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Seropersistence and booster response following vaccination with FSME-IMMUN in children, adolescents, and young adults

E. Poellabauer [a], R. Angermayr [b], U. Behre [c], P. Zhang [d], L. Harper [d], HJ. Schmitt [e], W. Erber [f,*]

[a] Institute of Specific Prophylaxis and Tropical Medicine, Medical University of Vienna, Austria
[b] Private Practice, Wels, Austria
[c] Private Practice, Kehl, Germany
[d] Pfizer Inc., Collegeville, PA, USA
[e] Pfizer Inc., Paris, France
[f] Pfizer Inc., Vienna, Austria

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ABSTRACT

Background: Tick-borne encephalitis (TBE) is a viral disease that can have a severe clinical course and considerable long-term morbidity. As no curative treatment exists, vaccination is the primary means of prevention. Long-term antibody seropersistence 2–5 years after the 3-dose primary immunization and 3–10 years after first booster was evaluated, as well as booster responses in children, adolescents and young adults.

Methods: Subjects who participated in these phase 4 prospective, open-label follow-up studies received all vaccinations with FSME-IMMUN. After 3-dose primary immunization, subjects were followed for 2–5 years. Overall, 205 out of 358 subjects (57%) received the first booster and 179 of these subjects (87%) enrolled in a further 10-year follow-up. Antibody seropersistence was assessed annually. Subjects with a TBE antibody titer below a pre-specified cut-off at the yearly blood draw received a booster. Seropositivity rates and geometric mean fold rises (GMFRs) were assessed.

Results: In children who received their 3-dose primary immunization between 1 and 15 years of age, the seropositivity rate 5 years after the 3rd dose was 84.9% by NT and 72.0% by ELISA. One month post-first booster, all subjects were seropositive by NT and 98.5% by ELISA. Response to first booster by GMFR ranged from 3.7 to 11.4. At 5 years post-first booster, seropositivity was 99.4% by NT and 97.5% by ELISA, and at 10 years, was 90.3% by NT and 87.7% by ELISA. Although seropositivity rates differed between age groups, all subjects (100%) who received a second booster responded with a robust increase of TBEV antibodies.

Discussion: Long-lasting seropersistence of TBEV antibodies after the 3-dose primary immunization and first booster was demonstrated as well as a competent immune memory response in those who received a first or second booster at any time during the 15-year follow-up. Therefore, an extension of FSME-IMMUN booster interval up to 10 years after the 3-dose primary immunization seems warranted.

ClinicalTrials.gov Identifier: NCT00894686.

1. Introduction

Tick-borne encephalitis (TBE) is a viral disease with a severe acute clinical course and often considerable long-term morbidity and occasionally even death [1,2]. The disease is widespread and endemic over a huge area of central/middle and Northern Europe, Siberia, Russia, China and Japan [2]. As there is no curative treatment currently available for TBE, prophylactic vaccination is the only feasible way to reduce cases in endemic areas [3,4]. The rates of TBE disease have increased in recent years [5], likely due to changes in environmental factors, increased awareness, increased outdoor activities, improved and more widespread use of affordable diagnostic tools and/or increased travel to endemic areas. While active vaccination has been successfully implemented in many countries, the seropersistence of antibodies and booster responses generated subsequent to repeat vaccination is not fully known and thus an area of continued interest.

FSME-IMMUN is indicated for active prophylaxis against TBE in two dosages; FSME-IMMUN 0.25 mL Junior is approved for

* Corresponding author.
E-mail address: wilhelm.erber@pfizer.com (W. Erber).

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children and adolescents aged 1–15 years, while FSME-IMMUN 0.5 mL is approved for use in those ≥16 years of age. Both include the same formaldehyde-inactivated, sucrose gradient purified TBE virus (TBEV) antigen solution, adsorbed on aluminum hydroxide and stabilized with human serum albumin. The first booster vaccination is recommended to be given 3 years after completion of the 3-dose primary immunization. Subsequent boosters are recommended at 5 year intervals for individuals <60 years of age and at 3 year intervals for individuals 60 years and older.

Here we present data from two studies, the first of which (NCT00161967) was conducted to provide information on the seropersistence of TBEV antibodies up to 5 years after the 3-dose primary immunization and response to the first booster (with either FSME-IMMUN 0.25 mL Junior or FSME-IMMUN 0.5 mL according to age). The subsequent follow-up study (NCT00894686) was conducted to provide information on TBEV antibody seropersistence and booster response up to 10 years after the first booster (with either FSME-IMMUN 0.25 mL Junior or FSME-IMMUN 0.5 mL according to age) and response to a second booster.

