

The first TBE vaccines were produced in the former Soviet Union (Barret 1999), but they had limited efficacy and undesirable adverse effects, which stimulated the development of a more purified vaccine called KKhv (Popov 1985). This led to the development of different vaccines (Appendix 2), of which only two are currently licensed for use: FSME-IMMUN (new) and FSME-IMMUN (Junior), which is a paediatric formulation; and Encepur adults and Encepur children.

Studies have investigated the adverse effects of different vaccine formulations and routes of administration, and have compared a reduced with a standard dose in children. Also, increasing movement of travellers and military forces into TBE-endemic areas (such as deployment of troops to the former Yugoslavia) have stimulated investigations of the effectiveness of an abbreviated vaccination schedule in achieving immunity within a short period of time while minimizing adverse effects.

Specific immunoglobulin as post-exposure or immediate prophylaxis is used in some high-risk areas. This must be given before exposure or within 96 hours of a tick bite. The use of this method in children under 14 years is not recommended due to case reports of enhanced infection in this age group (Barret 1999). The protection rate has been estimated in 50% to 60% on the basis of a survey findings (Rendi-Wagner 2004).

OBJECTIVES

To evaluate vaccines for preventing TBE in terms of effectiveness and adverse effects.

METHODS

Criteria for considering studies for this review

Types of studies

Randomized and quasi-randomized controlled trials.

Types of participants

Well adults or children irrespective of immune status or special risk category.

Types of interventions

Intervention

Live or killed TBE vaccines or fractions thereof administered by any route.

Control

Placebo, control vaccine, or no intervention; or different dose or schedule of intervention vaccines.

Types of outcome measures

Primary

- Cases of clinical TBE.
- Antibody titre (seroconversion).

Adverse events

- Serious adverse events (defined as life threatening or recurring hospitalization).
- Any adverse events (systemic or local).

Search methods for identification of studies

We attempted to identify all relevant trials regardless of language or publication status (published, unpublished, in press, and in progress). We searched the following databases using the search terms and strategy described in Appendix 3: Cochrane Infectious Diseases Group Specialized Register (June 2008); Cochrane Central Register of Controlled Trials (CENTRAL), published in *The Cochrane Library* (2008, Issue 2); MEDLINE (1966 to June 2008); EMBASE (1974 to June 2008); and LILACS (1982 to June 2008). We also searched *meta*Register of Controlled Trials (*m*RCT) in June 2008 using 'tick-borne' and 'encephalitis' as search terms.

We checked the reference lists of all studies identified through the database searches.

Data collection and analysis

Selection of studies

Alessandro Rivetti (AR) and Maria Grazia Debalini (MGD) screened all trials identified by the search strategy, and independently applied the inclusion criteria. The full trial reports were scrutinized to ensure that multiple publications from the same trial were only included once. The trials' investigators were contacted for clarification if it was unclear whether a trial was eligible for inclusion in the review. Vittorio Demicheli (VD) was consulted to resolve any differences in opinion.

Data extraction and management

MGD and AR independently extracted relevant data from trial reports and entered the data into Review Manager 5. VD supervised data extraction and arbitrated in cases of disagreement.

Assessment of risk of bias in included studies

AR and MGD independently assessed the risk of bias. The generation of allocation sequence and allocation concealment were classified as adequate, inadequate, or unclear according to Jüni 2001. Blinding was recorded and considered to be double (neither the participant or care provider/assessor knew the treatment), single (participant or care provider/assessor aware of the treatment), open (all parties aware of the treatment), or unclear. The inclusion of all randomized participants in the analysis was classified to be adequate if 90% or more randomized participants were included in the analysis, inadequate if less than 90%, unclear, or not described.

Data synthesis

We have provided a narrative synthesis of the data. Had the data permitted, we would have analysed the data using the risk ratio (RR) for dichotomous outcomes and the mean difference for continuous data, and presented each result with a 95% confidence interval (CI).

RESULTS

Description of studies

We identified 25 potentially relevant trials. Eleven trials met our inclusion criteria; two trials were reported in one article (Eder 2003i; Eder 2003ii). They enrolled 8184 participants of which 6586 were adults and 1598 were children ('Characteristics of included studies'). Only four trials (4769 adults and 294 children) tested vaccines that are currently in use (Ehrlich 2003; Loew-Baselli 2006; Schoendorf 2007; Schöndorf 2007). None of the trials had been designed to determine the efficacy of the tested vaccines, but instead they aimed to identify the lowest dose that could preserve immunogenicity while minimizing adverse effects, especially in children, and to assess the frequency and type of adverse effects of various vaccine formulations, routes of administration, and dosing schedules. Thirteen trials identified by the search did not meet our criteria for the reasons given in the 'Characteristics of excluded studies', and two studies are awaiting classification (see 'Characteristics of studies awaiting classification'). A further 10 ongoing studies were identified (see 'Characteristics of ongoing studies').

The variability between trial design, choice of dose and schedule, and outcomes reported meant that it was not possible to combine any of the trials for meta-analysis. We have therefore provided a narrative summary of the results.

As none of the trials provided data on the efficacy of the vaccines in preventing TBE, we focused on the immunogenicity and safety of the vaccines. We presented the results in four sections: vaccine versus placebo; comparison of different vaccine types; dose-finding studies; and dosing schedules.

Participants

Four trials of children included 1076 children aged from six months to 17 years (Pavlova 1999; Eder 2003i; Eder 2003ii; Schoendorf

2007). The other trials included 6586 adults. One trial, Girgsdies 1996, included 522 children and 191 adults (see below for further explanation).

The population involved in trials of currently licensed vaccines consisted of 5063 participants. Schoendorf 2007 was the only trial to include children only (294 children aged one to 11 years).

Interventions

Different versions of three types of tick-borne encephalitis vaccines were tested (IPVE, FSME-IMMUN, and Encepur)

The 11 trials tested different versions of three types of TBE vaccines were tested (IPVE, FSME-IMMUN, and Encepur) (see Appendix 2). Only three are still in use: FSME-IMMUN (new); Encepur adults; and Encepur children. The reporting of information on vaccine content and schedule varied considerably between the trials. Only two reported vaccine identification information including adjuvants, preservatives, strains, product, and manufacturer (Eder 2003i; Eder 2003ii). All trials reported number of doses and schedule. Six trials identified the adjuvant and stabilizer (Bock 1990; Harabacz 1992; Girgsdies 1996; Eder 2003i; Eder 2003ii; Ehrlich 2003; Loew-Baselli 2006), three reported only the adjuvant (Pavlova 1999; Schoendorf 2007; Schöndorf 2007), and one documented the lot number (Bock 1990). We have summarized the vaccine characteristics in Appendix 2.

IPVE

Pavlova 1999 assessed the immunological activity and reactogenicity of the IPVE vaccine against FSME-IMMUN produced by FSME-IMMUN Inject. The trial was conducted in Russia and included 223 healthy children aged between seven and 17 years.

FSME-IMMUN

FSME-IMMUN [1980]

Immuno 1996, a four-arm trial compared FSME-IMMUN with an "investigational vaccine" (not otherwise specified) plus thimerosal, the investigational vaccine without thimerosal, and placebo (no details). Pavlova 1999 compared this with IPVE vaccine (see above).

TicoVac

Eder 2003i and Eder 2003ii are two trials reported in a single publication. They compared the immunogenicity and safety of half an adult dose with a full adult dose in 298 children aged six months to three years in Austria (Eder 2003i), and 261 children aged four to 12 years in Germany (Eder 2003ii).

FSME-IMMUN (new)

Ehrlich 2003, a Phase II dose-finding trial, assessed immunogenicity and safety in 405 healthy volunteers to one of three doses of this vaccine: 0.6 µg/0.5 mL; 1.2 µg/0.5 mL; or 2.4 µg/0.5 mL. The preparations were administered in three doses (days zero, 21 to 35, and six months after the second dose). Loew-Baselli 2006 compared adverse effects between the 2.4 µg dose of FSME-IMMU with Encepur (containing polygeline as stabilizer) in 3927 adults and adolescents.

Encepur

Encepur

Bock 1990, a dose-finding study, compared five doses between 0.03 and 3.00 µg in 56 healthy male volunteers. Harabacz 1992 was a multicentre trial of three different doses (1.0, 1.5, and 2 µg) and two immunization schedules (conventional at zero, 28, and 300 days; and abbreviated at zero, seven, and 21 days) in 379 healthy volunteers. Girgsdies 1996 randomized 522 healthy children to one of three doses (0.4, 0.75, or 1.5 µg); the trial was designed to determine whether a lower dose in children than that recommended for adults (1.5 µg) would produce adequate seroconversion with fewer adverse effects. A 'control' (non-randomized) group consisted of 191 adults who received 1.5 µg to provide comparative data on the seroconversion rates expected for that dose. The vaccine was administered on the 'abbreviated' schedule (zero, seven, and 21 days). Occurrence of adverse effects following administration of two doses of Encepur (1.5 µg/0.5 mL dose, schedule zero, 21 to 35 days) within four days after immunization was assessed in comparison with FSME-IMMUN (new) in Loew-Baselli 2006.

Encepur adults

Schöndorf 2007 assessed four different immunization schedules in 298 adults and adolescents: rapid schedule with vaccination on days zero, seven, and 21; conventional schedule with vaccination on days zero, 28, and 300; modified conventional schedule with vaccination on days zero, 21, and 300; and an accelerated conventional schedule with vaccination on days zero, 14, and 300.

Encepur children

Schoendorf 2007 compared three different dose schedules in 294 children aged between one and 11 years: rapid (days zero, seven, and 21), conventional (days zero, 28, and 300), and modified conventional (days zero, 21, and 300).

Outcome measures

None of the trials reported cases of clinical TBE. All trials reported serological changes in the form of ELISA, neutralization tests, or haemagglutination inhibition tests. The adverse effects in the Immuno 1996 trial were not available in the unpublished abstract, but they were given by personal communication from the Immuno AG company (Marianne Kunschak, 10 March 1997).

Risk of bias in included studies

See Appendix 4 for a summary of the risk of bias assessment.

Generation of the allocation sequence

One trial used an adequate method to generate the allocation sequence (Immuno 1996). Ehrlich 2003 reported block randomization but did not describe the method used to generate the sequence. The methods used in the other nine trials was unclear.

