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Three-dose versus four-dose primary schedules for tick-borne encephalitis (TBE) vaccine FSME-immun for those aged 50 years or older: A single-centre, open-label, randomized controlled trial

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ABSTRACT

Background: TBE vaccination failures among those past middle age have raised concern about immune response declining with age. We investigated immunogenicity of the TBE-vaccine FSME-Immun among those aged 50+ years using the standard three-dose primary series and alternative four-dose schedules.
Methods: In this single-centre, open-label, randomized controlled trial, 200 TBE-naive Swedish adults were given primary TBE vaccination with FSME-Immun. Those aged 50+ years (n = 150) were randomized to receive the standard three-dose (days 0–30–360) or one of two four-dose series (0–7–21–360; 0–30–90–360). For participants < 50 years (n = 50) the standard three-dose schedule was used. Titres of neutralizing antibodies were determined on days 0, 60, 120, 360, and 400. The main outcome was the log titre of TBE virus-specific neutralizing antibodies on day 400.
Results: The three-dose schedule yielded lower antibody titres among those aged 50+ years than the younger participants on day 400 (geometric mean titre 41 versus 74, $p < 0.05$). The older group showed higher titres for the four-dose 0–7–21–360 than the standard three-dose schedule both on day 400 (103 versus 41, $p < 0.01$; primary end point) and at the other testing points (days 60, 120, 360). Using the other four-dose schedule (0–30–90–360), no such difference was observed on day 400 (63 versus 41, NS).
Conclusion: Immune response to the TBE vaccine declined with age. A four-dose schedule (0–7–21–360) may benefit those aged 50 years or older. This study is registered at ClinicalTrials.gov, NCT01361776.

1. Introduction

Vaccination is the most effective means of protection against tick-borne encephalitis (TBE), a major cause of viral encephalitis in many parts of Europe and Asia, with new foci emerging over the past decades [1,2]. The two inactivated TBE vaccines currently available in Europe, FSME-Immun (TicoVac; Pfizer Vaccines) and Encepur (currently marketed and distributed by Bavarian Nordic and Valneva) are based on different TBEV strains, but can be used interchangeably [3,4]. The three FSME-Immun doses are administered at 0, 1–3 months, and 5–12 months after the second dose.

The recommendations draw on immunogenicity and effectiveness data. In Austria, the disease incidence declined after mass vaccinations [5]. Heinz et al have estimated an effectiveness of > 90% [5]. In lack of direct efficacy data, neutralizing antibodies above a certain threshold (e.g. titre $\geq$ 10) are used as surrogate marker for protection [6].

Middle-aged and older adults constitute a special risk group with increased incidence, more severe course of disease [5,7,8], and higher rate of breakthrough infections despite vaccination [9,10]. These findings support both deterioration in immune response with age [11] and lower post-vaccination TBE antibody titres among those past middle age [12–15]. Likewise, neutralizing

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antibody titres decrease more rapidly among those aged ≥ 50 years [16–21].

Focusing on the age group 50+, we assessed TBE-specific immune responses using various regimens for FSME-Immun: the standard three-dose schedule and two alternatives with an additional fourth dose.

2. Methods

2.1. Study design

We conducted a single-centre, open-label, randomized controlled trial investigating the immunogenicity of FSME-Immun among those aged ≥ 50 years with those < 50 years as controls. All participants were recruited at the Centre for Clinical Research, Mälarsjukhuset Hospital, Eskilstuna, Sweden. The protocol was approved by the ethics committees of the Karolinska Institute and the Helsinki University Hospital, and by the Swedish Medicines Agency (EudraCT 2011 001348-31). ClinicalTrials.gov: identifier NCT01361776.

2.2. Participants

Study brochures were handed out at the Mälarsjukhuset hospital and pensioners' associations. The exclusion criteria comprised age < 18 years, history of TBE infection or vaccination, acute febrile illness, hypersensitivity to vaccine components, pregnancy, and disease or medication judged by the investigator as immunosuppressive. Fertile women were to use contraceptives. All volunteers provided written informed consent.