2. Methods

2.1. Study design

Both studies evaluated were phase 4, prospective, open-label, multicenter follow-up studies in children, adolescents and young adults who had received their 3-dose primary immunization (FSME-IMMUN 0.25 mL Junior) in study 209 (NCT00161863). Patient flow and study breakdown can be seen in Fig. 1.

For those subjects who continued in the follow-up, yearly blood samples were drawn from 2 to 5 years after the 3rd dose to assess antibody seropersistence. Subjects with an TBEV antibody level (ELISA ≤ 1000 VIE U/mL and/or NT < 10) at their blood draw visit approximately 3, 4, or 5 years after the 3rd dose received the first booster dose approximately 2 months after blood sampling. At the time of initiating this 2–5 years post-primary immunization follow-up study, no prospective clinical data on seropersistence of TBEV antibodies were available from which the cut-off concentrations could have been derived, so the selection of an ELISA cut-off value of 1000 VIE U/mL was based on a very conservative approach in order to not put subjects, who were all enrolled at sites located in TBE endemic countries (Austria, Germany, and Poland), at risk of infection with TBE. Blood was drawn approximately 1 month after the first booster to assess the immune memory response.

Subjects who received the first booster dose were invited to continue in further follow-up with blood drawn yearly from years 3–10. Subjects with an TBEV antibody level (ELISA ≤ 126 VIE U/mL and/or NT ≤ 20) at their yearly blood draw visit received a second booster dose (the 5th dose) approximately 2 months later and a blood sample was drawn approximately 1 month after the second booster to assess the immune memory response.

When the 3–10 years post-first booster follow-up study was later initiated, the cut-offs for a second booster dose (ELISA ≤ 126 VIE U/mL and/or NT titer ≤ 20) were determined based on a newly