Allocation concealment

Allocation concealment was adequate in one trial (Immuno 1996). The methods used to conceal allocation were unclear in the remaining 10 trials.

Blinding

One trial was double blind (Immuno 1996), and two were classified as open (Schoendorf 2007; Schöndorf 2007). One trial did not mention the use of blinding (Pavlova 1999). The other trials were described as double blind (Harabacz 1992; Girgsdies 1996; Eder 2003i; Eder 2003ii; Ehrlich 2003) or single blind (Bock 1990; Loew-Baselli 2006) in the method sections; no further information was given other than the third dose in Ehrlich 2003 was open-label administered.

Inclusion of all randomized participants in the analysis

All but two trials included over 90% of the randomized participants in the analysis. Pavlova 1999 included over 90% for the safety outcome measures, but not the immunogenicity assessment. Schöndorf 2007 included the per-protocol study population (89.5% of the allocated participants) in the efficacy analysis, but it is unclear how many were included in the safety analysis.

Effects of interventions

Results of all vaccines are presented. Refer to Appendix 2 for information about the license status of the individual vaccines; FSME-IMMUN (new), Encepur children, and Encepur adults are those currently in use.

1. Vaccine versus placebo

Immuno 1996 compared the FSME-IMMUN [1980] vaccine and a new investigational TBE vaccine (with and without thimerosal (preservative)) with a placebo (composition not given), mainly to assess adverse effects.

1.1. Antibody titre (seroconversion)

FSME-IMMUN [1980]

Immuno 1996 defined seroconversion as a two-fold increase in TBE antibody titre by ELISA and neutralization test 28 to 35 days after second dose compared to baseline. All three groups were reported to be highly immunogenic with seroconversion rates of 88% to 94% in the vaccine groups (FSME-IMMUN [1980]: 261/283; new investigational TBE vaccine: 264/279 with thiomersal, and 248/280 without thimerosal) and 2% in the placebo group (6/300).

1.2. Adverse effects

FSME-IMMUN [1980]

Immuno 1996 reported that local and systemic adverse effects (including crawling, formication, headache, fever, feeling unwell, dizziness, nausea, loss of appetite, myalgia, abdominal pain, fatigue, sleeplessness, and tremor) occurred in 18.7% (56/300) of participant in the FSME-IMMUN [1980] group, 23% (70/298) of recipients of the new investigational TBE vaccine (without thimerosal), and 17% (50/296) of those receiving the new investigational TBE vaccine (with thimerosal (preservative)). The rate in the placebo group was 13.8% (41/297). These rates represent the sum of events occurring after both first and second doses. Adverse effects were more frequent after the first dose. Immuno 1996 reported that serious adverse events did not occur.

2. Different vaccine types

Two trials compared different vaccine types. Pavlova 1999 compared the IPVE vaccine with the FSME-IMMUN [1980] in 223 healthy children aged between seven and 17 years. Loew-Baselli 2006 compared FSME-IMMUN (new) with Encepur in 3966 participants aged at least 12 years in the first phase of the trial in two doses given 21 to 35 days apart. In the second phase of the study, all participants were immunized with one dose of FSME-IMMUN (new), and antibody titres before and after this administration were measured.

2.1. Antibody titre (seroconversion)

IPVE versus FSME-IMMUN [1980]

Pavlova 1999 reported seroconversion (defined as a four-fold antibody titre increase) in 91.5% (65/71) children immunized with IPVE and in 98.7% children (75/76) immunized with FSME-IMMUN (new). The corresponding risk ratio (RR) is 0.93 (95% confidence interval (CI) 0.86 to 1.00).

2.2. Adverse effects

IPVE versus FSME-IMMUN [1980]

Pavlova 1999 determined safety by monitoring for fever (mild, moderate, or severe) and local reactions (pain and redness at injection site) within five to seven days after each dose. No moderate or severe fever was reported in the FSME-IMMUN [1980] group after the first dose, while these symptoms were observed in the IPVE group (moderate fever 5.2%, severe fever 0.9%). Mild fever after the second dose was also less frequent in the FSME-IMMUN [1980] group. Local reactions were more frequent in the IPVE group. Pavlova 1999 did not report serious adverse events.

FSME-IMMUN (new) vs Encepur (aged at least 12 years)

Loew-Baselli 2006 observed fever more frequently in the Encepur group (5.6%) compared with the FSME-IMMUN (new) group (0.8%); the difference was statistically significant ($P < 0.0001$). Systemic reactions after the first vaccination occurred more often in the Encepur group (31%) compared with the FSME-IMMUN group (13.6%). A similar result was obtained for local reactions (44.75% versus 35.6%).

Loew-Baselli 2006 reported that serious adverse events did not occur.

3. Dose-finding

Six trials comparing three different vaccines investigated different doses: one studied FSME-IMMUN (new) (Ehrlich 2003); three studied Encepur (Bock 1990; Harabacz 1992; Girgsdies 1996); and two studied TicoVac (Eder 2003i; Eder 2003ii).

3.1. Antibody titre (seroconversion): in adults

See Appendix 5 for details.

FSME-IMMUN (new)

Ehrlich 2003 administered FSME-IMMUN (new) in three antigenic concentrations (0.6 µg, 1.2 µg, and 2.4 µg) in a three-dose schedule. Seroconversion rates (by ELISA) after the second dose were 85.1%, 96.2%, and 97% for the three doses respectively. The rates increased to 96%, 99.2%, and 100% respectively after the third dose. Using neutralization tests, seroconversion was 77%, 93%, and 96.6% respectively.

Encepur

Bock 1990 reported that a 1 µg dose was required to induce greater than 90% seroconversion after two doses, while Harabacz 1992 found that doses of 1 µg or greater resulted in seroconversion rates over 99% after two doses.

3.1.2. Antibody titre (seroconversion): in children

See Appendix 5 for details.

Encepur

Girgsdies 1996 compared doses of 0.4 µg and 0.75 µg in children aged 18 months to 14 years with the standard adult dose (1.5 µg). Seroconversion rates (by ELISA) were greater than 99% for all doses tested.

TicoVac

Eder 2003i and Eder 2003ii compared half the adult TicoVac dose (1.65 µg) with the full adult dose (3.29 µg) in a three-dose schedule (days zero, 14 to 32, and 284 to 330). Seroconversion rates following the second dose were lower in the children aged four to 12 years who were given the half dose (95% versus 100%), but there was no difference for children aged six months to four years (72% versus 71.4%). After the third dose, a seroconversion rate of 100% was achieved in all groups.

Eder 2003i also reported that there was a lower seroconversion rate after the second dose in children aged up to one year if the mother had a high TBE antibody titre. Seroconversion was observed in 54% of children in this group who were immunized with the half dose and in 62% of those who received the adult dose, compared to 82% and 100% respectively in non-immune mothers.

3.2. Adverse effects

FSME-IMMUN (new)

Ehrlich 2003 reported that severe adverse events did not occur.

Encepur

Girgsdies 1996 reported adverse events per vaccination rather than per individual. The incidence of fever (≥ 38 °C) was less for both of the lower doses than for the standard dose of 1.5 µg: 18.4% versus 30.1% for the 0.4 µg dose (RR 0.62, 95% CI 0.52 to 0.73); and 18.9% versus 30.1% for the 0.75 µg (RR 0.56, 95% CI 0.47 to 0.67). Girgsdies 1996 reported four serious adverse events (resulting in hospital admission) to the Council for International Organisation of Medical Sciences (CIOMS), but the trial authors noted that a "causal relationship with the study medication was not present in any of the cases".

Bock 1990 (56 participants) reported the occurrence of "Adverse Drug Events" but did not split the data between the intervention arms; there were four of the local type (excluding swelling, redness, and induration) and six of the systemic adverse events (headache, flu-like symptoms, and nausea). Bock 1990 did not mention serious adverse events, while Harabacz 1992 reported that serious adverse events did not occur.

TicoVac

Eder 2003i and Eder 2003ii reported that serious adverse events did not occur.

4. Abbreviated versus regular schedule

Three trials, each comparing a different Encepur vaccine, compared vaccine schedules. Harabacz 1992 compared an abbreviated schedule (days zero, seven, and 21) with a conventional schedule (days zero, 28, and 300) for giving three different doses (1.0, 1.5, and 2.0 µg) of Encepur in 379 healthy adults aged 18 to 69 years.

Schoendorf 2007 compared three different schedules of the Encepur children vaccine – rapid (days zero, seven, and 21), conventional (days zero, 28, and 300), and modified conventional (days zero, 21, and 300) – in 294 children aged one to 11 years.

Schöndorf 2007 compared four different schedules of the Encepur adults vaccine – rapid (days zero, seven, and 21), conventional (days zero, 28, and 300), modified conventional (days zero, 21, and 300), accelerated conventional one (days zero, 14, and 300) – 398 adults aged 12 to 64 years.

4.1. Antibody titre (seroconversion)

Encepur

Harabacz 1992 reported that the abbreviated schedule was as efficacious in achieving seroconversion as a conventional immunization schedule; there was 100% seroconversion using all three assays (ELISA, neutralization test, and haemagglutination inhibition test) after two doses.

Encepur children

Schoendorf 2007 determined the antibody titre using ELISA and the neutralization test.

By day 42 (ELISA, with no limit indicated), all participants in the rapid and conventional schedule, and most in the modified conventional schedule, reached seroconversion. Using the neutralization test, the proportion of participants in each group for whom values were equal to or greater than 10 was 99% (rapid schedule), 100% (conventional schedule), and 97% (modified conventional schedule).

On day 300, the percentages were maintained among participants immunized with rapid schedule, whereas for those in conventional and modified schedule it declined to 90% and 86% respectively. Analysis of the day 300 seroconversion data (using the neutralization test) resulted in RR 1.09 (95% CI 1.01 to 1.18) for the rapid versus conventional schedule, and RR 0.95 (95% CI 0.86 to 1.06) for the modified conventional versus conventional schedule.

Encepur adults

Schöndorf 2007 collected analysed antibody response (neutralization test and ELISA) on days zero, 21, 42, 180, 300, and 321. On day 42, seroconversion (neutralization test antibody titre ≥ 10) was achieved in 92% and 95% of participants immunized following rapid and conventional schedule respectively. Lower percentages of participants with seroconversion were observed among those immunized with modified conventional or accelerated conventional schedule.