2.3. Procedures

Fig. 1 shows the four groups; three with participants ≥ 50 years of age and one with controls < 50 years, totalling 200 volunteers, 50/group. The groups ≥ 50 years were further divided into two subgroups, 50–59 and ≥ 60 years of age.

Those aged ≥ 50 years were recruited 1:1 to the subgroups 50–59 and ≥ 60, in which each participant was randomized into one of three groups with different vaccination series (schedules A, B, C). For randomization, the volunteers picked one of twelve envelopes (four sets of three identical ones mixed).

A 0.5-mL dose of FSME-Immun (Baxter; currently Pfizer Vaccines) was administered into the deltoid muscle. A primary series was given participants aged ≥ 50 years using one of three schedules: A) three doses on days 0, 30, 360 (according with the standard schedule currently licensed for FSME-Immun), B) four doses on days 0, 7, 21, 360 (exploratory schedule), or, C) four doses on days 0, 30, 90, 360 (exploratory schedule). Those < 50 years of age were administered the standard three-dose series (schedule A).

Serum samples were collected on days 0 (before first dose), 60, 120, 360 (before last dose), and 400. For vaccination schedule and serum sampling, see Fig. 2.

2.4. Serological analyses

Neutralizing antibodies were assessed by Baxter in 2012 from blinded serum samples according to a protocol described by Adner et al. [22]. The TBEV Neutralization test (NT) was based on the ability of the antibodies in each sample to prevent propagation of TBEV in Vero cells. Briefly, serial dilutions of sera were incubated with a predetermined amount of virus. These mixtures were added to Vero cell cultures and incubated for seven days as described earlier [22]. After incubation, supernatants were tested for virus propagation by a TBEV-specific ELISA. The neutralizing NT_{50} titre was defined as the reciprocal of the serum dilution sufficient to inhibit viral growth in 50% of events. Seropositivity was defined as an NT_{50} titre of ≥ 10. Seropositivity rate (SPR) indicated the proportion of subjects with NT_{50} titres ≥ 10.

2.5. Statistical analysis

Determining sample size, we assumed a standard deviation of 0.6 log10 neutralization test titres [4,17], and inclusion of the participants into one of the three groups by schedules A, B, and C, with contrast A-B and A-C planned at a significance level of 5% and a power of 80%. The primary endpoint was defined as the log titre of TBE-specific neutralizing antibodies on day 400, i.e. 40 days after completing primary immunization. Under these conditions 45 individuals per group were needed to detect an effect size of 0.67 (corresponding to a 2.5-fold titre difference). An additional comparison between older and younger age group was devised for the standard schedule A. To account for loss of follow-up and seropositivity before vaccination, sample size was increased to 50 individuals per group.

Geometric mean titres (GMTs) and 95% confidence intervals were computed for each post-vaccination time point and each group. SPRs were computed within the groups for all post-vaccination time points with Clopper-Pearson confidence intervals. Log titres were evaluated by analysis of variance with a within-subject factor (time points) and a between-subject factor (4 groups). Linear contrasts were applied to compare the vaccination schedules B and C against the standard schedule A and those < 50 against those ≥ 50 years of age concerning standard schedule A. These contrasts were computed for each time point. In addition, those 50–59 years of age were compared to those aged ≥ 60 years for each schedule and time point applying Bonferroni correction. *P* values < 0.05 were considered significant. Statistical analyses were conducted using Stata 13.1.

3. Results

We recruited two hundred adults between 22 August and 8 September 2011. Seven were excluded from the immunogenicity analyses, either for pre-existing TBE antibodies (n = 4) or not providing any follow-up samples (n = 3).

Table 1 summarizes the demographics of the 193 participants included in the analyses.

Table 2 gathers the GMTs of the neutralizing antibodies and Table 3 the SPRs for the younger (<50 years) and the older (≥50 years) volunteers in the various vaccination groups. Table 4 and Table 5 present these data for the subgroups 50–59 and 60+.

Volunteers aged ≥ 50 years showed higher neutralizing antibody titres for the four-dose schedule B (0–7–21–360) than the standard schedule A (0–30–360) on day 400 (primary end point; GMT 103 versus 41, $p < 0.01$) and at all the other post-vaccination time points (day 60, $p < 0.01$; day 120, $p < 0.01$; day 360, $p < 0.05$).

