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Review

Prevention of tick-borne encephalitis by FSME-IMMUN® vaccines: Review of a clinical development programme

Alexandra Loew-Baselli, Eva Maria Poellabauer, Borislava G. Pavlova, Sandor Fritsch, Clair Firth, Robert Petermann, P. Noel Barrett, Hartmut J. Ehrlich*

Global R&D, Baxter BioScience, Wagramer Str. 17-19, A-1221 Vienna, Austria

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ABSTRACT

The need for highly effective tick-borne encephalitis (TBE) vaccines has increased globally due to a variety of factors including climate, social, economic and demographic changes, which are thought to have promoted the expansion of the endemic region of TBE viruses. The first TBE vaccine, FSME-IMMUN® Inject, was introduced in the 1970s and has been continually improved since then to enhance both its safety and immunogenicity. The current formulation was established in 2001 and is marketed as FSME-IMMUN®. This review summarizes findings of the clinical development programme since 2001 regarding determination of the optimal dose, conventional and rapid vaccination schedules, vaccination in adults, the elderly and special patient populations, safety, immunogenicity, and immunopersistence in adults and children, comparison of FSME-IMMUN® with another commercially available TBE vaccine as well as post-marketing vaccination outcome. This successful research programme demonstrated the strong immunogenicity and continued safety of the FSME-IMMUN® vaccine, which is further confirmed by the performance reported under field conditions.

Contents

1. Introduction

Tick-borne encephalitis virus (TBEV), one of the major human pathogenic flaviviruses, is endemic in many European countries and also across Central and Eastern Asia to Northern Japan and China [1,2]. Although most infections with TBEV are asymptomatic,

* Corresponding author. Tel.: +43 1 20 100 2472420; fax: +43 1 20 100 2475758.
E-mail address: borislava_pavlova@baxter.com (H.J. Ehrlich).

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10–12,000 clinical tick-borne encephalitis (TBE) cases are reported worldwide each year, and morbidity appears to be increasing [1–4]. Approximately 3000 cases of TBE requiring hospitalization are recorded annually in Europe [5]. Disease manifestations include meningitis, meningoencephalitis and meningoencephalomyelitis, which may result in life-long disability or death. No effective curative treatments currently exist for TBEV infection, and therefore prophylactic vaccination remains the primary defence. Increasing prevalence of TBE in areas where it was previously rare has generated additional focus on the most effective vaccination schedules and monitoring practices in preventing the disease [6,7].

The first prophylactic TBEV vaccine, FSME-IMMUN® Inject, was introduced in the 1970s in Austria and tested on approximately 30,000 at-risk individuals (e.g. forest workers) in endemic areas, none of whom subsequently developed TBE (compared to a pre-vaccine infection rate of around 1/1000 in at-risk individuals in Austria) [8,9]. The vaccine was continually improved to further enhance both its safety and immunogenicity [10,11] and the final modified formulation was established in 2001 and marketed as FSME-IMMUN® (Baxter AG, Vienna, Austria). In 2003, Baxter's first dedicated vaccine for children and adolescents (FSME-IMMUN Junior®, based on half the adult dose) was introduced.

An extensive clinical trial programme was undertaken to characterize both the adult and paediatric FSME-IMMUN vaccines with regard to dose, schedule, safety, immunogenicity, comparison with Encepur® and Encepur® Children (Novartis Vaccines and Diagnostics GmbH & Co., Marburg, Germany) and antibody persistence. Both the conventional and rapid immunisation schedules were assessed. A rapid immunisation schedule has long been established for travellers to TBE-endemic areas requiring protection at short notice or for rapid protection of endemic area populations during seasons with widespread tick activity (i.e. spring to autumn).

TBEV vaccinees require periodic booster shots to maintain adequate protection, and recently the optimal booster intervals have been much debated. Clinical studies suggested that the first booster establishes sufficient immunity and that subsequent boosters can be spaced further apart, at least in those aged <60 years. The FSME-IMMUN® clinical development programme therefore includes investigation of immunopersistence to support the rationale for the booster intervals.

This review summarizes the outcome of the FSME-IMMUN® clinical development programme encompassing completed and ongoing phase I/II, phase II/III clinical trials, observational studies, as well as findings of other published data pertaining to the immunogenicity, safety, and field effectiveness of the adult and paediatric vaccine formulations in healthy subjects of all age groups and special patient populations.

2. Immunogenicity evaluation

The FSME-IMMUN® clinical development programme encompasses 13 studies which investigated the immunogenicity of the vaccine in adult and paediatric populations. Additional review and analysis of published literature on FSME-IMMUN (4 further studies) is also included here. Tables 1–3 provide details of all studies covered in this review.

2.1. Dose finding

The optimal adult dose of FSME-IMMUN® was assessed in a prospective study of 16–65 year olds who received 0.6, 1.2 or 2.4 μg of TBEV antigen (Table 1) [12]. As shown in Fig. 1(a), while the two higher doses led to comparable seroconversion rates, the geometric mean concentration (GMC) was significantly higher following the second vaccination with 2.4 μg than with 1.2 μg TBEV antigen. Based on predefined immunogenicity and safety criteria for dose selection, 2.4 μg was determined to be the optimal dose for an adult population [12].

Prior to the development of a paediatric vaccine formulation, clinical practice in Austria was to administer the full or half of the adult dose to children living in TBE-endemic areas. Following active post-marketing surveillance in 1899 children (aged 1–12 years) who received half the adult dose of FSME-IMMUN® vaccine (approximately 1.2 μg TBE antigen) [13], 101 children (92% of whom were 1–3 years) were administered a prefilled 1.2 μg TBEV antigen dose in a prospective pilot study (Table 1) [10]. Almost all subjects in this study achieved seroconversion after the second vaccination, with the GMC reaching 1807.2 VIE U/ml and increasing to 5239.0 VIE U/ml after the third vaccination. Consequently, it was decided to carry out dose-finding studies in children and adolescents in order to ascertain the ideal antigen level for this age group.

As children and adolescents respond differently to vaccination due to variations in the level of immune system maturity [14,15], dose-finding studies in an extended population aged ≤15 years[1] were included in the vaccine development programme to compare immunogenicity results from this adolescent population (aged 12–15 years) with that previously obtained from adults. Two companion dose-finding studies investigated the immunogenicity and safety of 0.3, 0.6 or 1.2 μg doses in paediatric populations aged 1–5 and 6–15 years (Table 1) [16]. Both the 0.6 μg and the 1.2 μg doses were found to be highly immunogenic in the younger age group. As shown in Fig. 1(e), a dose-dependent GMC response to increasing concentrations of antigen was observed after the second and third vaccinations in 1–5 year olds. The vaccine also induced high, but slightly lower seroconversion rates in 6–15 year olds than in the younger age group (Fig. 1(c)). Likewise, a dose-dependent GMC response was evident after the second and third vaccinations among these older children (Fig. 1(f)). Based on these immunogenicity data (and predefined safety parameters), 1.2 μg was assessed as being the preferred dose in children 1–15 years old.