Seroconversion rates on day 300 remained higher for both rapid (74%) and conventional schedule (71%) than for the modified conventional schedule (60%) or accelerated conventional schedule (59%). An analysis of the different schedules found no statistical difference between the rapid and conventional schedule (RR 1.04,

95% CI 0.85 to 1.29), modified conventional and conventional schedule (RR 0.84, 95% CI 0.69 to 1.04), accelerated conventional and conventional (RR 0.82, 95% CI 0.67 to 1.02), and the modified conventional and accelerated conventional (RR 1.03, 95% CI 0.84 to 1.25). The rapid schedule resulted in more seroconversions than the accelerated conventional schedule (RR 1.27, 95% CI 1.04 to 1.55) and the modified conventional schedule (RR 1.23, 95% CI 1.01 to 1.51).

4.2. Adverse effects

Encepur

Harabacz 1992 summarized the rates of systemic adverse events for all dose groups over the whole immunization course of three doses. The rate was higher after the first vaccination; for example, the frequency of fever between 38.1 °C and 39 °C was 2.6% after the first dose, while it reduced to 0.5% after the second and third doses. Overall the rate of local and systemic adverse events was 59% for the abbreviated and 46% for the conventional schedule. The statistical significance of this difference was marginal (RR 1.12, 95% CI 1.00 to 1.47). The most frequent events included headache, fever, weakness, malaise, and local injection site irritation.

Encepur children

In Schoendorf 2007 the most frequently observed local reactions were tenderness in age subgroup from one to two years and pain for the older children (aged three to 11 years). Regarding systemic reactions, irritability (age group one to two years), myalgia and malaise, headache (age group three to 11 years) were the most common observed events. During the trial 25 serious adverse events were reported, but the trial authors did not consider them to be related to the vaccine.

Encepur adults

Local pain was the most frequently observed local reaction (observed in 9% of participants after dose one, in 5% after dose two, and 6% after dose three). Myalgia, headache and fever (≥ 38°C) were also reported with minor frequency after the second and third dose (Schöndorf 2007).

DISCUSSION

The TBE vaccines assessed in the review are highly immunogenic. In the one trial with a placebo control group (Immuno 1996), local and systemic adverse effects were observed more frequently in the vaccine groups.

A lower dose of Encepur in children (0.4 or 0.75 µg instead of 1.5 µg) appeared to provide equivalent seroconversion with fewer adverse effects (Girgsdies 1996). A similar result was observed with TicoVac following immunization of children (Eder 2003ii) and toddlers (Eder 2003i) with a half-dose preparation (1.65 µg) in comparison with the full adult dose (3.29 µg). However, when mothers were immune, the seroconversion rate was much lower in children aged under one year, and this should be taken into account in endemic areas or where mothers are mainly already immunized (Eder 2003i; Eder 2003ii).

In adults, a higher seroconversion rate was achieved through administration of three doses (2.4 µg) of FSME-IMMUN (new) with a conventional schedule compared to the rates with lower doses (0.6 and 1.2 µg) (Ehrlich 2003). Adverse reactions occurred with almost the same frequency in all three groups.

A shortened immunization schedule provides a seroconversion rate after three weeks, which is equivalent to that achieved by the conventional schedule (ie > 99%), without significant increase in the frequency of adverse effects (Harabacz 1992). Similar results were obtained by immunization of adults or children with the specific formulation of Encepur vaccine by comparison of rapid and conventional immunization schedule: rapid schedule induces an high, stabile seroconversion rate in both adults and children (Schoendorf 2007; Schöndorf 2007).

The main methodological difficulty with these trials was the exclusive reliance on antibody titre as a proxy for clinical protection. The only evidence that seroconversion after vaccination is equivalent to protection from TBE is provided by observational studies on the decline in incidence in TBE following vaccination campaigns, such as that in Austria. Before introduction of annual vaccination campaign in 1981 incidence of TBE was about 600 cases/year. As results of immunization, disease incidence decreased dramatically (41 cases in 1999 and 60 in 2000 as vaccination coverage reached 84% of the population (Kunz 1992; Süss 2003). Now that the TBE vaccine is included in routine immunizations for infants and children in some high-risk areas (eg Austria and Germany), it would be unethical to conduct a placebo-controlled trial in such areas to assess vaccine efficacy.

Adverse effects were commonly observed, but none were serious or life-threatening.

AUTHORS' CONCLUSIONS

Implications for practice

The included trials indicate that the vaccines are highly immunogenic, but that they have a relatively high rate of short-term adverse effects.

Currently licensed vaccines (FSME-IMMUN (new), Encepur adults, and Encepur children), when administered accordingly to an abbreviated immunization schedule (days zero, seven, and 21), appear to be at least as immunogenic as when administered following a conventional schedule (days zero, 28, and 300) without increase in adverse events occurrence.

Since the TBE vaccine is one of the few vaccines aimed at a disease with obvious seasonality (period of tick activity), the ideal period for active immunization would be during the winter months (first and second dose of the normal long term schedule) in order to achieve immunity before the beginning of seasonal tick activity (spring).

Implications for research

Evidence from well-conducted and well-reported observational studies or possibly from case-control studies considering TBE cases as outcome would be needed to better estimate vaccine effectiveness and to investigate the gap existing between protection from disease and seroconversion in different assay types. Combined with information about the duration of vaccine-induced antibodies (particularly neutralizing antibodies), this would enable the optimization of vaccine and booster schedule.

There is a need for more work on long-term adverse effects in vaccinated populations.

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CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Bock 1990

Methods	**Design:** randomized controlled trial **Generation of allocation sequence:** not described **Allocation concealment:** not described **Blinding:** single blind **Inclusion of all randomized participants in the analysis:** none lost to follow up **Length of follow up:** 56 days
Participants	**Number:** 56 healthy male aged 20 to 50 years **Inclusion criteria:** not reported **Exclusion criteria:** not reported
Interventions	**Vaccine:** Encepur **Dose-finding study:** 1. 0.03 µg, 6 participants 2. 0.18 µg, 5 participants 3. 0.35 µg, 18 participants 4. 1.00 µg, 16 participants 5. 3.00 µg, 11 participants **Schedule:** 2 inoculations on days 0 and 28 at 5 different dosages in 0.5 mL
Outcomes	1. Geometric means of tick-borne encephalitis (TBE) antibody titres 28 days after second inoculation (as assayed by enzyme-linked immunosorbent assay (ELISA), haemagglutination inhibition test, and neutralization test): minimum, median, and maximum values 2. Reactogenicity assessed by medical check-up on vaccination day, 2 days later and for a follow-up period of 28 days after each injection: local and systemic "Adverse Drug Events" (ADEs)
Notes	**Location:** Germany

Eder 2003i

Methods	**Design:** randomized controlled trial **Generation of allocation sequence:** not described **Allocation concealment:** not described **Blinding:** double blind **Inclusion of all randomized participants in the analysis:** no participants lost to follow in immunogenicity analysis; 21/298 participants lost from safety (93% included in analysis)

Eder 2003i *(Continued)*

	Length of follow up: for immunogenicity, serological tests were performed before first dose and 4 weeks after second and third dose (about 12 months after the first dose administration); for adverse effects, within 7 days after each of the 3 doses
Participants	**Number:** 298 toddlers aged 6 months to 3 years **Inclusion criteria:** not described **Exclusion criteria:** for immunogenicity positive tick-borne encephalitis (TBE) antibody at screening; tick bite during the study; retraction of informed consent or failure to appear at scheduled examination (36 participants)
Interventions	**Vaccine:** TicoVac **Immunogenicity trial, comparison of 2 doses:** 1. 1.29 µg TBE virus antigen/0.25mL vs 2.57 µg TBE virus antigen/0.5 mL 2. 1.29 µg TBE virus antigen/0.25mL vs 2.57 µg TBE virus antigen/0.5 mL 3. 1.65 µg TBE virus antigen/0.25mL vs 3.29 µg TBE virus antigen/0.5 mL **Schedule:** dose 1, day 0; dose 2, 14 to 32 days after dose 1; dose 3, 9 to 10 months after dose 2
Outcomes	1. Antibody responses determined by enzyme-linked immunosorbent assay (ELISA) before dose 1 and after doses 2 and 3: 1.1. Seroconversion, defined as a positive ELISA result of at least 126 Vienna International Units (VIEU)/mL (Kiessig 93) or 4-fold titre increase 1.2. Geometrical mean concentration (VIEU/mL by ELISA) 2. Adverse events (follow up for 7 days after each vaccination, diary card filled by parents and reviewed by study physicians): fever (mild: < 38.5 °C; moderate: 38.5 °C to 40 °C; severe: > 40 °C)
Notes	**Location:** Austria

Eder 2003ii

Methods	**Design:** randomized controlled trial **Generation of allocation sequence:** not described **Allocation concealment:** not described **Blinding:** double blind **Inclusion of all randomized participants in the analysis:** no participants lost to follow up in immunogenicity analysis 21 participants lost from safety (92% included in analysis) **Length of follow up:** for immunogenicity, serological texts were performed before first dose and 4 weeks after second and third dose (about 12 months after the first dose administration); for adverse effects, within 7 days after each of the 3 doses
Participants	**Number:** 261 children aged 4 to 12 years **Inclusion criteria:** not described **Exclusion criteria:** for immunogenicity positive tick-borne encephalitis (TBE) antibody at screening; tick bite during the study; retraction of informed consent or failure to appear at scheduled examination (36 participants)
Interventions	**Vaccine:** TicoVac **Immunogenicity trial, comparison of 2 doses (see** Eder 2003i**):**

Eder 2003ii *(Continued)*

	1. 1.65 µg of TBE virus antigen/0.25 mL vs 3.29 µg of TBE virus antigen/0.5 mL 2. 1.65 µg of TBE virus antigen/0.25 mL vs 3.29 µg of TBE virus antigen/0.5 mL 3. 1.65 µg of TBE virus antigen/0.25 mL vs 3.29 µg of TBE virus antigen/0.5 mL **Schedule:** dose 1, day 0; dose 2, 14 to 32 days after dose 1; dose 3, 9 to 10 months after dose 2
Outcomes	1. Antibody responses determined by enzyme-linked immunosorbent assay (ELISA) before dose 1 and after doses 2 and 3 1.1. Seroconversion, defined as a positive ELISA result of at least 126 Vienna International Units (VIEU)/mL (Kiessig 93) or 4-fold titre increase 1.2. Geometrical mean concentration (VIEU/mL by ELISA) 2. Adverse events (follow-up for 7 days after each vaccination, diary card filled by parents and reviewed by study physicians): fever (mild: < 38.5 °C; moderate: 38.5 °C to 40 °C; severe: > 40 °C)
Notes	**Location:** Germany