The titres recorded for the other four-dose regimen, schedule C (0–30–90–360), by contrast, were not higher than for the standard schedule A on day 400 (primary end point; GMT 53 vs 41, p = NS). Schedule C yielded significantly higher titres ($p < 0.01$) than schedule A only on days 120 and 360.

Among those aged ≥ 50 years, the standard three-dose schedule A yielded a GMT of 15 and an SPR of 78% one month after the second dose (day 60). At the time of administering the final third dose (day 360), the GMT had decreased to < 5 and the SPR to 23%. Forty days after completing the series (day 400), the titres of neutralizing antibodies were 65 and 26 (for subgroups 50–59 and 60+ years), and the respective SPRs 96% and 74%. A comparison between the

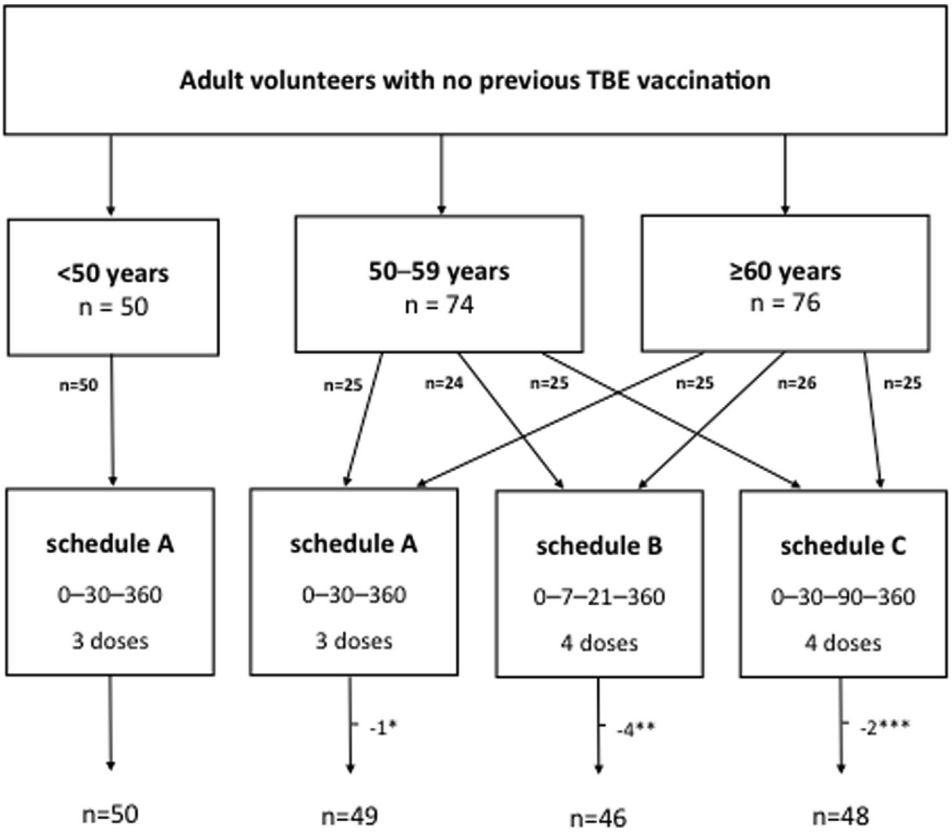

Fig. 1. Subject groups. Flow chart of study, randomization protocol, and final number of subjects in each vaccination group. * 1 subject excluded: did not provide follow-up samples. ** 4 subjects excluded: 3 seropositive at baseline, 1 did not provide follow-up samples. *** 2 subjects excluded: 1 seropositive at baseline, 1 did not provide follow-up samples.