A multicentre study further confirmed the immunogenicity of the 1.2 μg vaccine dose in a subgroup ($n = 373$) of children and adolescents aged 1–15 years [17]. After the second vaccination, seroconversion rates as well as GMC and GMT were high (>10-fold above cut-off levels) (Table 1). Among adolescents aged 12–15 years ($n = 64$), seroconversion after the second vaccination was 96.9%, with a GMC of 820 VIE U/ml. Comparison of immunogenicity between adolescents (aged 12–15 years) vaccinated with the optimal paediatric dose (1.2 μg) and adults (aged 16–35 years) vaccinated with the 2.4 μg formulation of FSME-IMMUN®, demonstrated similarly high seroconversion rates. The FSME-IMMUN® vaccine formulation was thus found to be appropriate not only for children < 12 years but also for adolescents < 16 years [17]. Consequently, Baxter's first dedicated vaccine for children and adolescents (FSME-IMMUN Junior®) was introduced in 2003.

2.2. Primary immunogenicity

Primary immunogenicity according to the conventional immunisation schedule with the FSME-IMMUN® and FSME-IMMUN Junior® vaccines refers to the first and second vaccinations administered one to three months apart, followed by the third vaccination approximately 6–12 months later. Rapid immunisation refers to the first two vaccinations being administered 14 days apart, followed by the third vaccination 9–12 months later. The immunogenicity

[1] Subjects were eligible for participation in the studies if they were aged between 1 year and 16 years old (until the last day before their 16th birthday).

Table 1
Dose-finding FSME-IMMUN® studies using a conventional vaccination schedule with 0.6–2.4 μg in adults and 0.3–1.2 μ g in children.

Study description	N analysed (immunogenicity/ safety datasets)	Study design	Immunogenicity outcome seroconversion	Safety outcome (after the 1st vaccination)
Adults aged 16–65 years	405	Prospective, single centre study FSME-IMMUN®: 3 dose groups (0.6, 1.2 and 2.4 μg), subjects vaccinated on Day 0, Day 21–35 and Day 180	ELISA *After the 2nd vacc:* 0.6 μg = 85.1% 1.2 μg = 96.2% 2.4 μg = 97.0% *After the 3rd vacc:* 0.6 μg = 96.0% 1.2 μg = 99.2% 2.4 μg = 100%	*Fever rate* 0.6 μg = 0.0% 1.2 μg = 2.2% 2.4 μg = 0.0% *Systemic reactions (inc. fever)* 0.6 μg = 19.0% 1.2 μg = 18.8% 2.4 μg = 22.2% *Local reactions* 0.6 μg = 29.2% 1.2 μg = 36.9% 2.4 μg = 32.6%
Children aged 6 months–12 years	1899	Post-marketing surveillance – estimated children's dose of 1.2 μg/0.25 ml FSME-IMMUN®	Not done	*Fever rate:* 20.3%[a] (of which 15.8% was mild [≤39.0 °C])
Children aged 1–12 years	101	Prospective pilot study, prefilled 1.2 μg dose of FSME-IMMUN® Subjects vaccinated on Day 0, Day 14–32, Day 284–360	ELISA and/or NT *After the 2nd vacc:* 99% *After the 3rd vacc:* 100%	*Fever rate*: 29.7% (of which 22.8% was mild [≤39.0 °C])[b] *Local reactions:* 34.0% *Systemic reactions* (*excl. fever*): 31.0%
Children aged 1–5 years	618	Prospective, multicentre study, FSME-IMMUN Junior®: 3 dose groups (0.3, 0.6 or 1.2 μg), subjects vaccinated on Day 0, Day 21–35 and Day 180	ELISA and/or NT *After the 2nd vacc*: 0.3 μg = 93.2% 0.6 μg = 98.1% 1.2 μg = 100% *After the 3rd vacc*: 0.3 μg = 98.5% 0.6 μg = 99.5% 1.2 μg = 100%	*Fever rate* 0.3 μg = 19.8% 0.6 μg = 16.3% 1.2 μg = 15.9% *Systemic reactions (excl. fever)* 0.3 μg = 8.3% 0.6 μg = 13.0% 1.2 μg = 7.7% *Local reactions* 0.3 μg = 13.4% 0.6 μg = 16.7% 1.2 μg = 12.0%
Children aged 6–15 years	619	Prospective, multicentre study, FSME-IMMUN Junior®: 3 dose groups (0.3, 0.6 or 1.2 μg), subjects vaccinated on Day 0, Day 21–35, and Day 180	ELISA and/or NT *After the 2nd vacc:* 0.3 μg = 88.4% 0.6 μg = 96.3% 1.2 μg = 98.5% *After the 3rd vacc:* 0.3 μg = 95.8% 0.6 μg = 99.1% 1.2 μg = 100%	*Fever rate* 0.3 μg = 4.5% 0.6 μg = 3.3% 1.2 μg = 3.4% *Systemic reactions* (*excl. fever*) 0.3 μg = 10.2% 0.6 μg = 12.2% 1.2 μg = 10.4% *Local reactions* 0.3 μg = 21.8% 0.6 μg = 24.9% 1.2 μg = 17.5%
Children aged 1–15 years	373/2417	Prospective, multicentre, confirmatory study FSME-IMMUN Junior® (1.2 μg), subjects vaccinated on Day 0, Day 28, and Day 180	*After the 2nd vacc*: ELISA = 96.0% NT = 95.7% *After the 3rd vacc*: ELISA/NT = 100%	*Fever rate*: 9.7% *Local reactions*: 24.6% *Systemic reactions* (*excl. fever*): 20.3%

[a] 88% of the children aged <3 years.
[b] 92% of the children aged 1–3 years.

Table 2
Primary immunogenicity following vaccination with FSME-IMMUN® and comparator product (Encepur®) in adults and children.

Study description	N analysed (immunogenicity/ safety datasets)	Study design	Immunogenicity outcome	Safety outcome (after the 1st vaccination)
Adults aged 16–65 years	566/3705	Multicentre, randomized, comparative study: FSME-IMMUN® (2.4 μg) or Encepur® – 1st and 2nd vaccinations; 3rd FSME-IMMUN® vaccination, administered on Day 0, Day 21, Day 180	ELISA and/or NT (seroconversion) *After the 2nd vacc:* N/A as safety study only *After the 3rd vacc:* FSME-IMMUN® only group = 99.5% Encepur®/FSME-IMMUN® group = 99.3%	*Fever rate*: FSME-IMMUN® = 0.8% Encepur® = 5.6% *Local reactions*: FSME-IMMUN® = 35.6% Encepur® = 44.7% *Systemic reactions* (*inc. fever*): FSME-IMMUN® = 14.0% Encepur® = 32.3%
Children aged 1–11 years	303	Multicentre, randomized, comparative study: FSME-IMMUN Junior® (1.2 μg) or Encepur Children® (0.75 μg) – 1st and 2nd vaccinations; 3rd FSME-IMMUN Junior® vaccination, administered on Day 0, Day 28 and Day 360)	*Seropositivity after the 2nd vacc:* FSME-IMMUN Junior®: ELISA Immunozym[a] = 100% ELISA Enzygnost[b] = 100% NT = 100% Encepur Children®: ELISA Immunozym = 94.0% ELISA Enzygnost = 96.7% NT = 97.8% *After the 3rd vacc with FSME-IMMUN Junior®:* ELISA Immunozym = 100% ELISA Enzygnost = 100% NT = 100%	*Fever rate*: FSME-IMMUN Junior® = 8.0% Encepur Children® = 9.2% *Local reactions:* FSME-IMMUN Junior® = 12.7% Encepur Children® = 28.9% *Systemic reactions* (*excl. fever*): FSME-IMMUN Junior® = 9.3% Encepur Children® = 11.8%
Elderly (>60 years) (Jilkova et al. [21])	185	Serological response to tick-borne encephalitis (TBE) vaccination in the elderly—results from an observational study: FSME-IMMUN® or Encepur® administered to previously unvaccinated subjects	*Seropositivity 4–8 weeks after 2nd vacc:* FSME-IMMUN®: ELISA Immunozym approx. 95% ELISA Enzygnost approx. 80% NT approx. 80% Encepur®: ELISA Immunozym approx. 65% ELISA Enzygnost approx. 80% NT approx. 55%	Not reported
Adults aged 16–65 years	60	Open, single-centre study: FSME-IMMUN®, subjects vaccinated according to rapid immunisation schedule on Day 0, Day 12 ± 2, Day 360	*Seropositivity 14 days after the 2nd vacc:* ELISA = 92.9% NT = 98.2% *Seropositivity 21 days after the 2nd vacc:* ELISA = 96.4% NT = 100% *After 3rd vacc:* ELISA = 100% NT = 100%	*Fever rate:* 0% *Local reactions:* 38.3% *Systemic reactions:* 15.0%