Ehrlich 2003

Methods	**Design:** randomized controlled trial **Generation of allocation sequence:** unclear **Allocation concealment:** not described **Blinding:** double blind for the first 2 doses, open label for dose 3 **Inclusion of all randomized participants in the analysis:** immunogenicity analysis was carried out on 397 participants out of 405 enrolled (98%); all participants were included in safety assessment for dose 1 (100%), 398 were included in safety analysis after dose 2 (98%), and 372 in safety analysis after dose 3 (92%) **Length of follow up:** for immunogenicity, blood samples taken at baseline, 21 to 35 days after second dose, and 21 to 28 days after third dose; enzyme-linked immunosorbent assay (ELISA) determined at baseline and after second and third doses; neutralization test after third dose only **Length of follow up:** for safety, fever measured daily orally measured for 4 days after immunization; local and systemic reactions (with exclusion of fever) measured by physical examination 7 to 10 days after first dose, 21 to 35 days after second dose, 21 to 28 days after third dose, and 35 to 42 days after the third
Participants	**Number:** 405 healthy adults aged 16 to 65 years **Inclusion criteria:** not reported **Exclusion criteria:** positive ELISA at baseline
Interventions	**Vaccine:** FSME-IMMUN (new) **Immunogenicity study:** 1. 0.6 µg/0.5 mL 2. 1.2 µg/0.5 mL 3. 2.4 µg/0.5 mL **Schedule (3 doses):** dose 1 on day 0; dose 2 on 21 to 35 days after dose 1; dose 3 at 6 months (± 14 days) after dose 2
Outcomes	1. Antibody responses determined by ELISA (after dose 1 and 2) and by ELISA and neutralization test (after dose 3):

Ehrlich 2003 *(Continued)*

	a. Seroconversion, defined as ELISA value was < 63 Vienna International Units (VIEU)/mL before study entry and at least 126 VIEU/mL after the respective vaccination, or if the neutralization test 100 value was > 10 b. Geometrical mean concentration (by ELISA and neutralization test) measured after dose 2 and 3 2. Adverse events: a. Local reactions: mild (pain at injection site; tenderness), moderate and severe; physical examination 7 to 10 days after dose 1, 21 to 35 days after dose 2, 35 to 42 days after dose 3 b. Fever: mild (38.0 °C to 39.0 °C); moderate (39.1 °C to 40.0 °C); severe (> 40 °C) measured orally for at least 4 days after each of vaccinations c. Systemic reactions (excluding fever): mild, moderate, and severe; physical examination as for local reactions
Notes	**Location:** Belgium

Girgsdies 1996

Methods	**Design:** randomized controlled trial with 40 sites **Generation of allocation sequence:** not described **Allocation concealment:** not described **Blinding:** double blind **Inclusion of all randomized participants in the analysis:** 506/522 (97%) for immunogenicity; 519/522 (99%) for safety **Length of follow up:** 42 ± 5 days after dose 1 for immunogenicity, 2 days after each dose for safety
Participants	**Number:** 522 healthy children (aged 1.5 to 14 years) and 191 healthy adults (aged 18 to 60 years); only children randomized – adults included as comparison group for antibody titres **Inclusion criteria:** children residing in endemic areas; participants had to be tick-borne encephalitis (TBE) negative before immunization **Exclusion criteria:** not reported
Interventions	**Vaccine:** Encepur **Dose-finding study:** 1. 0.4 µg/0.5 mL (173 children) 2. 0.75 µg/0.5 mL (175 children) 3. 1.5 µg/0.5 mL (174 children, 191 adults) **Schedule (3 doses):** days 0, 7, and 21
Outcomes	1. TBE antibody responses assayed by enzyme-linked immunosorbent assay (ELISA) and neutralization test at day 42 (± 5 days) after dose 1: a. Seroconversion, defined as ELISA antibody > 200 at day 42 (± 5 days); neutralization test, when samples neutralize 50% of an amount of virus corresponding to 100 µL diluted 1: 20; serum samples of 243 children were available for this determinations b. Geometrical mean titre (ELISA), geometrical mean titre (neutralization test), only about 243 children 2. Adverse reaction during 2 days after each inoculation: a. Local reactions: reddening, swelling, and pain b. General reactions: raised temperature 38 °C to 39 °C, asthenia, joint pain (arthralgia), headache, nausea and vomiting

Girgsdies 1996 *(Continued)*

Notes	**Location:** TBE-endemic areas near 40 different medical practices (paediatricians, general practitioners, and industrial medicine physicians) in Germany

Harabacz 1992

Methods	**Design:** randomized controlled trial with 7 centres **Generation of allocation sequence:** not described **Allocation concealment:** not described **Blinding:** double blind **Inclusion of all randomized participants in the analysis:** 379/379 (100%) for safety; 356/379 (94%) for efficacy **Length of follow up:** for immunogenicity (328 days for conventional schedule; 321 for abbreviated schedule); for safety (28 days after each immunization respect to adverse drug events and 5 days for axillary body temperature)
Participants	**Number:** 379 healthy adults aged 18 to 69 years (240 male and 139 female) **Inclusion criteria:** not described **Exclusion criteria:** not described
Interventions	**Vaccine:** Encepur **Dose-finding study (3 different doses and 2 immunization schedules):** 1. 1.0 µg/0.5 mL 2. 1.5 µg/0.5 mL 3. 2.0 µg/0.5 mL **Schedules (3 doses):** 1. Conventional (days 0, 28, and 300) 2. Abbreviated (days 0, 7, and 21) Immunization was intramuscular in the deltoid
Outcomes	1. Seroconversion at days 28, 42, 56, 300, 314, and 328 (conventional) and at days 21, 35, and 321 (abbreviated); antibody titres were assayed by enzyme-linked immunosorbent assay (ELISA), haemagglutination inhibition test, and neutralization test; lower limit for seroconversion defined as 8 in haemagglutination inhibition test, 2 in neutralization test and 160 in ELISA; geometric mean of tick-borne encephalitis (TBE) antibody titres on the same days 2. Adverse events assessed up to 28 days following each vaccination: asthenia, malaise, fever (> 37.5 °C; within 5 days after each dose), injection site hypersensitivity and/or pain, headache
Notes	**Location:** TBE-endemic areas near 7 study centres (3 in Germany, 1 in Czechoslovakia, 2 in Yugoslavia, and 1 in Switzerland)

Immuno 1996

Methods	**Design:** randomized controlled trial **Generation of allocation sequence:** computer algorithm based on pseudo random numbers

Immuno 1996 *(Continued)*

	Allocation concealment: identically labelled syringes with 3-digit code **Blinding:** double blind **Inclusion of all randomized participants in the analysis:** 1125/1191 (94%) for immunogenicity; 1149/1191 (96%) for safety **Length of follow up:** 49 to 70 days
Participants	**Number:** 1191 volunteers; stratified by age range (< 45 years and ≥ 45 years); not specified but probably carried out on adult population **Inclusion criteria:** tick-borne encephalitis (TBE) antibody titre < 50 Vienna International Units (VIEU)/mL in the enzyme-linked immunosorbent assay (ELISA) at the pre-vaccination screening **Exclusion criteria:** not reported
Interventions	**Vaccine:** FSME-IMMUN **Vaccine vs placebo:** 1. FSME-IMMUN, 1 µg/dose (300 participants) 2. New investigational TBE vaccine plus thimerosal (preservative) (296 participants) 3. New investigational TBE vaccine without thimerosal (298 participants) 4. Placebo (composition not given) (297 participants) **Schedule (2 doses):** 2 x 0.5 mL (1 µg) doses at day 0, then after 21 to 35 days
Outcomes	1. Seroconversion, defined as 2-fold increase in the TBE antibody titre by ELISA and neutralization test 28 to 35 days after dose 2 compared to baseline 2. Adverse events (mild/moderate/severe, further classified into local only/systemic only/local and systemic): symptoms included local reactions, crawling, formication, headache, fever, feeling unwell, dizziness, nausea, loss of appetite, myalgia, abdominal pain, fatigue, sleeplessness, and tremor; measured 1 month after each dose by diary cards
Notes	**Location:** living near 2 centres in Hungary

Loew-Baselli 2006

Methods	**Design:** randomized controlled trial (multicentred)
	
	Generation of allocation sequence: not described
	
	Allocation concealment: not described
	
	Blinding: single blind (participants)
	
	Inclusion of all randomized participants in the analysis: 150 did not return to the screening visit; 23 did not receive third vaccination but gave information about adverse effects; 49 not immunized because resulted seropositive
	
	• Safety:
	  • Systemic reaction excluding fever: 3966/3966 (100%) were included in safety analysis after dose 1, 3927/3966 (99%) after dose 2, and 3705/3966 (93%) after dose 3
	  • Systemic reactions including fever only: 3922/3966 (99%) were included in safety analysis after dose 1, 3891/3966 (98%) after dose 2, and 3692/3966 (93%) after dose 3
	  • Immunogenicity analysis carried out on a subset of the study population (564/3966, 14%)

Participants	**Number:** 3966 healthy volunteers aged 16 to 65 years

Loew-Baselli 2006 *(Continued)*

	Inclusion criteria: not described **Exclusion criteria:** history of tick-borne encephalitis (TBE) infection or vaccination were excluded from per protocol analysis
Interventions	**Vaccines:** FSME-IMMUN (new) and Encepur **Comparison of different vaccines:** 1. FSME-IMMUN (new) 2. Encepur Participants randomized 3:1 in order to receive 2 doses of each vaccine 21 to 35 days apart. All participants who received 2 vaccine doses received 1 dose of FSME-IMMUN 6 months after first dose
Outcomes	1. Adverse events occurred within 4 days after immunization, determined accordingly to Common Toxicity Criteria a. Temperature: mild (38.0 °C to 39.0 °C), moderate (39.1 °C to 40.0 °C), severe (> 40 °C) b. Local reactions c. Systemic reactions (headache, muscle pain, joint pain, fatigue, malaise)
Notes	**Location:** 14 centres in Poland