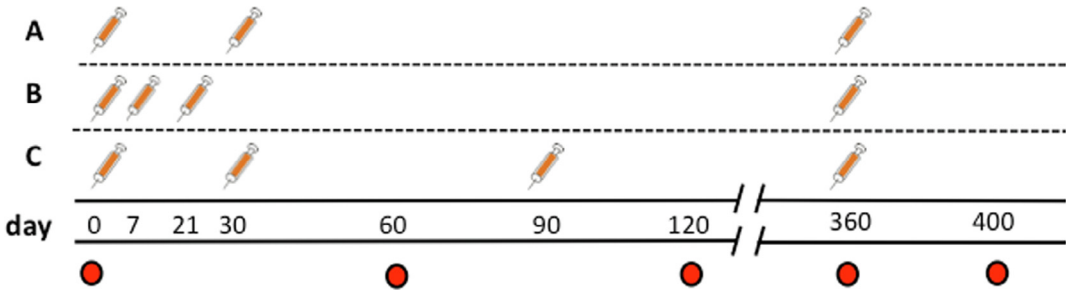

Fig. 2. Timing of vaccinations and serum sampling. The three schedules for primary vaccination with FSME-Immun (schedule A, B, and C), and timing of serum sampling (red dots). Schedule A: three doses on days 0, 30, and 360; schedule B: four doses on days 0, 7, 21, and 360; schedule C: four doses on days 0, 30, 90, and 360. Serum samples were collected on days 0, 60, 120, 360, and 400.

Table 1
Age and gender of the 193 volunteers included in the analyses.

	<50 years schedule A	≥50 years schedule A	≥50 years schedule B	≥50 years schedule C
	(0–30–360)	(0–30–360)	(0–7–21–360)	(0–30–90–360)
Number of subjects	50	49	46	48
Age, years				
median (range)	42 (20–49)	60 (50–83)	60 (50–72)	59 (50–75)
Gender				
male	16 (32%)	25 (51%)	18 (39%)	19 (40%)
female	34 (68%)	24 (49%)	28 (61%)	29 (60%)

age groups showed for the three-dose schedule A significantly lower antibody titres among the older (≥50 years) than the younger (<50 years) on day 400 (GMT 41 vs 74, $p < 0.05$).

Those following schedule B had GMTs of 46 and 23 (age groups 50–59 and 60+ years), and respective SPRs of 96% and 74% on day 60 (one month after third dose). On day 360 their GMTs were only

Table 2
Geometric mean titres and 95% confidence intervals for time points of blood sampling according to age and TBE vaccination schedule. Results of statistical comparisons are given in footnotes.

	Those < 50 years	**Those ≥ 50 years**		
	schedule A	schedule A	schedule B	schedule C
Day 0	<5	<5	<5	<5
	–	–	–	–
Day 60	23	15	33**	16
	(17–33)	(11–22)	(22–49)	(12–22)
Day 120	8	7	14**	32**
	(6–11)	(5–9)	(10–19)	(22–45)
Day 360	4	4	7*	7**
	(3–5)	(3–5)	(5–9)	(6–10)
Day 400	74+	41	103**	53
	(49–111)	(26–67)	(64–168)	(36–78)

Schedule A: 0–30-360; schedule B: 0–7-21–360; schedule C: 0–30-90–360
* p < 0.05; ** p < 0.01 comparison schedule B, C against A in older group (50+).
+ p < 0.05; ++ p < 0.01 comparison younger against older (50+) schedule A.
All comparisons by linear contrasts Bonferroni-corrected.

Table 3
Seropositivity rates and 95% confidence intervals for time points of blood sampling according to age and TBE vaccination schedule.

	Those younger (<50)	**Those older (50 ≤)**		
	schedule A	schedule A	schedule B	schedule C
Day 0	0% (0/50)	0% (0/49)	0% (0/49)	0% (0/49)
	–	–	–	–
Day 60	88% (44/50)	78% (38/49)	85% (39/46)	77% (37/48)
	76–95%	63–88%	71–94%	63–88%
Day 120	62% (31/50)	51% (24/47)	72% (33/46)	89% (42/47)
	47–75%	36–66%	57–84%	77–96%
Day 360	30% (15/50)	23% (11/47)	47% (20/43)	58% (28/48)
	18–45%	12–38%	31–62%	43–72%
Day 400	96% (48/50)	85% (40/47)	95% (41/43)	98% (47/48)
	86–100%	72–94%	84–99%	89–100%

Schedule A: 0–30–360; schedule B: 0–7–21–360; schedule C: 0–30–90–360.