Adults aged 16–65 years	340	Prospective, multicentre study, stratification by age Subjects vaccinated according to rapid immunisation schedule on Day 0, Day 12 ± 2, Day 180	ELISA and/or NT *Seropositivity 14 days after the 2nd vacc:* 16–49 years = 94.8% 50+ years = 82.2% Seropositivity 21 days after the 2nd vacc: 16–49 years = 98.0% 50+ years = 89.9% *Seropositivity 21 days after the 3rd vacc:* 16–49 years = 100% 50+ years = 99.3%	*Fever rate*: 16–49 years = 1.2% ≥50 years 0% *Local reactions:* 16–49 years = 17.6% ≥50 years 13.5% *Systemic reactions* (*inc. fever*): 16–49 years = 10.0% ≥50 years 9.4%
Children aged 1–11 years (Wittermann et al. [24])	334	Antibody response following administration of two different paediatric tick-borne encephalitis vaccines using two different vaccination schedules. Children in the FSME-14 group received FSME-IMMUN Junior® on Day 0, Day 14, and Encepur Children® on Day 300. Results of the rapid schedule are presented here	NT (Neudoerfl strain) *Seropositivity 14 days after the 2nd vacc:* FSME-IMMUN Junior® approx. 95% Encepur Children® approx. 100% *Seropositivity 21 days after the 2nd vacc:* FSME-IMMUN Junior® approx. 85% Encepur Children® approx. 100% *Seropositivity 21 days after the 3rd vacc:* FSME-IMMUN Junior® approx. 95% Encepur Children® approx. 100%	*Fever rate* (*>39 °C*) FSME-IMMUN Junior® 1% Encepur Children® 1% *Injection site pain, malaise and headache in children > 3* years FSME-IMMUN Junior® 31% Encepur Children® 36%

[a] ELISA based on the Neudoerfl strain of TBEV, used in the FSME-IMMUN® vaccine.
[b] ELISA based on the K23 strain of TBEV, used in the Encepur® vaccine.

Table 3
Immunopersistence and booster response studies following vaccination with FSME-IMMUN® in children and adults.

Study description	N analysed (immunogenicity/safety datasets)	Study design	Immunogenicity outcome	Safety outcome (after the booster vaccination)
Adults aged 18–50 years and 51–67 years	347	Multicentre, prospective study, to assess seropersistence 2 and 3 years after completion of the primary vaccination	Seropositivity rate (ELISA and/or NT) *1 month after 3rd vacc: 100%* *2 years after 3rd vacc: 96.0%* *3 years after 3rd vacc: 95.0%*	*Fever rate:* 0% *Local reactions:* 6.7% *Systemic reactions:* 0.6%
Adults aged 18–52 years and >52 years	315/328	Multicentre, prospective study, to assess seropersistence 3 years after the first booster and the response to a second booster vaccination	Seropositivity rate (ELISA and/or NT) *Approx. 2 years after 1st booster* 18–52 years: 98.8% >52 years: 98.2% *Approx 3 years after 1st booster* 18–52 years: 100% >52 years: 100% *Approx 4 years after 1st booster* 18–52 years: 98.0% >52 years: 90.4% *Approx 5 years after 1st booster* 18–52 years: 96.8% >52 years: 86.3% *21–35 d after 2nd booster* (given at either 3, 4 or 5 years, according to subjects' immune status) 18–52 years: 100% >52 years: 100%	After the second booster *Fever rate:* 0% *Local reactions:* 3.1%. *Systemic reactions:* 6.3%
Children and adolescents aged 3–18[a] years	375	Multicentre, prospective study, age dependent dose (1.2 μg or 2.4 μg) to assess duration of immunity following primary vaccination and prior to the booster vaccination	Seropositivity rate (ELISA and/or NT) *1 month after 3rd vacc:* 100% *2 years after 3rd vacc:* 98.3% *3 years after 3rd vacc:* 98.0% *4 years after 3rd vacc:* 95% *5 years after 3rd vacc:* 86.9%	*Fever rate:* FSME-IMMUN® 0.5 ml 0% FSME-IMMUN® 0.25 ml 0% *Local reactions:* FSME-IMMUN® 0.5 ml 18.9% FSME-IMMUN® 0.25 ml 17.4% *Systemic reactions:* FSME-IMMUN® 0.5 ml 2.7% FSME-IMMUN® 0.25 ml 5.8%
Children aged 7–9 years	97	Seropersistence 3 years after booster vaccination with FSME-IMMUN Junior®	Seropositivity ELISA 100% NT 100%	N/A as no vaccine administered
Elderly, aged 50–90 years (Weinberger et al. [27])	79	Decreased antibody titres and booster responses in tick-borne encephalitis vaccinees aged 50–90 years – stratified by age	Data for subjects >59 years *3–4 years since last vaccination:* ELISA approx 2000 VIE U/ml NT approx. 40 Post-booster: ELISA approx. 7000 VIE U/ml NT approx. 130 5–7 years since last vaccination: ELISA < 1000 VIE U/ml NT < 50 Post-booster: ELISA approx. 4000 VIE U/ml NT approx. 100	Not reported
Adults, aged 18–49 years and ≥50 years (Rendi-Wagner et al. [28])	430	Persistence of protective immunity following vaccination against tick-borne encephalitis – longer than expected? All subjects previously vaccinated with FSME-IMMUN. Stratified by age	Seropositivity rate *3–5 years since last vaccination:* 18–49 years ELISA Enzygnost 100% NT 100% ≥50 years ELISA Enzygnost 96% NT 100% *6–7 years since last vaccination:* 18–49 years ELISA Enzygnost 99% NT 100% ≥50 years ELISA Enzygnost 96% NT 100% *≥8 years since last vaccination:* 18–49 years ELISA Enzygnost 99% NT 100% ≥50 years ELISA Enzygnost 81% NT 100%	Not reported

[a] NB. The 18 year old adults included in this study were initially 15–16 years old when included in the original study and were then vaccinated with FSME-IMMUN Junior, for subsequent boosters they now receive the adult formulation.