Pavlova 1999

Methods	**Design:** randomized controlled trial **Generation of allocation sequence:** not described **Allocation concealment:** not described **Blinding:** unclear **Inclusion of all randomized participants in the analysis:** 147/223 (66%) included in immunogenicity analysis; 201/223 included in safety analysis (90%) **Length of follow up:** 6 months for immunogenicity; 6 to 7 days after each dose for safety
Participants	**Number:** 223 healthy children aged 7 to 17 years **Inclusion criteria:** not ill with tick-borne encephalitis (TBE); not inoculated against TBE; no contraindications **Exclusion criteria:** not described
Interventions	**Vaccines:** IPVE and FSME-IMMUN **Comparison of different vaccine types:** 1. IPVE vaccine (prepared for use in 1-dose ampoules of 0.5 mL) 2. FSME-IMMUN (prepared for use with a tube-syringe 1 dose of 0.5 mL) **Schedule:** 2 intramuscular 0.5 mL doses, 4 months apart
Outcomes	1. Antibody titre determined by haemagglutination inhibition test (commercial test NPO "Virion") before and within 28 days after each vaccination: a. Seroconversion: 4-fold titre increase b. Geometrical mean titre 2. Adverse events: evaluated 5 to 7 days after administration: fever (weak: 37.1 °C to 37.5 °C; moderate: 37.6 °C to 38.5 °C; severe: ≥ 38.6 °C)

Pavlova 1999 *(Continued)*

Notes	**Location:** an unspecified TBE-endemic region in Russia **FSME-IMMUN:** even if not reported in the paper, the commercial preparation used until 1999 containing 1 to 3.5 µg antigen/0.5 mL-dose, should have been used

Schoendorf 2007

Methods	**Design:** randomized controlled trial **Generation of allocation sequence:** not described **Allocation concealment:** not described **Blinding:** not blind (open) **Inclusion of all randomized participants in the analysis:** all participants included in safety evaluation; only per-protocol participants included in efficacy data analysis (mainly due to time window violation, 3 participants in group R and 3 in group M excluded because seropositive on day 0); they represent 91% in Group R, 93% in group M, and 92% in group C
Participants	**Number:** 294 healthy children aged 1 to 11 years **Inclusion criteria:** not described **Exclusion criteria:** history of tick-borne encephalitis (TBE) infection; TBE or yellow fever vaccination; hypersensitivity to any vaccine component; receiving any treatment interfering with immune response; severe disease or already enrolled in an investigational trial
Interventions	**Vaccine:** Encepur children **Comparison of different vaccine schedules:** 1. Rapid (group R): days 0, 7, and 21 (82 participants) 2. Conventional (group C): days 0, 28, and 300 (73 participants) 3. Modified conventional (group M): days 0, 21, and 300 (139 participants) Participants stratified by age (1 to 5 and 6 to 11 years) and randomized at 1:1:2 ratio to 1 of 3 schedules Administered intramuscularly in the M. deltoideus
Outcomes	1. TBE antibody response determined by enzyme-linked immunosorbent assay (ELISA) or neutralization test on serum samples taken on days 0, 42, 180, and 300. Another sample on day 321 taken from groups M and C; seroconversion was generically described for ELISA determination (on day 42), but an exact number of individuals not provided; for neutralization test, the proportions of individuals with a value of at least 10 at days 42, 300, and 321 were reported 2. Adverse events (participants observed for 30 minutes after immunization, participants' parents noted reactions on diary cards within 4 days after immunization): • For participants aged up to 2 years: systemic (sleepiness, irritability, change in eating habits) and local (erythema, swelling, tenderness) • For participants aged at least 3 years: systemic (headache, nausea, myalgia, malaise, arthralgia) and local (erythema, swelling pain) Temperature rectally measured in younger children and orally in those aged from 3 and over
Notes	**Location:** Hungary (Budapest and Vasc Regions)

Schöndorf 2007

Methods	**Design:** randomized controlled trial **Generation of allocation sequence:** not described **Allocation concealment:** not described **Blinding:** not blind (open) **Inclusion of all randomized participants in the analysis:** 356/398 (89.5%) for efficacy; exact number of participants for whom data were available not provided for safety **Length of follow up:** 321 days for efficacy; 4 days for safety
Participants	**Number:** 398 healthy adults and adolescents of both sexes aged 12 to 65 years **Inclusion criteria:** not reported **Exclusion criteria:** allergy to any vaccine components; severe chronic or acute disease; previous known tick-borne encephalitis (TBE) infection; previous TBE or yellow fever vaccination
Interventions	**Vaccine:** Encepur adults **Comparison of 4 different schedules:** 1. Group R: rapid schedule with vaccination on days 0, 7, and 21 2. Group C: conventional schedule with vaccination on days 0, 28, and 300 3. Group M: modified conventional schedule with vaccination on days 0, 21, and 300 4. Group A: accelerated conventional schedule with vaccination on days 0, 14, and 300 Participants randomized in a 1:1:2:2 ratio to 1 of the 4 groups
Outcomes	1. Antibody response determined by neutralization test (reciprocal dilution leading to complete protection of at least 50% of the cell culture) or enzyme-linked immunosorbent assay (ELISA) (commercial Enzygnost test, Dade Behring); on serum samples taken on days 0, 21, 42, 180, 300, and 321 were determined: a. Seropositivity (neutralization test ≥ 2) or seroconversion (neutralization test ≥ 10) b. Geometrical mean titre determined with neutralization test and ELISA 2. Adverse effects: participants observed for 30 minutes after immunization, local and systemic reactions occurred within 4 days after immunization were recorded for 4 days after each vaccination
Notes	**Location:** not specified but all participants were Caucasian

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Baumhackl 2003	Small cohort study carried out on 30 participants with confirmed diagnosis of multiple sclerosis
Craig 1999	Cohort study to state an accelerated immunization schedule for military personnel or travellers
Dengler 1999	Study carried out in heart transplanted recipients with the aim to evaluate vaccine efficacy in a risk population
Hedenstrom 1995	Randomized study comparing the effect on immunogenicity and adverse events of TBE vaccine alone or TBE vaccine plus immunoglobulin in 128 adults; no unvaccinated or placebo groups
Leonova 2007	Study in which antibody response to Encepur vaccine was determined; no control group

Study	Reason for exclusion
Mamoli 1981	Randomized study comparing the effect of TBE vaccine and placebo on electroencephalogram (EEG) as a marker of a post-vaccine reaction
Panasiuk 2003	Small non-randomized study (8 women, 21 men) carried out in HIV-infected people to investigate immunogenicity and safety of the vaccine against TBE
Rosenkranz 1997	Not original data; definition of equivalence criterion on data from Girgsdies 1996
Schöndorf 2006	No control group; effect of booster dose administration in participants who were already immunized with rapid schedule at least 2 years before
Vene 2007	Not comparative design; serological comparison of 3 groups of participants with different immunization history
Zent 2003	Multicentre study with no control group to investigate immune response after booster immunization with new TBE vaccine for adults (Encepur)
Zoulek 1986	Small study (20 participants) comparing immune response following intradermal or intramuscular administration of FSME-IMMUN to young adults in Germany; no randomization mentioned

HIV: human immunodeficiency virus; TBE: tick-borne encephalitis.

Characteristics of studies awaiting assessment *[ordered by study ID]*

Popov 1985

Methods	**Design:** unclear; this study was included in the previous version of this review, but the review authors have re-examined the study and are seeking clarification about the study design before the data can be included or excluded in a future update **Length of follow up:** for immunogenicity 60 to 74 days for scheme 1; 180 to 194 days for scheme 2; 21 days for safety
Participants	**Number:** young men aged 18 to 25 years without contraindications for the vaccine Reported that a number of 100 to 115 participants enrolled in each arm, but total number of enrolled participants not reported
Interventions	**Vaccine:** KKhv (dried chromatographic concentrated and purified TBE vaccine) **Vaccine vs placebo (administered to 6 groups on 2 different schedules):** KKhV vaccine at month 0 and 6: 1. MID50 4.9 µL; administered by syringe subcutaneously 2 x 1 mL doses (94 men) 2. MID50 4.9 µL; administered by syringe subcutaneously in 2 x 0.5 mL doses (203 men) 3. MID50 4.9 µL; administered by BI-3 injector 2 x 1 mL doses (113 men) 4. MID50 4.9 µL; administered by BI-3 injector 2 x 0.5 mL doses (114 men) KKhV vaccine at month 0 and 2: 5. MID50 4.9 µL; administered by syringe subcutaneously 2 x 1 mL doses (number unclear) 6. MID50 4.9 µL; administered by syringe subcutaneously 2 x 0.5 mL doses (number unclear) Placebo (all vaccines components except for the virus), administered to 2 groups, at months 0 and 2 or 6 (not specified in the text): 7. Placebo, syringe subcutaneously, 1.0 mL dose (78 men) 8. Placebo, injector, 1.0 mL dose (unclear number of participants)

Popov 1985 *(Continued)*

	Control (isotonic sodium chloride solution) administered to 2 groups at months 0 and 2 or 6 (not specified in the text): 9. Control, syringe subcutaneously, 1.0 mL dose (136 men) 10. Control, injector, 1.0 mL dose (104 men) **Schedule:** preparations 1 to 6 were administered at months 0 and 6; preparations in comparisons 1 were also administered at months 0 and 2
Outcomes	1. Seroconversion of tick-borne encephalitis (TBE) antibody titres (detected by haemagglutination inhibition test and neutralization test) at day 14 after termination of the vaccination course (samples taken before vaccination and on 14 days after dose 2); seroconversion definition was difficult to assess 2. Geometrical mean titre detected by haemagglutination inhibition test 3. SIN (mean magnitude of neutralization test) by neutralization test 4. Number of post vaccination reactions after each inoculation over a 21-day period: a. Temperature reactions (37 °C to 37.5 °C, 37.6 °C to 38.5 °C, > 38.6 °C) b. General reactions (headaches, malaise) c. Local reactions (swelling, flushes) d. Induration (to 2.5 cm, 2.5 to 5 cm, > 5 cm)
Notes	**Location:** former USSR (exact location not given)