Table 4
Geometric mean titres and 95% confidence intervals for time points of blood sampling in age-based subgroups 50–59 and 60+. Results of statistical comparisons are given in footnotes.

	50–59			**60+**		
	schedule A	**schedule B**	**schedule C**	**schedule A**	**schedule B**	**schedule C**
Day 0	<5	<5	<5	<5	<5	<5
	–	–	–	–	–	–
Day 60	21	46	17	11	23	16
	(13–35)	(27–80)	(11–25)	(7–19)	(13–42)	(9–26)
Day 120	9	22##	34	5	9	29
	(5–14)	(14–33)	(21–54)	(4–8)	(5–14)	(16–53)
Day 360	5	8	7	4	5	8
	(3–7)	(5–13)	(5–10)	(3–5)	(4–8)	(512)
Day 400	65#	169#	48	26	65	59
	(36–117)	(92–310)	(29–80)	(12–55)	(31–135)	(31–110)

# p < 0.05: ## p < 0.01 comparison 50–59 against 60+
All comparisons by linear contrasts Bonferroni-corrected.

8 and 5, and the respective SPRs 57% and 36% (age groups 50–59 and 60+ years, respectively). On day 400 (forty days after fourth dose) their GMTs were 169 and 65, and the SPRs 100% and 91%.

Those immunized using schedule C had GMTs of 34 and 29 (age groups 50–59 and 60+ years), and the respective SPRs of 92% and 86% on day 120 (one month after third dose). On day 360 the GMTs were only 8 and 7 (age groups 50–59 and 60+ years), and the respective SPRs 61% and 56%. On day 400 (forty days after fourth dose), the GMTs were 59 and 48, and the SPRs 100% and 96% (age groups 50–59 and 60+, respectively).

Eleven participants (6% of study population) did not show neutralizing titres of ≥ 10 at any of the time points. Among them, schedule A was used for nine, schedule B for one, and schedule C for one. The non-responders belonged to age groups 18–49 (n = 2), 50–59 (n = 1), and 60+ (n = 8). The majority were males (n = 9).

One subject among those aged 60+ years died during the study period; the decease was considered unrelated to vaccination. No other serious adverse events were recorded.

4. Discussion

Immune response to vaccinations declines with age [11]. TBE vaccine failures especially in the oldest age groups have raised concern over the sufficiency of the standard vaccination schedule for ageing people. To address this, we evaluated the immunogenicity

Table 5
Seropositivity rates and 95% confidence intervals for time points of blood sampling in age-based subgroups 50–59 and 60+.

	50–59			60+		
	schedule A	**schedule B**	**schedule C**	**schedule A**	**schedule B**	**schedule C**
Day 0	0% (0/24)	0% (0/24)	0% (0/24)	0% (0/25)	0% (0/25)	0% (0/25)
	–	–	–	–	–	–
Day 60	83% (20/24)	96% (22/23)	84% (21/25)	72% (18/25)	74% (17/23)	70% (16/23)
	63–95%	78–100%	64–95%	51–88%	52–90%	47–87%
Day 120	58% (14/24)	91% (21/23)	92% (23/25)	43% (10/23)	52% (12/23)	86% (19/22)
	37–78%	72–99%	74–99%	23–66%	31–73%	65–97%
Day 360	33% (8/24)	57% (12/21)	56% (14/25)	13% (3/23)	36% (8/22)	61% (14/23)
	16–55%	34–78%	35–76%	3–34%	17–59%	39–80%
Day 400	96% (23/24)	100% (21/21)	100% (25/25)	74% (17/23)	91% (20/22)	96% (22/23)
	79–100%	84–100%	86–100%	52–90%	71–99%	78–100%

Schedule A: 0–30–360; schedule B: 0–7–21–360; schedule C: 0–30–90–360.

of the standard three-dose regimen of FSME-Immun in various age groups, and explored whether the response could be improved for those aged 50+ years by adding a fourth dose using either of two alternative schedules.