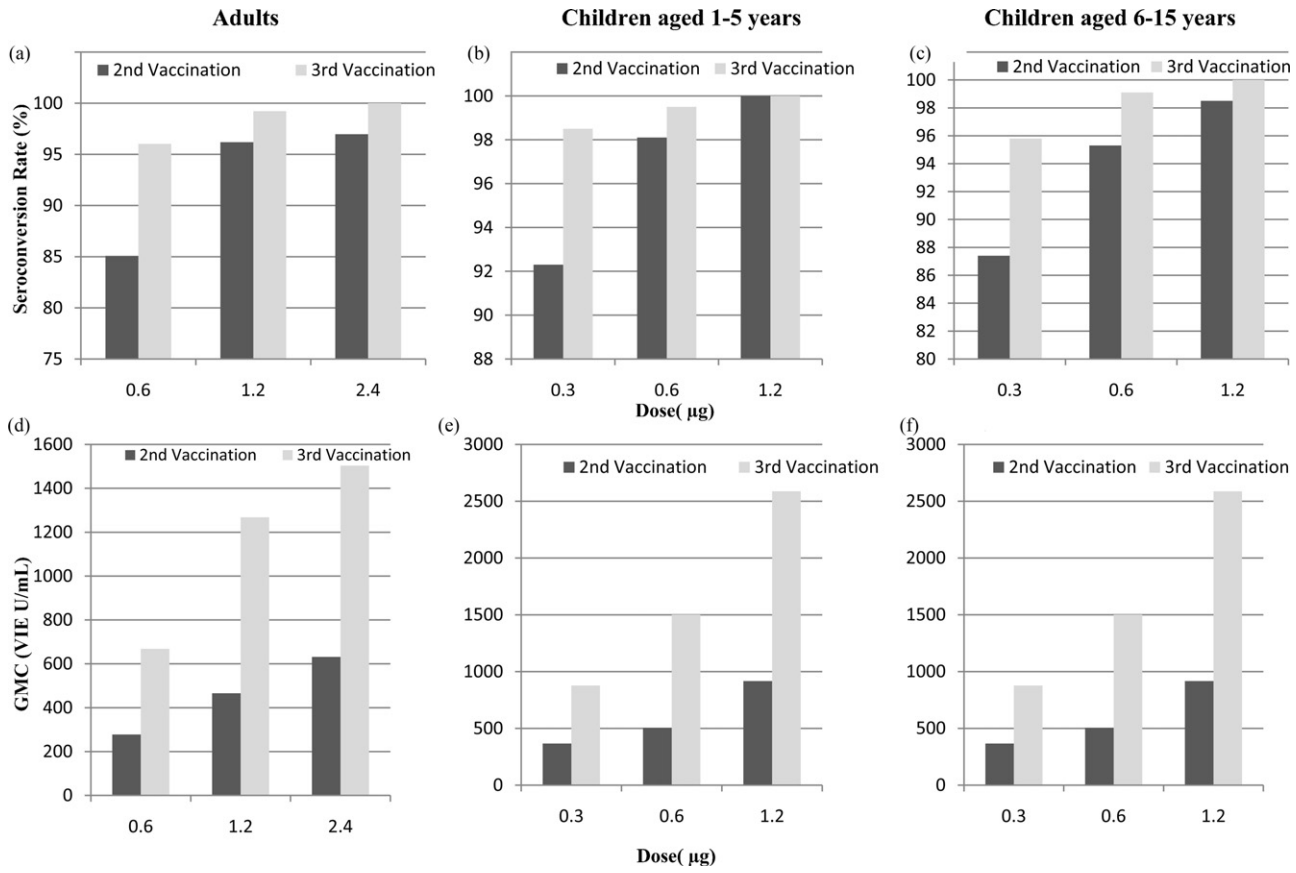

Fig. 1. Dose responses to the second and third FSME-IMMUN® vaccinations using a conventional vaccination schedule with 0.6–2.4 µg in adults and 0.3–1.2 µg in children. Seroconversion rates as determined by an Immunozym FSME-IgG ELISA value > 126 Vienna units (VIE U) per ml and/or neutralization titre (NT) ≥ 1:10 are shown in (a) adults and children, (b) 1–5 years and (c) 6–15 years old. GMC findings are presented for the same age groups ((d), (e) and (f), respectively). *Abbreviation*: GMC, geometric mean concentration.

of the primary vaccination series according to the conventional schedule was investigated in a subset of subjects (16–65 years old) participating in a multicentre, randomized safety study (Table 2). Subjects received either FSME-IMMUN® or Encepur® (earlier formulation stabilised with polygeline) TBE vaccine for the first two vaccinations, and all received FSME-IMMUN® for the third [18]. Comparable GMCs of the FSME-IMMUN® and Encepur® groups immediately before the third vaccination (Fig. 2), and the strong immune response to the third vaccination with FSME-IMMUN® regardless of previous TBEV vaccine administered, demonstrated that two vaccinations with Encepur® can be successfully followed by a third vaccination with FSME-IMMUN®.

It is generally accepted that immunosenescence among the elderly leads to a lowered immune response. Several authors have suggested that adults aged >50–60 years are less responsive to TBE vaccines [19,20]; antibody titres post-vaccination are lower and decrease more rapidly than those of children and younger adults [19]. As TBE disease is generally more severe in older adults, maintenance of immunological protection against TBEV infection in the elderly is a major clinical concern. In a retrospective analysis of a single-centre observational study of subjects aged >60 years ($N = 185$) undergoing routine vaccination in the Czech Republic (Table 2), 18% (33/185) had TBEV antibody concentrations below the accepted seropositivity cut-off levels following two vaccinations with either FSME-IMMUN® ($N = 105$) or Encepur® ($N = 80$) [21]. GMCs were higher in those vaccinated with FSME-IMMUN® than with Encepur® according to two different ELISAs. Since ELISAs have, in the past, been reported to favour antibodies elicited by their homologous vaccines [22], interpretation of comparative studies must take into consideration the assay used. However, it should be noted that no significant difference could be determined between vaccines in the Czech study, regardless of whether the Immunozym[2] ELISA or the Enzygnost[3] assay was used [21].

A multicentre, randomized clinical study of children aged 1–11 years ($N = 303$) compared the immunogenicity of FSME-IMMUN Junior® and Encepur Children® (Table 2) [23]. At 28 days after the second dose, seropositivity (by NT) was 100% for FSME-IMMUN Junior® and 97.8% for Encepur Children® (Fig. 2) and remained high at day 180 with both vaccines. Furthermore, higher seropersistence 180 days after the first vaccination with FSME-IMMUN Junior® than with Encepur Children® was observed when evaluating seropositivity rates using two different ELISAs, Immunozym[2] and Enzygnost[3].

Another multicentre randomized trial directly comparing FSME-IMMUN Junior® and Encepur Children® reported a higher response to Encepur® [22,24]. Children aged 1–11 years received either FSME-IMMUN Junior® or Encepur Children® for the first two primary vaccinations on a conventional or rapid schedule (Table 2), with the third vaccination with Encepur Children® administered on day 300. Notably, regardless of vaccine administered, immune response in paediatric subjects was lower among those vaccinated according to the rapid immunisation schedule compared to the conventional one.

[2] ELISA based on the Neudoerfl strain of TBEV, used in the FSME-IMMUN vaccine.
[3] ELISA based on the K23 strain of TBEV, used in the Encepur vaccine.