Wright 2008

Methods	**Design:** double-blind randomized placebo controlled study conducted in two phases (Phase 1:a first dose of vaccine or placebo administered to participants; Phase 2: a second dose of vaccine or placebo admnistered to participants) **Length of follow up:** 180 days for Phase 1 and Phase 2 studies
Participants	**Number:** 28 healthy adult volunteers
Interventions	**Vaccine:** live-attenuated Langat/dengue 4 chimeric virus vaccine **Placebo:** vaccine diluent **Schedule:** 2 x 0.5 mL/dose (Phase 1: first dose; Phase 2: second dose) subcutaneously in the deltoid region
Outcomes	1. Seroconversion defined as a serum neutralizing antibody titer of at least 1:20 compared with pre-vaccination titre < 1:5 2. Geometric mean titre 3. LGT/DEN4 virus infection; vaccine related meningoencephalitic-like syndrome 4. Local reactogenicity 5. Headache, rash, fever, neutropenia, elevated ALT level 5. Serious adverse events (hospitalization, congenital anomaly or birth defect, disability, death)
Notes	**Location:** Nashville area (USA)

Characteristics of ongoing studies *[ordered by study ID]*

NCT00118924

Trial name or title	"Phase 1 Study of the Safety and Immunogenicity of Tick-Borne Langat/Dengue 4 Chimera (LGT(T-P21)/DEN4), a Live Attenuated Vaccine for Tick-Borne Encephalitis"
Methods	Randomized controlled trial; Phase I study
Participants	**Inclusion criteria:** healthy adults aged 18 to 50 years; willingness to use contraception **Exclusion criteria:** pregnancy; clinically significant diseases; blood diseases; history of encephalitis, alcohol or drug use, allergic reaction or anaphylaxis; human immunodeficiency virus-1 (HIV-1) or hepatitis C infection; use of corticosteroids or immunosuppressive drugs; previously immunization with other vaccines; history of tick-borne encephalitis (TBE) or dengue or flavivirus infection
Interventions	1. Live-attenuated LGT(TP21)/DEN4 vaccine (10^3 or 10^5 PFU) 2. Placebo **Schedule:** 2 doses subcutaneously administered 6 months apart
Outcomes	1. Immunogenicity of vaccine against anti-Langat neutralizing antibody (at days 0, 28, 42, and 180) 2. Frequency of vaccine-related adverse effects, graded by intensity and severity through active and passive surveillance (throughout study)
Starting date	July 2005
Contact information	**Principal Investigators:** Anna Durbin, MD (Center for Immunization Research, Johns Hopkins School of Public Health); Peter Wright, MD (Vanderbilt University School of Medicine)
Notes	**Location:** Tennessee Vanderbilt University School of Medicine, Nashville, Tennessee, USA

NCT00161746

Trial name or title	"Multicentre Randomized Double-Blind Phase II/III Study on the Safety and Immunogenicity of Three Vaccinations With TICOVAC in Two Dosages in Healthy Children Aged Between Six Months and Three Years"
Methods	Randomized controlled trial; Phase II and III study
Participants	**Inclusion criteria:** healthy children aged between 6 and 47 months; no history of previous tick-borne encephalitis (TBE) vaccination **Exclusion criteria:** allergic reactions; diseases of the central nervous system; human immunodeficiency virus (HIV) positive; febrile disease; history of vaccination with yellow fever or Japanese encephalitis; participation in another clinical trial
Interventions	1. Inactivated TBE vaccine TICOVAC Schedule: 2 and/or 3 partial vaccinations with TICOVAC 0.25 mL and TICOVAC 0.5 mL
Outcomes	1. Seroconversion rates 2. Safety
Starting date	April 1998

NCT00161746 *(Continued)*

Contact information	Not available
Notes	**Location:** Austria **Sponsor:** Baxter Healthcare Corporation

NCT00161772

Trial name or title	"Double-Blind, Randomized, Multicenter Dose-Finding Study to Investigate the Safety and Immunogenicity of Two Vaccinations With FSME IMMUN NEW in Healthy Volunteers Aged 1 to 6 Years"
Methods	Randomized controlled trial; Phase II study
Participants	**Inclusion criteria:** healthy children aged between 1 and 5 years **Exclusion criteria:** history of previous tick-borne encephalitis (TBE) vaccination or TBE infection; allergic reactions; received antipyretics before immunization; chronic, degenerative and/or inflammatory disease of the central nervous system; human immunodeficiency virus (HIV) seropositivity; febrile illness at study entry; history of yellow fever and/or Japanese encephalitis
Interventions	Inactivated TBE vaccine administered in 3 different dosages
Outcomes	1. Safety 2. Immunogenicity
Starting date	March 2002
Contact information	**Principal investigator:** Ulrich Behre, MD Hauptstrasse 240, 77694 Kehl, Germany
Notes	Sponsor: Baxter Healthcare Corporation

NCT00161785

Trial name or title	"Investigation of the Seropersistence of TBE Antibodies and the Booster Response to FSME-IMMUN 0.5 ml in Adults Aged 18 - 67 Years"
Methods	Randomized controlled trial; Phase IV study
Participants	**Inclusion criteria:** age 18 to 67 years; received the third vaccination with FSME-IMMUN during the course of Baxter study 213 and had blood samples collected before it showing an enzyme-linked immunosorbent assay (ELISA) concentration > 126 Vienna International Units (VIEU)/mL and/or neutralization test (NT) titre ≥ 1:10 **Exclusion criteria:** receiving of any tick-borne encephalitis (TBE) vaccination after third vaccination with FSME-IMMUN; received yellow fever and/or Japanese encephalitis vaccine; human immunodeficiency virus (HIV)-positive; drug or alcohol abuse; blood transfusion; participation in other Baxter vaccine studies within the last 6 months
Interventions	Inactivated TBE vaccine "FSME-IMMUN" (0.5 mL)
Outcomes	1. TBE antibody persistence 2 and 3 years after the third TBE vaccination by means of ELISA and NT 2. TBE antibody response to a booster vaccination, by means of ELISA and NT

NCT00161785 *(Continued)*

Starting date	June 2004
Contact information	**Principal investigator:** Ryszard Konior, MD Szpital Jana Pawla II Oddzial Neuroinfekcji, Krakow, Poland
Notes	**Locations:** Hospital in Debica - Zespo Opieki Zdrowotnej w Debicy, Debica, Poland, 33-200; Szpital Jana Pawla II Oddzial Neuroinfekcji, Krakow, Poland **Sponsor:** Baxter Healthcare Corporation

NCT00161798

Trial name or title	"Double-Blind, Randomized, Multicenter Dose-Finding Study to Investigate the Safety and Immunogenicity of Two Vaccinations With FSME IMMUN NEW in Healthy Volunteers Aged 6 to 16 Years"
Methods	Randomized controlled trial; Phase II study
Participants	**Inclusion criteria:** healthy children aged between 6 and 15 years **Exclusion criteria:** previous tick-borne encephalitis (TBE) vaccination or infection (screening enzyme-linked immunosorbent assay (ELISA) > 126 Vienna International Units (VIEU)/mL and/or neutralization test > 1:10); allergic reactions; antipyretics within 4 hours before TBE vaccination; chronic, degenerative and/or inflammatory disease of the central nervous system; human immunodeficiency virus (HIV) positive; febrile illness at study entry; history of yellow fever and/or Japanese encephalitis vaccination; participation in another trial; pregnancy or breast feeding
Interventions	Inactivated TBE vaccine FSME-IMMUN NEW administered in 3 different dosages
Outcomes	1. Safety 2. Immunogenicity
Starting date	September 2001
Contact information	**Principal investigator:** Ulrich Behre, MD, Hauptstrasse 240, 77694 Kehl, Germany
Notes	**Location:** Germany **Sponsor:** Baxter Healthcare Corporation

NCT00161824

Trial name or title	"Single-Blind, Randomized, Multicenter Comparison of FSME IMMUN NEW and ENCEPUR: Safety and Tolerability of Two Vaccinations in Healthy Volunteers Aged 16 to 65 Years"
Methods	Randomized controlled trial; Phase III study
Participants	**Inclusion criteria:** healthy adults aged between 16 and 65 years; not pregnant **Exclusion criteria:** history of tick-borne encephalitis (TBE) vaccination or TBE infection (screening enzyme-linked immunosorbent assay (ELISA) > 126 Vienna International Units (VIEU)/mL); allergic reactions; previously receiving of products containing polygeline; antipyretics within 4 hours before first dose of TBE vaccine; chronic, degenerative and/or inflammatory disease of the central nervous system; use of immunosuppressive drugs; problems with drug or alcohol abuse; plasma or

NCT00161824 *(Continued)*

	blood donation within 1 month of study start; human immunodeficiency virus (HIV) positive; febrile illness at study entry; history of yellow fever and/or Japanese encephalitis vaccination; participation in another trial; pregnancy or breastfeeding
Interventions	Inactivated TBE vaccines 1. FSME-IMMUN NEW (5 different lots) 2. Encepur adults (2 different lots) **Schedule:** administered in 2 doses 21 to 35 days apart
Outcomes	Safety
Starting date	October 2001
Contact information	**Principal investigator:** Jerzy Romaszko, MD PANTAMED sp. z o o. Olsztyn, Poland, 10-461
Notes	**Location:** Poland **Sponsor:** Baxter Healthcare Corporation

NCT00161850

Trial name or title	"Follow-Up Study to Investigate the Safety and Immunogenicity of a Third Vaccination With Three Different Antigen Concentrations of FSME IMMUN NEW in Children Aged 1 to 6 Years"
Methods	Randomized controlled trial; Phase II study
Participants	**Inclusion criteria:** volunteers (age 1 to 6 years) who participated in Baxter study 199 and received 2 vaccinations with 1 of 3 different dosage of FSME IMMUN NEW **Exclusion criteria:** to be not clinically healthy; third dose of tick-borne encephalitis (TBE) vaccine elsewhere administered; developed allergic reactions to 1 vaccine component since vaccination in study Baxter 199; disease influencing immunological functions; have received blood or immunoglobulins within 1 month of study entry; vaccination against yellow fever and/or Japanese encephalitis
Interventions	Vaccination with 3 different antigen concentrations of FSME IMMUN NEW
Outcomes	1. Safety 2. Immunogenicity
Starting date	February 2002
Contact information	Not provided
Notes	**Location:** Germany **Sponsor:** Baxter Healthcare Corporation