Our data on the standard three-dose primary regimen indicate that the immune response to the FSME-Immun declines with age: those ≥ 50 years showed considerably lower antibody titres than those < 50 years. In the oldest age group (≥60 years), only 74% were seropositive (NT_{50} titres of ≥ 10) at 40 days after completing the series, compared to 96% of the younger.

These data accord with previous TBE vaccination studies reporting reduced immunogenicity among ageing people [12–21]. Aberle et al., who investigated the immunogenicity of FSME-Immun among older (60–80 years) and younger (20–31 years) adults [14], recorded reduced numbers of TBEV-specific memory B-cells and lower levels of neutralizing TBEV-antibody titres for the older participants. They also found age-related decrease in TBEV-specific CD4+T-cell help. In a retrospective study with > 700 participants, Hainz et al. report an age-dependent decline in post-vaccination antibody titres against TBE and tetanus toxoid [12]. Likewise, in another retrospective investigation among 533 residents of the highly TBE endemic Åland Islands, the TBE vaccination response declined with age [15].

Several long-term follow-up studies have proposed that the immune responses to TBE vaccines are impaired already at the age of 50 [16–21]. In a series of five investigations spanning 10 years, Rendi-Wagner et al. [16,19] followed up 430 adults immunized with FSME-Immun and boosted with Encepur, recording substantially lower titres for those aged 50+ years than the younger. Konior et al., who conducted a 10-year follow-up of 315 Polish adults after their first FSME-Immun booster dose [21], also show antibody levels to decline faster in the oldest age groups: NT_{50} titres of ≥ 10 were found for the majority (89%) of those under 50 years of age, but only 38% of those over 60. Indeed, because of waning long-term immunity, the manufacturer of FSME-Immun currently recommends a booster interval of three years, not five, for the age group 60 years and older [23].

The data on immune responses among those in late middle age and older are somewhat controversial. Vaccination coverage and disease incidence data from Austria show high (>90%) effectiveness for the TBE vaccine even in the oldest age groups [5]. It is noteworthy that the age at priming appears to significantly influence the duration of protection [24]. In Austria, many of those belonging to the elderly age group received their primary vaccination in the 1980s when the mass vaccination campaigns were commenced. Although many studies have recorded lower neutralizing antibody titres among vaccinees aged 50–60+ years, several have shown high seropositivity rates after primary immunization for adults in various age groups [4,23,25,26]. In a study by Wanke and colleagues, the vast majority (>99%) of healthy participants aged 70 + years (n = 137) were seropositive 4 weeks after the third dose of FSME-Immun, although the antibody titres were lower than previously recorded for those younger [27]. On the other hand, decreased immunogenicity among the elderly has, besides TBE, also been recorded for other viral vaccines, such as those against influenza, hepatitis A, hepatitis B, and for another inactivated flavivirus vaccine, Japanese encephalitis [11,28].

Besides assessing the response to the three-dose schedule, we also sought to identify alternative schedules with improved immunogenicity among those in late middle age or older. Both four-dose schedules (accelerated 0–7–21–360 and extended 0–3 0–90–360) proved highly immunogenic, post-vaccination SPRs ranging from 91% to 100%. Those aged >60 years were given particular attention due to their suboptimal immune response to the standard three-dose schedule: SPRs of 91% and 96% were recorded after the four-dose primary series, whereas the three-dose schedule yielded an SPR of 74%.

In terms of immunogenicity, our data suggest the four-dose schedule 0–7–21–360 to be the most suitable for the middle-aged and older population. In the entire age group 50+, this alternative proved more immunogenic than the standard regimen at all four time points tested. The other four-dose option (0–30–90–360) proved superior to the standard schedule only at two time points: day 120 and day 360, but not on day 60 or day 400, the primary end point.

The few studies that have assessed four-dose regimens in TBE primary immunization accord with our data. A statistical model in a retrospective investigation by Lindblom et al. suggests that increasing TBE vaccine doses from three to four could compensate for 35 years' age difference in terms of magnitude of antibody response [15]. In a prospective investigation by Hertzell et al, a four-dose schedule (0–30–90–360) yielded one month after the last dose a seropositivity rate of 81% for healthy controls aged ≥60 years, but for medically immunosuppressed patients only 31% [29].