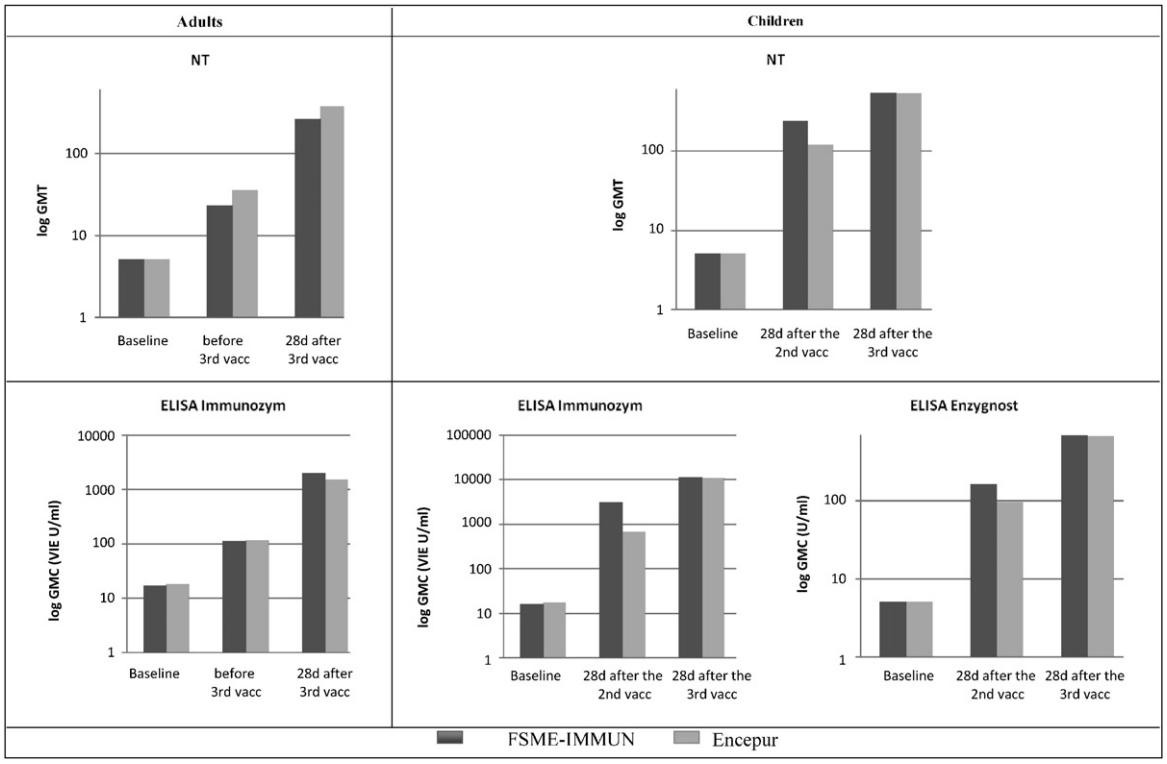

Fig. 2. Primary immunogenicity in adults and children vaccinated with either FSME-IMMUN® or Encepur® (adult or paediatric formulation as required). Geometric mean titres and concentrations as determined by a variety of serological tests. *Abbreviations*: GMC, geometric mean concentration; GMT, geometric mean titre; NT, neutralization titre.

The practice of administering the first and second doses according to a rapid schedule 14 days apart has been widely adopted in a number of European countries for many years. A clinical study of FSME-IMMUN® was undertaken in adults aged 16–65 years ($N = 60$) to determine antibody formation when using a rapid schedule (Table 2) [25]. Antibody titres were found to rise steadily and rapidly after the second vaccination. At approximately one year after the second dose, antibody levels declined to values close to or below the cut-off for seropositivity, and the third dose then induced an anamnestic booster response with higher antibody levels observed than after the second dose.

In a subsequent larger prospective study of adult subjects ($N = 340$) investigating the response to a rapid vaccination schedule with stratification by age (Table 2), 16–49 year olds predictably attained higher seropositivity rates than ≥50 year olds. The increase in seropositivity rates after the second vaccination demonstrates the suitability of the rapid immunisation schedule in providing substantial antibody titres after the first 2 vaccinations, and accelerated induction of high antibody titres in both age groups after the third vaccination confirms effective priming by the first two vaccinations when using a rapid immunisation schedule.

2.3. Immunopersistence

Traditionally, regular boosters were recommended every 3 years to maintain adequate protection for all age groups. To confirm this booster interval, a multicentre prospective study of FSME-IMMUN® assessed the persistence of TBEV antibodies 2 and 3 years after primary vaccination in adults ($N = 347$, Table 3) [26]. The investigation was a continuation of an earlier primary immunisation course study in adults using a conventional schedule [18]. Pre-booster seropositivity rates after 2 and 3 years were higher in 18–50 years olds than in 51–67 years olds. Seropositivity, as well as GMC and GMT levels, decreased most in the first two years and remained relatively constant during year 3 (Fig. 3). Based on NT, the estimated mean annual decline rate of antibodies was 0.58 after completion of the primary immunisation series. Seropositivity rates following booster vaccination were 100%, regardless of age and method of immunogenicity analysis. Notably, post-booster GMCs were approximately 2.5 and GMTs 1.5 times higher than those obtained upon completion of the primary vaccination series, indicating a robust booster response. This study suggests that the first booster can be administered >3 years after primary immunisation in a population aged 18–50 years; however, these findings need to be confirmed by further research.

In a follow up study ($N = 315$, Table 3 and Fig. 3), the vast majority of subjects did not require another booster vaccination within three to five years after the administration of the first booster vaccination. As expected, seropositivity rates were higher among subjects aged 18–52 years than for those aged >52 years. Logistic regression showed age to be the only variable with a significant effect on the probability of remaining TBE-seropositive after a first booster vaccination.

In a recently published study, antibody titres before and after a booster vaccination were determined in healthy subjects ($N = 79$) stratified into four age groups: <30 years, 50–59 years, 60–69 years and >69 years (Table 3) [27]. The subjects had received their last FSME-IMMUN® vaccination either 5–7 years or 3–4 years previously. Pre-booster antibody concentrations as well as neutralising titres were significantly higher among those aged < 30 years than in the three older age groups. The importance of regular booster intervals in elderly subjects was further highlighted by significantly lower antibody concentrations among subjects >60 years of age who had received their last TBE vaccination 5–7 years previously than in those vaccinated 3–4 years previously. Post-booster antibody concentrations and neutralising titres were also significantly