NCT00161889

Trial name or title	"Follow-Up Study to Investigate the Safety and Immunogenicity of a Third Vaccination With Three Different Antigen Concentrations of FSME IMMUN NEW in Children Aged 6 to 16 Years"
Methods	Randomized controlled trial; Phase II study
Participants	**Inclusion criteria:** volunteers who participated in Baxter study 205; received 2 vaccination with 1 of 3 different dosage of FSME IMMUN NEW **Exclusion criteria:** to be not clinically healthy; third dose of tick-borne encephalitis (TBE) vaccine elsewhere administered; developed allergic reactions to 1 vaccine component since vaccination in study Baxter 205; disease influencing immunological functions; have received blood or immunoglobulins within 1 month of study entry; vaccination against yellow fever and/or Japanese encephalitis
Interventions	Vaccination with 3 different antigen concentrations of FSME IMMUN NEW
Outcomes	1. Safety 2. Immunogenicity
Starting date	February 2002
Contact information	Not provided
Notes	**Location:** Germany **Sponsor:** Baxter Healthcare Corporation

NCT00311441

Trial name or title	"A Phase IV, Randomized, Controlled, Single-Blind, Multi-Center Study in Children to Evaluate the Safety, Tolerability and Immunogenicity of Two TBE Vaccines Administered According to Two Different Schedules"
Methods	Randomized controlled trial; Phase IV study
Participants	**Inclusion criteria:** healthy male and female children; 1 to 10 years of age **Exclusion criteria:** documented tick-borne encephalitis (TBE) infection and/or have been previously vaccinated with TBE vaccine
Interventions	2 TBE vaccines administered according 2 different schedules.
Outcomes	1. Immunogenicity measured by neutralization test and enzyme-linked immunosorbent assay (ELISA) on days 28, 42, 300, and 321 2. Tolerability with respect to local and systemic reactions including fever
Starting date	March 2005
Contact information	Not provided
Notes	**Location:** Germany **Sponsor:** Novartis

NCT00311493	
Trial name or title	"A Phase IV, Randomized, Open-Label, Multi-Center Study in Adults: Evaluation of Long-Term Immunogenicity in Subjects Boosted With a New TBE Vaccine for Adults (Free of Protein-Derived Stabilizer) in Study V48P2E1, 5 Years After First Booster Immunization and Evaluation of Booster Kinetics in Subjects Boosted With a New TBE Vaccine for Adults (Free of Protein-Derived Stabilizer), 5 Years After First Booster Immunization"
Methods	Randomized controlled trial; Phase IV study
Participants	**Inclusion criteria:** healthy volunteers of both sexes aged >18 who participated in another study on tick-borne encephalitis (TBE) vaccination **Exclusion criteria:** subjects with any condition, in the opinion of the Investigator, might interfere with the evaluation of the study objectives
Interventions	Inactivated TBE vaccine
Outcomes	1. Long-term antibody kinetics as measured both by enzyme-linked immunosorbent assay (ELISA) and neutralization test (NT) 5 years after first booster immunization 2. Booster response in a subset of subjects as measured by NT, ELISA, and cellular immunity on days 3, 5, 7, and 21 after second booster immunization
Starting date	February 2006
Contact information	Not provided
Notes	**Location:** Germany **Sponsor:** Novartis

APPENDICES

Appendix 1. Country profiles: endemic for tick-borne encephalitis

Country	Cases	Peak areas	Main *Ixodes* vectors	Vaccination
Austria	2003: 87 cases Incidence rate: 1.09/100,000 2007: 46 cases Incidence rate: 0.6/100,000 (Donoso Mantke 2008)	South-Austrian endemic areas (Steiermark/Styria) (Beran 2004)	*I. ricinus*	1981: voluntary immunization campaign (highly purified FSME-IMMUN vaccine)
Czech Republic	2000: 37.4 cases/100,000 in South Bohemia 2004: 507 cases Incidence rate: 5.0/100,000 2007: 546 cases	South Bohemia, Prague, North Moravian region, valleys of Berounka and Vltava rivers, regions around Vranov and	*I. ricinus*	Partial financial support for vaccination of children and adolescents aged < 18 years across the whole country

(Continued)

	Incidence rate: 5.3/100,000 (Donoso Mantke 2008)	Kninic dams in south Moravia		
Finland	1990s: 10 to 20 cases per year 2000: 41 cases (Strauss 2004) 2004: 29 cases Incidence rate: 0.6/100,000 2007: 20 cases Incidence rate: 0.4/100,000 (Donoso Mantke 2008)	Coastal regions of Finland and near Saimaa Lake; Åland islands; Archipelago of Turku, the Kokkola and Lappeenranta regions	*I. ricinus*	Vaccination recommended for all people aged > 7 years living in endemic areas; thus vaccine not part of the Finnish National Immunisation Program
Germany	1991 to 2001: about 1723 cases, with mean incidence of 1.2% in Baden-Württemberg 2001: 256 cases 2004: 274 cases Incidence rate: 0.3/100,000 2007: 236 cases Incidence rate: 0.3/100,000 (Donoso Mantke 2008)	Bayern and Baden/Württemberg regions	*I. ricinus*	Recommended for those at high risk of exposure
Hungary	1977 to 1996: average incidence of 2.5/100,000 (range 1.3 to 3.8) (Strauss 2004) 2004: 76 cases Incidence rate: 0.8/100,000 2007: 63 cases Incidence rate: 0.6/100,000 (Donoso Mantke 2008)	Counties of Zala, Somogy, Vas (western Hungary), and Nograd (northern Hungary)	*I. ricinus*	Introduced in 1977 for risk groups and offered to all since 1991
Latvia	1997 to 2000: average of 26.9/100,000 2004: 251 cases Incidence rate: 10.8/100,000 2007: 157 cases Incidence rate: 6.9/100,000 (Donoso Mantke 2008)	Region of Riga, the city park results strong contaminated; thus virus has spread in the whole country	*I. ricinus* (active April to November in western and central Latvia), and *I. persulcatus* (active from March to July in east)	1994: campaign to vaccinate children started in the areas with higher risk (Lucenko 2004)
Lithuania	Incidence 1993: 5.3 1994: 7.6 1995: 11.5 1996: 8.4	All districts of the country	*I. ricinus*	Vaccination recommended, but government does not provide financial assistance for this, and people have to pay the full costs themselves; coverage too low to

(Continued)

	1998: 14.8 (Süss 2003) 2003: 763 cases; 22/100,000 2004: 425 cases Incidence: 12.3/100,000 2007: 233 cases Incidence: 6.5/100,000 (Donoso Mantke 2008)			control the disease (Asokliene 2004)
Poland	2002: incidence 0.33/100,000; 126 cases 2003: 0.89/100,000; 339 cases 2004: 262 cases Incidence: 0.7/100,000 2007: 233 cases Incidence rate: 0.6/100,000 (Donoso Mantke 2008)	North-east provinces (Gdansk, Elblag and Olsztyn), and east (Suwalki and Byalistok) and southern regions (Opole) (Süss 2003)	*I. ricinus*	Recommended for high-risk groups living in endemic areas and tourists visiting endemic places
Slovenia	2001: 260 cases 2002: 262 cases 2003: 272 cases; incidence of 13.6/100,000 2004: 204 cases Incidence rate: 10.2/100,000 2006: 373 cases Incidence rate: 18.6/100,000 (Donoso Mantke 2008)	Central and mountainous parts	*I. ricinus*	Obligatory only for military personnel and other professional categories; recommended to anybody who spends time outdoor in the endemic areas, including short-term visitors
Russia	Average annual incidence rate exceeds 12 cases/100,000 (Süss 2003) 2004: 4221 cases Incidence rate: 2.9/100,000 2007: 3162 Incidence rate: 2.2/100,000 (Donoso Mantke 2008)	Ural, Siberia, and in the Far East regions	*I. persulcatus* (active May to mid-June)	Reccommended for high-risk groups (Zlobin 2005)
China	No precise data about morbidity available 1994: 3500 cases reported	2 foci have been identified: 1 in Hunchun area (Jilin Province) and other in western Yunnan	*I. ovatus* (strongly related to the Far Eastern subtype)	No information
Japan	Only 1 severe case diagnosed in 1993 (Hokkaido Island); no other confirmed cases have since been reported	None	*I. ovatus*	No information

Appendix 2. Types of vaccines

Vaccine type	Specific vaccine	Status	Year developed (approximate)	Components	Notes	Producer	Trials
—	KKhv	Unclear	1985	TBE strain K23 (grown on chick-embryo cells, formalin inactivated, purified, stabilized with polygeline and adsorbed onto 0.2% alum) Prepared from the Sofin strain, which is of the Far Eastern TBE subtype	—	Academy of Medical Sciences, former USSR	Popov 1985 (awaiting assessment)
—	IPVE	Unclear	1999	Inactivated, dry, purified concentrated suspension of the Sofin strain Contains no more than 30 µg of extrinsic protein and aluminium hydroxide gel as solvent	Prepared for use in 1-dose ampoules (0.5 mL)	Chumakov Institute of Poliomyelitis and Viral Encephalitides (IPVE)	Pavlova 1999
FSME-IMMUN	FSME-IMMUN [1976]	Not licensed	1976	Neudoerfl strain TBE virus (European subtype) grown in a chick-embryo cell culture partially purified by hydroxyapatite chromatography and inactivated by formalin with aluminium hydroxide as an adjuvant	In Western Europe, First TBE vaccine developed in Western Europe (Kunz 1992) Reports of adverse effects (headache, malaise, pyrexia) were common	Baxter (Immuno AG)	—
	FSME-IMMUN [1980]	Not licensed	1980	A "highly purified" version consisting of TBE-virus antigen purified by continuous flow zonal ultracentrifugation (1 µg/dose) Formaldehyde-inactivated TBE virus (1 to 3.5 µg) prepared from a "seed virus" cultivated on mouse brain suspension and containing aluminium hydroxide (1 mg) as adjuvant Stabilized with addition of human seroalbumin (0.5 µg)	Developed in response to adverse effects with 1976 version Led to the development of the highly purified version 3 intramuscular doses of 0.5 mL each containing 2 to 3 µg of inactivated TBE virus antigen at 0, 3, and 10 to 13 months, with booster doses recommended every 3 years (Kunz 1992)	Baxter (Immuno AG)	Immuno 1996 Pavlova 1999