The four-dose regimen 0–7–21–360 closely resembles the rapid schedule of the TBE vaccine Encepur, with primary doses on days 0, 7, and 21, and the first booster 12–18 months later. Using this schedule, SPRs of 92% and 100% have been shown three weeks after the third dose among immunocompetent individuals of various ages [26,30]. In a study by Plentz et al, an SPR of 99% was recorded for adults (aged 19–51 years) five years after the first booster / fourth dose [31]. Beran et al found neutralizing antibodies among the majority of participants aged 15–60+ years even ≥10 years after the first booster of the rapid schedule [32].

The main limitation of our study is that we used immune responses as surrogate markers of protection. The same approach has been adopted in several other studies: since efficacy data on

TBE vaccines are difficult to attain, neutralizing antibodies exceeding a certain level (e.g. titre $\geq$ 10) are commonly accepted as a surrogate marker for protection, despite lack of conclusive data to support it [6]. The timing of serological testing may vary from one investigation to another. The primary endpoint of our study was the GMT on day 400, i.e. 40 days after the last dose of the primary series, while some others have chosen to test at an earlier time point, 21 days after vaccination [23]. Because of differences in neutralizing test protocols and timing of serum sampling, results may not be fully compatible.

Although our investigation was carried out in the early 2010 s, the question of TBE vaccine immunogenicity among those aged 50 + years has not lost its relevance. Indeed, Hansson and colleagues recently suggested an extra priming dose for this age group, on the basis of their retrospective data on > 1000 TBE cases where the majority of vaccine failures (81%; 43/53) were recorded for patients > 50 years of age [33], whereas no failures were found among persons $\geq$ 60 years of age who had received a four-dose primary series. Likewise, Rampa and colleagues propose a fourth priming dose for older vaccinees basing their suggestion on a systematic review of TBE vaccine immunogenicity and safety [24]. In another systematic review, on the other hand, Steffen and colleagues recommend harmonization of TBE vaccine schedules and extension of booster intervals to ten years for all age groups [34]. Recent studies have highlighted that adherence to primary vaccination schedule and regular booster doses remains a continuous challenge [35,36].

To our knowledge, this is the only randomized controlled trial thus far to compare the immunogenicity of three and four-dose primary regimens of TBE vaccine among adults aged $\geq$ 50 years. Firstly, our data confirm previous findings indicating that immune response to FSME-Immun declines with age. Of the three alternative primary schedules tested, the accelerated four-dose regimen (0–7–21–360) appears most immunogenic for those past middle age. In the entire age group 50+, this schedule induced higher antibody titres than the standard regimen at all testing points (days 60, 120, 360, and 400). In terms of immunogenicity, a four-dose primary schedule (0–7–21–360) may benefit those aged 50 years or older. More data are needed, however, on the effectiveness of TBE vaccination in this age group in clinical practice. For those at risk of infections with TBE virus, the importance of completing the primary schedule and adhering to regular booster doses should be stressed.

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The vaccines were provided by Baxter. Serological analyses of blinded samples were conducted by Baxter in 2012. At that time, Baxter was the manufacturer and marketing authorization holder of FSME-Immun. Apart from that described above, the funding sources had no role in study design, data collection, data interpretation, writing of the report, or the decision to submit the article for publication. The corresponding author had full access to all the study data and ultimate responsibility for the decision to submit for publication.

Potential conflicts of interest

LR, MK and LL have received honorary for lectures (LR, MK and LL Pfizer, GSK, MSD, Valneva), and AK and MK have received investigator-initiated grants (AK Pfizer, Valneva; MK Pfizer). LR, LL and AK have on individual occasions consulted advisory boards (LR and LL GSK, Valneva and Pfizer; AK Valneva). AK acts as head of the Meilahti Vaccine Research Center, MeVac, Helsinki, Finland. MK is a member of the Austrian national vaccination committee. None of the interests listed above are relevant to the current manuscript. All other authors report no potential conflicts of interest.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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