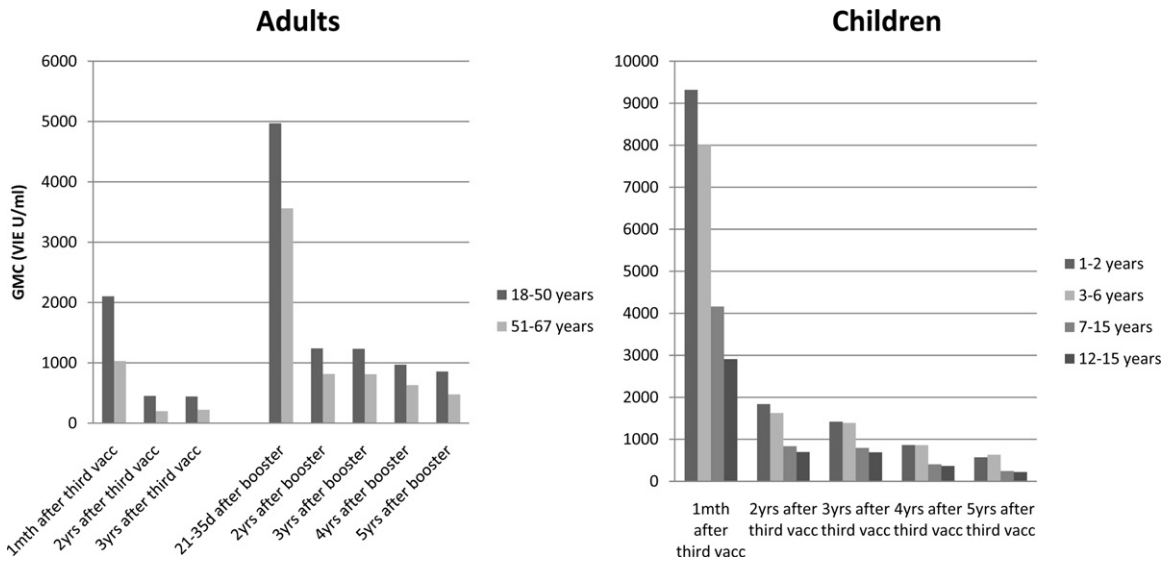

Fig. 3. Seropersistence in adults and children following vaccination with either FSME-IMMUN® or FSME-IMMUN® Junior. *Abbreviation*: GMC, geometric mean concentration.

higher in the <30 year age group, and did not differ between the three older age groups.

TBEV antibody persistence was also assessed in a retrospective study of adults ($N = 430$) previously vaccinated with FSME-IMMUN® (Table 3) [28,29]. Subjects were stratified by age (18–49 or ≥50 years) and by interval since the last TBE vaccination (3–5, 6–7 or ≥8 years). At ≥8 years since the last FSME-IMMUN® vaccination, 81–100% of subjects were seropositive, depending on assay used. Analysis of subjects who had received only primary immunisation and no boosters showed an estimated annual decline in neutralising antibodies starting at 3 years after the primary series of 14.6%, as determined by NT [29], compared to only 0.7% of subjects with at least one prior booster vaccination. This suggests that after the first and subsequent boosters, immunity is maintained for longer periods. Protective immunity can be achieved with less frequent boosters, at least in younger adults. The authors also concluded that re-start of primary immunisation, if booster intervals were exceeded, was unnecessary, provided the subject had initially received a complete primary vaccination series.

In summary, recent studies have further confirmed that seropositivity is maintained in a very high proportion of individuals up to 5 years after booster doses. After a primary immunisation series and one booster vaccination, booster intervals of 5 years in adults <60 years old and of 3 years in the elderly are currently recommended for TBE prophylaxis.

Duration of immunity following primary vaccination with FSME-IMMUN Junior® in children and adolescents ($N = 375$) aged 3–18[4] years old was investigated in a prospective multicentre study (Table 3). Seropositivity rates were high 24 and 34 months after the third vaccination. Subjects whose antibody levels fell below 1000 VIE U/ml 3, 4 or 5 years after primary immunisation were administered a booster vaccination. After the first booster at 3 years, seropositivity was 100% in all age groups. Furthermore, 33% of subjects still had very high antibody levels 5 years after primary immunisation and did not receive any booster vaccination during this follow-up study.

In a further multicenter study in Austria, children aged 7–9 years ($N = 97$) received their first booster with FSME-IMMUN Junior® 3–4 years after the third primary vaccination with an earlier FSME-IMMUN® vaccine formulation (without human serum albumin) (Table 3). All subjects (100%) included in the analysis of seropersistence ($n = 79$) were determined to be seropositive approximately 3 years after the booster, thus supporting the current recommendation that the first booster be administered 3 years after completion of the primary vaccination series, with subsequent boosters every 5 years in children and adolescents. Further results from ongoing prospective clinical studies in children will provide more insight into the long-term post-booster immunopersistence outcome.

3. Immunogenicity in special patient populations

The immunogenicity of FSME-IMMUN® has also been investigated in several patient groups with impaired immunity, such as HIV positive patients, cancer patients undergoing chemotherapy, thymectomized patients and those with chronic asthma [30–34]. After a modified 4 dose vaccination course (0, 1, 2, 9 months), 13/29 (44.8%) HIV-infected adults attained protective concentrations of anti-TBEV antibodies, which still persisted one year later [30]. As expected, these HIV-positive patients had higher mean CD4 cell counts than HIV-infected individuals who failed to produce an adequate immune response to TBE vaccination.

Likewise, antibody responses in HIV-positive haemophilia patients ($n = 4$) were lower (haemagglutination inhibition ≥1:10 in 50% of patients) after primary immunisation than in HIV-negative haemophilia patients ($n = 12$) and healthy subjects ($n = 16$), where >90% of subjects achieved a seropositive titre after vaccination with FSME-IMMUN® [31].

Chemotherapy has also been reported to impair response to FSME-IMMUN® vaccination [32]. In an Austrian study, breast cancer patients ($N = 24$) first vaccinated after the start of cyclophosphamide and 5-fluoruracil chemotherapy ($n = 6$) and those who received the primary vaccination 6–12 months after the end of chemotherapy ($n = 9$) failed to develop a protective titre. However, 88.9% of patients vaccinated before the initiation of chemotherapy ($n = 9$) developed significant anti-TBEV antibody titres (>600 VIE U/ml) which persisted throughout the course of

[4] NB. The 18 year old adults included in this study were initially 15–16 years old when included in the original study and were then vaccinated with FSME-IMMUN Junior, for subsequent boosters they now receive the adult formulation.

adjuvant treatment and could be boostered by revaccination during the course of chemotherapy.

A three dose primary vaccination course was assessed in children ($N = 22$) thymectomized during open heart surgery. Although significantly lower TBEV IgG antibody levels ($p = 0.03$) were observed after the second dose of FSME-IMMUN Junior® compared to healthy age-matched controls, the third vaccination was effective in eliciting sufficient antibody responses [33].

Children with chronic asthma ($N = 37$) vaccinated according to a rapid immunisation schedule (first and second vaccination 10 days apart) with the FSME-IMMUN® adult formulation (as no paediatric formulation was available at the time), showed virtually identical seropositivity rates to healthy children vaccinated according to the standard schedule: 92% vs. 94%, tested by haemaglutination inhibition, and a rate of 95% as determined by ELISA [34].

4. Cross-immunity

Three genetically closely related subtypes of TBEV exist: the European (or Western), the Far Eastern and the Siberian, all of which have overlapping regions of endemicity, e.g. in the Baltic states [35]. TBEV's glycoprotein E, the major target of the immune response following natural immunisation has been determined to vary a maximum of approximately 2% within subtypes and 5–9% between the subtypes [36]. These findings suggest the effectiveness of vaccines based on the European subtype in affording protection against the other subtypes and vice versa. Consistent with the close antigenic relationship of all three TBEV subtypes, immunisation studies in animals have revealed a high degree of cross-protection between virus strains belonging to different subtypes [37].

The question whether a TBEV vaccine which is based on a Western European strain is also protective against Far Eastern and Siberian strains is of great relevance as human mobility is increasing and the distribution of non-European TBEV strains appear to be expanding, e.g. the Siberian TBEV strain has been reported in Finland, considerably northwest of the previously known range in eastern Europe and Siberia [38].

FSME-IMMUN® (based on a European subtype – Neudoerfl strain) has been shown to provide cross-neutralization against other subtypes and strains in both mouse models and human subjects [39–42].