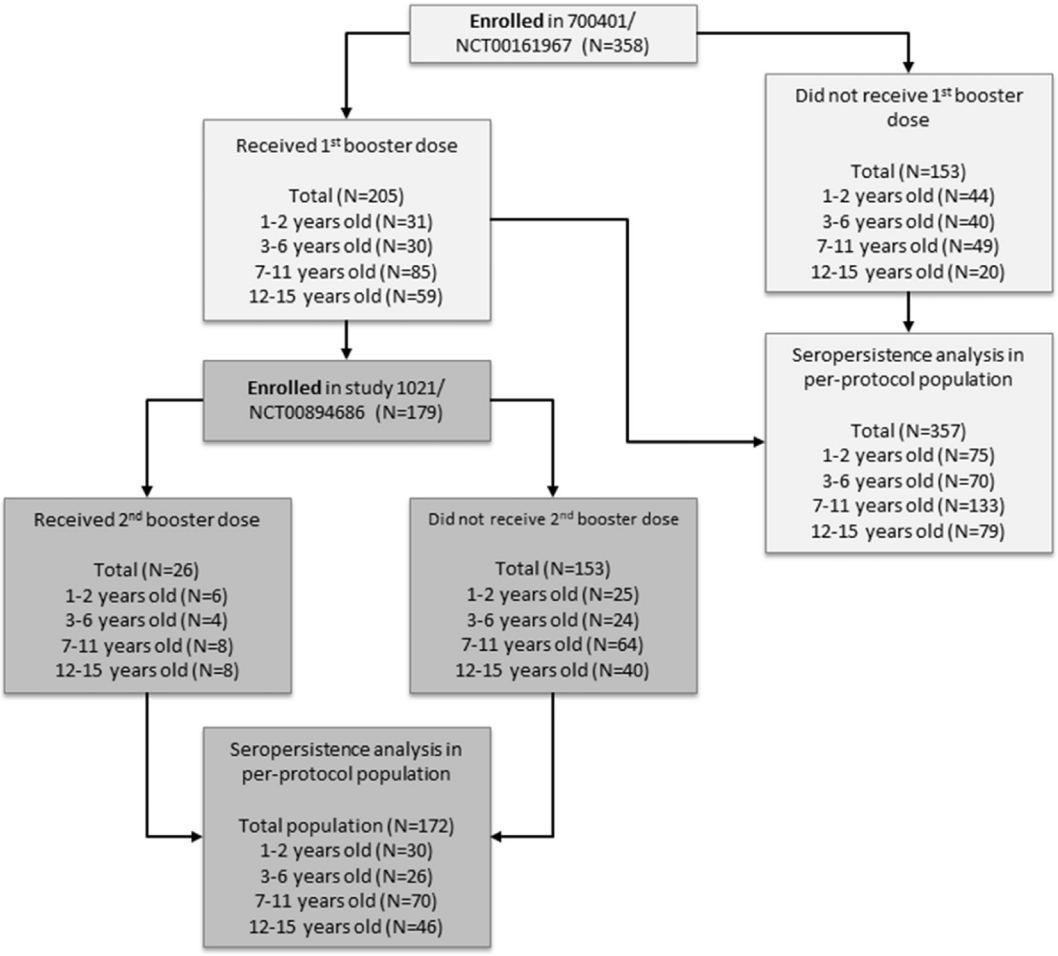

Fig. 1. CONSORT diagram of subject flow.

calculated decline rate [6]. This NT titer was expected to provide protection against TBE for an entire further tick season.

2.2. Study subjects

To be included in the study population, subjects and/or a parent or legal guardian had to provide written informed consent/assent. Subjects had to be seropositive 1-month after the 3-dose primary immunization to continue in the 5-years post-primary immunization follow-up and had to have assay results 1 month after the first booster to continue in the 10-years post-first booster follow-up.

Subjects were excluded if they received any TBE vaccination outside the scope of the study, or had a history of infection with or vaccination against other flaviviruses (e.g. Dengue fever, Yellow fever, Japanese B encephalitis) since their first study vaccination. Additionally, subjects were excluded if they were HIV positive, abused alcohol or drugs, or had received a blood product or immunoglobulin within 30 days of a blood draw (applicable for the 5-years post-primary immunization follow-up period) or within 90 days of a blood draw or in the period between a blood draw and the booster vaccination (applicable for the 10-years post-first booster follow-up period).

2.3. Analysis populations

The primary analysis population for the immunogenicity analysis was the per-protocol (PP) population, which included subjects who: (1) were enrolled; (2) met all inclusion/exclusion criteria at all visits; (3) had the planned blood samplings as well as valid and determinate assay results for the proposed analysis; (4) had received no vaccines or treatment prohibited per protocol and; (5) had no other major protocol deviations. Safety analysis was based on the all-enrolled population, which consisted of all subjects enrolled into the study.

2.4. Study intervention

Recommendation as to whether or not to administer a booster vaccination with FSME-IMMUN 0.25 mL Junior or FSME-IMMUN 0.5 mL according to age was based on a subject's individual TBEV serum antibody levels (i.e. below or above the protocol-specified cut-off level) at each yearly blood draw visit. Before administration, the syringe was warmed to room temperature, shaken vigorously for 5–10 s and checked for visible particles and discolorations. Syringes containing solid particles or discolored or leaking syringes were not used. The vaccine was given by intramuscular injection into the right or left upper arm (deltoid).

2.5. Measurements

Demographics including age, gender, height, weight, were recorded at the first visit of both studies. Medical history, history of tick bites, vital signs, physical examination, and blood draws were completed at each yearly visit. For those requiring a booster dose, pregnancy test was evaluated before the vaccination and blood was drawn approximately 1 month after the booster dose. Safety was assessed by fever rate, local and systemic reactions after the vaccination, as well as other AEs and SAEs.

2.6. Statistical methodology

For each subject, TBEV antibody levels as measured by NT or ELISA were assumed to follow an exponential curve over time after the 3-dose primary immunization and after the first booster (4th dose). Therefore, the antibody levels measured at 1-, 24-, 34-, 46-, 58-months following the 3-dose primary immunization were logarithmically transformed and used as the dependent variable, with days after the 3rd dose as the independent variable, to calculate the annual decline rate for each subject. If subjects received a first booster at 36- or 48-months (or withdrew from the study) the antibody level(s) at a subsequent visit(s) (i.e. 46- and 58-months if the subject was boosted at 36-months; 58-months if subject boostered at 48-months) were estimated from this antibody curve. A similar analysis was performed for the 10-years post-first booster period.