(Continued)

			Preparation also contained thiomerosal (0.05 mg) as preservative and 0.35 mg of Na-EDTA as stabilizer			
FSME-IMMUN [1999]	Not licensed	1999	Preparation had same composition of the precedent vaccine (quantity of sugary and buffer solutions were unvaried), but it did not contain conservant thiomerosal and stabilizer Na-EDTA	With the aim to observe the new instructions of the "European Pharmacopoeia" (Council of Europe 1999), this new FSME-IMMUN vaccine was introduced on the market	Baxter (Immuno AG)	—
TicoVac	Not licensed	2000	Concerns of contamination from mouse brain proteins led producers to cultivate seed virus using chick embryo cells instead First vaccine not to contain human seroalbumin stabilizer and prepared with adjuvant only (aluminium hydroxide) Formaldehyde-inactivated prepared with aluminium hydroxide as an adjuvant TBE virus strain Neudorfl grown on primary chick embryo fibroblasts, purified and concentrated by sucrose density centrifugation No albumin or thiomersal Antigen content 2.7 µg target; 2 to 3.5 µg range	High rate of adverse events (eg fever and convulsions in children) meant this vaccine not successful	Baxter (Immuno AG)	Eder 2003i Eder 2003ii
FSME-IMMUN (new)	Licensed	2001	Human seroalbumin re-included in formulation	Conventional vaccination schedule consists of 3 doses at birth, 1 to 3 months, and 9 to 12 months after second dose Rapid immunization schedule involves 2 vaccine doses given 2 or 3 weeks apart (Beran 2004) Fewer adverse reactions observed	Baxter (Immuno AG)	Ehrlich 2003 Loew-Baselli 2006

(Continued)

	FSME-IMMUN (Junior)	Licensed	2002	Paediatric formulation containing the half dose of all components present in the adult formulation (Barrett 2003)	—	Baxter (Immuno AG)	—
Encepur	Encepur (aged at least 12 years)	Not licensed	1991	Contains TBE virus (K23, European subtype) isolated from a tick near Karlsruhe, Germany Virus grown on primary chick embryo cells, inactivated by formaldehyde, purified with continuous-flow density gradient centrifugation, adjuvated with aluminium hydroxide and stabilized with polygeline (gelatine + Tris-EDTA-buffer, + K glutamate 0.1%)	—	Chiron-Behring (now part of Novartis)	Bock 1990 Harabacz 1992 Girgsdies 1996 Loew-Baselli 2006
	Encepur K (paediatric formulation)	Not licensed	1991	Contains half dose of antigen, excipients, adjuvant of Encepur	Many adverse reactions observed in consequence to the high IgE response to the gelatin stabilizer, and Encepur K withdrawn from the market	Chiron-Behring (now part of Novartis)	—
	Encepur adults	Licensed	Unclear	Contains inactivated TBE virus antigen (strain K23, 1.5 µg), aluminium hydroxide (1 mg), formaldehyde (max 5 µg), salts, sucrose, and water Poligeline free Each 0.5 mL dose contains 1.5 µg of TBE virus strain K23 formalin inactivated and adjuvanted with 1.0 mg aluminium hydroxide, and sucrose (25 mg) as stabilizer an was intramuscularly administered	Licensed for rapid immunization schedule on days 0, 7, and 21 followed by a fourth dose 12 to 18 months later (Barrett 2003)	Novartis	Schöndorf 2007
	Encepur children	Licensed	Unclear	Contains half the dose of antigen (0.75 µg antigen/0.25 mL dose), excipients, adjuvant compared to the adult preparation	Licensed for rapid immunization schedule on days 0, 7, and 21 followed by a fourth dose 12 to 18 months later (Barrett 2003)	Novartis	Schoendorf 2007

(Continued)

				Poligeline free			
—	Chimeric live-attenuated vaccines	Under study	—	Prepared with the use of a recombinant technique by replacing membrane precursor and envelope structural protein genes of non-neuroinvasive, mosquito-borne dengue 4 virus (DEN4) with the corresponding genes of langat virus strain TP21	—	—	Wright 2008

TBE: tick-borne encephalitis.

Appendix 3. Search methods: detailed search strategies

Search set	CIDG SR[a]	CENTRAL	MEDLINE[b]	EMBASE[b]	LILACS[b]
1	tick-borne encephalitis	tick-borne encephalitis	tick-borne encephalitis	TICK-BORNE ENCEPHALITIS	tick-borne encephalitis
2	tick borne encephalitis	tickborne encephalitis	tickborne encephalitis	tickborne encephalitis	tickborne encephalitis
3	1 or 2	ENCEPHALITIS, TICK-BORNE	ENCEPHALITIS, TICK-BORNE	tick NEXT borne NEXT encephalitis	1 or 2
4	vaccin*	1 or 2 or 3	1 or 2 or 3	1 or 2 or 3	vaccin*
5	3 and 4	vaccin*	vaccin*	vaccin$	3 and 4
6	—	4 and 5	4 and 5	4 and 5	—
8	—	—	Limit 5 to human	Limit 5 to human	—

[a]Cochrane Infectious Diseases Group Specialized Register.
[b]Search terms used in combination with the search strategy for retrieving trials developed by The Cochrane Collaboration (Lefebvre 2006); upper case: MeSH or EMTREE heading; lower case: free text term.

Appendix 4. Risk of bias assessment

Trial	Generation of allocation sequence	Allocation concealment	Blinding	Inclusion of all randomized participants
Bock 1990	Unclear	Unclear	Single	Adequate
Eder 2003i	Unclear	Unclear	Double	Adequate
Eder 2003ii	Unclear	Unclear	Double	Adequate
Ehrlich 2003	Adequate	Unclear	Double (first 2 doses) and open (for dose 3)	Adequate
Girgsdies 1996	Unclear	Unclear	Double	Adequate
Harabacz 1992	Unclear	Unclear	Double	Adequate
Immuno 1996	Adequate	Adequate	Double	Adequate
Loew-Baselli 2006	Unclear	Unclear	Single (participants)	Adequate
Pavlova 1999	Unclear	Unclear	Not mentioned	Inadequate for efficacy adequate for safety

(Continued)

Schoendorf 2007	Unclear	Unclear	Open	Adequate
Schöndorf 2007	Unclear	Unclear	Open	Inadequate for efficacy and unclear for safety

Appendix 5. Dose findings

Vaccine used	Trial	Population	Outcome measure	Results
Encepur	Bock 1990	56 healthy males aged 20 to 50 years	Geometric means of TBE antibody titres 28 days after second inoculation (as assayed by ELISA, haemagglutination inhibition test, and neutralization test): minimum, median, and maximum values	1 µg dose of vaccine required to induce > 90% seroconversion after 2 doses
Encepur	Harabacz 1992	279 healthy adults aged 18 to 69 years	Seroconversion at days 0, 28, 42, 56, 300, 314, and 328 (conventional schedule), and at days 0, 21, 28, 35, 49, and 321 (abbreviated schedule); seroconversion defined as 8 in haemagglutination inhibition test, 2 in neutralization test, and 160 in ELISA	"No major differences were detected between three dosage between 1 and 2 mcg either in immunogenicity or in respect of reactogenicity"
FSME-IMMUN (new)	Ehrlich 2003	405 healthy adults aged 16 to 65 years	Seroconversion, defined as ELISA value, was < 63 VIEU/mL before study entry and at least 126 VIEU/mL after respective vaccination, or if the neutralization test 100 value was > 10	After 2nd dose (ELISA) 1.2 vs 0.6 µg: RR 1.13 (1.05 to 1.22) 2.4 vs 0.6 µg: RR 1.14 (1.06 to 1.23) After 3rd dose (ELISA) 1.2 vs 0.6 µg: RR 1.03 (0.99 to 1.07) 2.4 vs 0.6 µg: RR 1.04 (1.01 to 1.08)
TicoVac	Eder 2003i	298 toddlers, aged 6 months to 3 years	Seroconversion defined as a positive ELISA result of at least 126 VIEU/mL or 4-fold titre increase	2.57 vs 1.29 µg 2nd dose: RR 1.13 (0.99 to 1.28) 3.29 vs 1.65 µg 3rd dose: all reached seroconversion
TicoVac	Eder 2003ii	261 children aged 4 to 12 years	Seroconversion defined as a positive ELISA result of at least 126 VIEU/mL or 4-fold titre increase	3.29 vs 1.65 µg 2nd dose: RR 1.06 (1.01 to 1.10) 3.29 vs 1.65 µg 3rd dose: all reached seroconversion

ELISA: enzyme-linked immunosorbent assay; RR: risk ratio: TBE: tick-borne encephalitis; VIEU: Vienna International Units.

WHAT'S NEW

Date	Event	Description
25 September 2008	New search has been performed	Search updated.

Date	Event	Description
23 November 2007	New citation required but conclusions have not changed	**Change in authorship:** MG Debalini and A Rivetti joined the author team, and P Graves, M Pratt, and T Jefferson stepped down. **New trials:** three new trials added as the result of an updated literature search. **Methods:** revised the methods for assessing risk of bias. **Results:** changed from a meta-analysis to a narrative summary because of differences in comparisons and outcome measures. **General text revision:** updated the text, including the background information.

HISTORY

Protocol first published: Issue 1, 1998
Review first published: Issue 1, 1998

Date	Event	Description
25 May 2003	Amended	Minor edits to text (including title (from 'Tick-borne encephalitis (TBE) vaccines' to current title), abstract, and objectives).

CONTRIBUTIONS OF AUTHORS

AR and MGD applied the inclusion criteria, extracted data from the new included trials, updated the background section, and revised the final version of the review. VD supervised and arbitrated when necessary during all phases of the updating.

DECLARATIONS OF INTEREST

None known.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

None stated.

INDEX TERMS

Medical Subject Headings (MeSH)

Encephalitis, Tick-Borne [immunology] [*prevention & control]; Randomized Controlled Trials as Topic; Viral Vaccines [immunology] [*therapeutic use]

MeSH check words

Adult; Child; Humans; Infant