A recent study quantitatively assessed the capacity of human sera to neutralise European (Neudoerfl, K23), Far-Eastern (Oshima, Sofjin), and Siberian (Vasilchenko) TBEV strains as well as a further flavivirus, Omsk Haemorrhagic Fever Virus (OHFV), following vaccination with FSME-IMMUN® [43]. Hybrid virus strains expressing the surface proteins of representative strains allowed for unbiased comparison in the neutralization assay and revealed comparable neutralizing antibody titres against European, Far Eastern and Siberian subtype viruses, indicating equally potent cross-protection against these TBEV strains, and a somewhat reduced but still protective neutralization capacity against more distantly related viruses such as *OHFV*.

5. Safety evaluation

The FSME-IMMUN® clinical development programme encompasses 12 studies which investigated the safety of the vaccine in adult and paediatric populations. Additional review of published literature on one study in children is also included (Tables 1–3).

5.1. Dose finding

In a prospective dose-finding study of adults ($N = 405$), determination of the optimal dose regarding safety was based on the fever rate after the first vaccination (in combination with immunological parameters) (Table 1) [12]. The overall fever rate following the first vaccination with FSME-IMMUN® was 0.8%, with no fever occurring in the highest dose group of 2.4 μg; thus, based on predefined safety criteria, 2.4 μg was determined as the optimal dose for an adult population [12].

Prior to the development of FSME-IMMUN Junior®, the tolerability of approximately one-half of the adult FSME-IMMUN dose was the focus of a large-scale post-marketing surveillance of 1899 healthy children aged 6 months to 12 years (Table 1) [13]. Following completion of this post-marketing surveillance, a study in 101 healthy children aged 1–12 years was carried out using a pre-filled 1.2 μg dose (Table 1). The vast majority of children included in this study were aged 1–3 years and as such fever rates after the first vaccination corresponded with this demographic.

In the prospective dose-finding studies in children, no dose-dependency was observed regarding tolerability [16]. As expected, fever rates were substantially lower in children aged 6–15 years ($N = 619$) than in those aged 1–5 years ($N = 618$) and fever was primarily mild. Immunogenicity and safety data from these studies demonstrated 1.2 μg to be the preferred dose in children aged 1–15 years.

5.2. Primary vaccination course

The largest study evaluating safety and tolerability of the current formulation of FSME-IMMUN® in adults was a multicentre randomized comparison of the first two primary vaccinations with either FSME-IMMUN® ($N = 2950$) or an earlier Encepur® formulation stabilised with polygeline ($N = 977$) using a conventional vaccination schedule [18]. All subjects received FSME-IMMUN® ($N = 3705$) for the third vaccination (Table 2).

As febrile reactions (≥38.0 °C) after the administration of FSME-IMMUN® occurred at a negligible level (0.8%) compared to 5.6% in the comparator group, the prospectively defined non-inferiority of FSME-IMMUN® to Encepur® regarding fever rate after the first vaccination was confirmed. No serious adverse reactions occurred.

The largest paediatric study ($N = 2417$) showed a fever rate of 9.7%, after first vaccination with the majority of cases being mild (≤38–39 °C) (Table 1) [17]. As expected, when stratified by age, fever occurred more frequently among younger children. Over 75% of all fever cases subsided within 24 h. There were no related SAEs reported during the study.

In a multicentre, randomized comparison of FSME-IMMUN Junior® and Encepur Children® in subjects aged 1–11 years ($N = 303$) during primary immunisation (Table 2), adverse reactions were predominantly mild, with no severe reactions in either group [23]. After the first vaccination, incidence of fever did not significantly differ between FSME-IMMUN Junior® and Encepur Children®, and lower fever rates were reported after the second vaccination compared to the first. Overall, results of this comparative study indicate that FSME-IMMUN Junior® induces lower local adverse reaction rates than Encepur Children®.

As HSA has previously been shown to inhibit the production of several cytokines considered important for the induction of local reactions, such as IL-1β, which is associated with increased sensitivity to pain (hyperalgesia) [44], the presence of this protein in the FSME-IMMUN Junior® formulation may improve the vaccine's local safety profile. In a subsequent report, the current Encepur Children® formulation was also found to increase these pro-inflammatory cytokines in vitro [45], which may explain the higher adverse event rate seen in the comparative studies presented in this review.

A study assessing conventional and rapid vaccination schedules in children ($N = 334$) aged 1–11 years (Table 3) [22] demonstrated comparable fever rates between FSME-IMMUN Junior® and

Encepur Children® after the first dose (regardless of vaccination schedule).

Similar rates of local and systemic reactions as observed during the large-scale safety study were reported in a prospective study involving a rapid immunisation schedule in adults ($N = 340$) (Table 3).

5.3. Booster vaccination

In all studies involving a booster vaccination, low fever, local and systemic reaction rates were observed after vaccination (Table 3).

5.4. Post-marketing observations

FSME-IMMUN® was also well-tolerated in a post-marketing surveillance in adults ($N = 570$) at 15 Swiss centres [46]. Reported adverse events were generally mild and transient, and no serious adverse events occurred. Injection site pain was the most frequent reaction, occurring in 12.1% of subjects. Oedema and redness developed in 2.5% and 1.2% of subjects, respectively. The most common systemic adverse events were headache (2.5%), muscle pain (1.9%) and fatigue (1.6%). As expected, adverse event rates reported during this observational period were lower than those generally observed during a formal clinical study.

During a Swiss post-marketing surveillance in 409 children aged 1–15 years who received FSME-IMMUN Junior®, the most common local reactions were local muscle pain (9.1%) and injection site tenderness (7.0%); the most frequent systemic event was headache (2.9%) [47]. Increased body temperature was reported in only 1.6% of children, and body temperature did not exceed 39.0 °C. Only 12% of subjects included in this surveillance were aged <5 years.

6. Safety in special patient populations

A possible link between a single vaccination against TBEV and the appearance of new cerebral lesions in magnetic resonance imaging (MRI) and/or a clinical relapse of multiple sclerosis (MS) has been investigated in MS patients ($N = 30$) of whom one group ($n = 15$) received a 3.3 μg antigen dose of FSME-IMMUN®. MRI which is used to measure disease activity and progression, in addition to neurological examination showed no association between TBE vaccination and MRI detected disease activity, clinical relapse or disease progression of MS [48].

The vaccine was found to be safe and well-tolerated in an immunogenicity-based study of HIV-positive patients ($N = 29$) vaccinated four times with FSME-IMMUN® [30].

Children aged 8–14 years with chronic asthma ($N = 37$) vaccinated according to a rapid immunisation schedule (first and second vaccination 10 days apart) with the FSME-IMMUN® adult formulation (no paediatric formulation was available at the time), showed a comparative safety profile to healthy children receiving the same vaccinations. No significant difference was determined between healthy and chronically ill children regarding fever, malaise and local reactions. No child experienced a temperature >39.0 °C. Healthy children reported headaches after the first vaccination significantly more frequently (26%) than asthmatic children (8%) vaccinated with FSME-IMMUN® [34]. In general, no safety issues regarding special patient populations have been identified to date.

7. Vaccination impact

The impact of immunisation against TBE with FSME-IMMUN has been demonstrated by an ongoing mass vaccination campaign initiated in 1981 in Austria, a country which previously suffered the highest morbidity from TBE in Europe [8]. FSME-IMMUN was either the sole (up to 1999) or predominant vaccine used during this campaign (2006: 90% market coverage), allowing a direct measure of its effectiveness [5,8]. High vaccination coverage in Austria (6% of the population in 1980 rising to an estimated 88% in 2006) resulted in a dramatic reduction in the incidence of clinical TBE infection; a published analysis of the field effectiveness for the years 2000–2006 indicated that overall effectiveness was approximately 99% in persons who had followed the recommended vaccination schedule [5]. A similarly high protection rate of 96–98% (after three or more vaccinations) was also reported in an earlier Austrian analysis covering the years 1994–2001 [8]. It should be noted, however, that most countries in which TBE vaccines are used do not monitor vaccine uptake, and so wide-ranging assumptions about the efficacy of vaccination among the general population and at-risk groups should be treated with caution.

While active immunisation is the most effective protective measure against TBE, vaccine failures have occasionally been reported [49–51]. Between 2000 and 2006, 494 documented cases of TBE occurred in Austria, 14 (2.8%) of which involved subjects with uncertain vaccination status [5]. Among those known to have been regularly vaccinated, all age groups had equally high protection. Moreover, the rate of protection in the TBE season following vaccination was as high in subjects who had received two of the three doses in the primary vaccination course (given two to four weeks apart) as in those who had completed the vaccination series by receiving a third dose (given 6–12 months after the first dose). Not a single case of vaccination breakthrough was recorded in this group from 2000 to 2006. Subjects with a record of irregular vaccination were, however, found to have a lower rate of protection (approximately 95%) [5].

Clinical trials to prove immunological protection against TBE are lacking and remain difficult to design due to a low incidence rate of the disease, however the scale and duration of the Austrian vaccination programme provides convincing evidence of the impact of immunisation using FSME-IMMUN®. The reduction in the incidence of TBE in Austria since the initiation of the vaccination campaign cannot be explained by socio-economic factors, climate change, a natural decline in tick populations or viral virulence, as TBE incidence rates in the neighbouring Czech Republic have continued to rise over the same period [5]. While TBE infection can still rarely occur after vaccination, the degree of protection provided is among the highest documented for any viral vaccine under field conditions.

8. Discussion and conclusion

The successful development of the FSME-IMMUN® vaccine rests on a comprehensive clinical programme identifying the optimal dose, establishing conventional and rapid vaccination schedules, comparing with a comparator product, assessing immunopersistence in adults and children, and on post-marketing observations and the impact on field effectiveness.

A series of prospective clinical studies demonstrated the current formulations of FSME-IMMUN® and FSME-IMMUN Junior® vaccines to be highly immunogenic and well-tolerated. Dose-finding studies identified the optimal dose for adults as 2.4 μg, and for children and adolescents aged 1–15 years as 1.2 μg [12,16]. Results presented here also demonstrate similarly high seropositivity rates in adolescents (aged 12–15 years) vaccinated with the optimal paediatric dose (1.2 μg) and adults (aged 16–35 years) vaccinated with the 2.4 μg formulation of FSME-IMMUN®, justifying the conclusion that FSME-IMMUN Junior® is appropriate not only for children <12 years but also for adolescents <16 years.

Both conventional and rapid schedules have proven effective in eliciting protective antibody responses, although one

comparative study suggested that the conventional schedule may produce a more robust response than the rapid schedule of two initial vaccinations administered 14 days apart. Following the third vaccination, no substantial difference was observed between the rapid and conventional schedules, demonstrating the excellent priming ability of two vaccinations with FSME-IMMUN®, regardless of schedule [24,25].

A comparative study of paediatric TBE vaccines FSME-IMMUN Junior® and Encepur Children® within a conventional primary vaccination series demonstrated higher immunological responses after vaccination with FSME-IMMUN Junior® than with Encepur Children® [23]. Recent studies in both adults and children have established the interchangeability of TBE vaccines, with the other vaccine for the third primary vaccination or boosters resulting in a robust immune response [18].

Although a reduced immune response was observed with both TBE vaccines among older adults due to the accepted process of immunosenescence, a retrospective observational evaluation in the elderly (>60 years) reported the superior immunogenicity of FSME-IMMUN® over Encepur® after two vaccinations [21]. Questions remain whether adults aged 50–59 years should receive more frequent boosters similar to those >60 years and whether they should be monitored more closely during the primary immunisation series. Data from previous clinical studies, however, led the Austrian Immunisation Board to recommend that regular boosters (following the first booster) be administered every 5 years for individuals aged <60 years [12,29]. Additional investigation into age-specific immunopersistence is necessary to determine whether further prolongation of booster vaccinations is feasible, while maintaining the level of immune protection needed to prevent TBE infection in the general population. The recommendation of 3-year intervals for regular booster immunisation in >60 year olds has, however, been retained, and the option of shortening TBE booster intervals to 3 years for individuals aged 50–60 years continues to be discussed.

The immunogenicity of FSME-IMMUN® was also assessed in patients with impaired immunity [30–34]. Patients with HIV infection did develop immunity following a modified four-dose vaccination regimen, although at a reduced level, as would be expected among individuals with diminished CD4 cell counts. Breast cancer patients vaccinated prior to chemotherapy developed immunity that persisted throughout adjuvant therapy, whereas those vaccinated during or immediately after chemotherapy elicited suboptimal responses to TBE vaccination. Studies have shown that children with compromised immune systems, such as thymectomized individuals or those suffering from primary immunodeficiency, fail to produce an effective immune response to vaccination, whereas children suffering from chronic asthma did not appear to be negatively affected regarding immunogenicity compared to healthy children.

Consistent with the close antigenic relationship of all three TBEV subtypes (the European, the Far Eastern and the Siberian), a high degree of cross-protection against virus strains of different subtypes has been reported with the European TBEV strain-based FSME-IMMUN® vaccine [6,40–43]. As such, the vaccine is suitable for use across a wide range of geographic regions to provide protection against a variety of TBEV strains.

Studies in the clinical development programme have demonstrated that both adult and paediatric formulations of FSME-IMMUN® are safe and well-tolerated in a wide variety of populations. Reactions to the vaccine are mostly mild and transient. Fever is most frequent in young children and is uncommon in adults. Lower local reaction rates were observed after vaccination with FSME-IMMUN Junior® than Encepur Children® [23]. As HSA has previously been shown to inhibit the production of pro-inflammatory cytokines [11], the presence of this protein in the FSME-IMMUN Junior® formulation may improve the vaccine's safety profile. No safety issues regarding special populations (multiple sclerosis sufferers, HIV patients, etc.) have been identified at present.

Antibody response to vaccination may vary depending on age and vaccination schedule and other unknown individual factors, without an impact on field effectiveness. The mass vaccination campaign in Austria has resulted in a dramatic reduction in clinical TBE virus infection. Since the beginning of the national vaccination programme, market coverage of FSME-IMMUN® has been 90–100%, meaning that disease incidence in this country correlates directly to the efficacy of the vaccine. Overall effectiveness of vaccination has been estimated at approximately 99% in those following the recommended vaccination schedule. Increase in vaccination uptake corresponded to a simultaneous sharp decline in TBE disease incidence in Austria, compared to other Central European countries such as the Czech Republic, where uptake was much lower (around 10% in high risk areas) and a total of 719 TBE cases were recorded in the year 2000 (compared to just 60 in Austria at this time) [5,8]. The continued refinement and clinical development of the FSME-IMMUN® vaccine over the decades since its introduction in 1976 has yielded an effective and well-tolerated solution to the endemic risk of TBE virus infection.

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