The primary immunogenicity endpoint was the seropositivity rate at each blood sampling visit. The extrapolated antibody data from the exponential curve were used to impute missing results at each yearly time point for those who withdrew or received a booster vaccination at a previous visit. Seropositivity was defined as an NT titer $\geq$10 (according to Adner et al. [7]) and an ELISA concentration (IMMUNOZYM FSME IgG, PROGEN Biotechnik, Heidelberg, Germany) of >126 VIE U/mL. An exact 95% CI (or Clopper Pearson confidence limit) was estimated for the seropositivity rates.

Additionally, NT titers and ELISA concentrations (both measured and imputed) at each blood sampling time point after the 3rd dose or after the 4th dose (first booster) were logarithmically transformed for analysis and geometric mean titers (GMTs) or geometric mean concentrations (GMCs) were computed with 95% CIs for each assay. Fold-rise of NT titers and ELISA concentrations from the prebooster to postbooster visit, were logarithmically transformed for analysis of geometric mean fold rise (GMFR). The 2-sided, 95% CIs for the GMTs/GMCs/GMFRs were constructed by back transformation of the CIs for the mean of the logarithmically transformed titers, concentrations, or fold-rise computed using the Student t distribution.

3. Results

3.1. Seropersistence and booster response up to 5 years after 3-dose primary immunization (NCT00161967)

A total of 358 subjects participated in the first follow-up study; 23 discontinued, 205 completed the study after receiving the first booster dose, and 130 subjects completed the study without requiring a booster dose. A total of 357 subjects were included in the PP population, with 49.9% female (n = 178). Subjects mean age at enrollment was 10.2 (±4.6) years.

The TBEV antibody seropositivity rate as measured by NT was 98.3%, 98.0%, 93.7%, and 84.9% at 2, 3, 4, and 5 years respectively after the 3-dose primary immunization. Results obtained by ELISA were slightly lower than results as measured by NT. After the first booster (4th dose), all (100%) of subjects were seropositive across all age groups (Table 1).

GMTs as measured by NT were high 1 month after the 3-dose primary immunization, then declined after 2 years, and then generally stabilized by year 3. The highest GMTs were observed for the two youngest age groups. Approximately 1 month after the 3-dose primary immunization, GMTs were 567.6, 461.5, 303.1 and 227.8, for those aged 1–2, 3–6, 7–11 and 12–15 years at first dose, respectively. At year 2, GMTs declined to 153.5, 204.0, 110.8 and 94.0, for the respective age groups. At year 3, GMTs remained at approximately the same titer as evidenced by values of 166.3, 188.4, 97.1 and 74.6, for the respective ascending age groups. GMTs were 73.9, 94.6, 54.8, and 41.8 at year 4 and 57.0, 81.6, 40.7, and 28.8 at year 5 for the respective ascending age groups (Fig. 2A and B).

The selection of 1000 VIE U/mL as the ELISA cut-off value was based on a very conservative approach in order to not put subjects at risk of infection with TBE. Even given this very conservative

Table 1
Seropositivity in the per-protocol population.

	Age at First Vaccination in Study 209									
	1–2 Years		3–6 Years		7–11 Years		12–15 Years		Total	
Assay Visit	n/N (%)	95% CI	n/N (%)	95% CI	n/N (%)	95% CI	n/N (%)	95% CI	n/N (%)	95% CI
ELISA										
1 month after 3rd dose (study 209)	75/75 (100.0)	(95.2, 100.0)	70/70 (100.0)	(94.9, 100.0)	133/133 (100.0)	(97.3, 100.0)	78/79 (98.7)	(93.1, 100.0)	356/357 (99.7)	(98.4, 100.0)
2 years	75/75 (100.0)	(95.2, 100.0)	69/70 (98.6)	(92.3, 100.0)	124/133 (93.2)	(87.5, 96.9)	73/79 (92.4)	(84.2, 97.2)	341/357 (95.5)	(92.8, 97.4)
3 years	N/A	(95.1, 100.0)	67/68 (98.5)	(92.1, 100.0)	127/133 (95.5)	(90.4, 98.3)	73/78 (93.6)	(85.7, 97.9)	340/352 (96.6)	(94.1, 98.2)
4 years[a]	71/73 (97.3)	(90.5, 99.7)	65/68 (95.6)	(87.6, 99.1)	114/131 (87.0)	(80.0, 92.3)	64/78 (82.1)	(71.7, 89.8)	314/350 (89.7)	(86.0, 92.7)
5 years[a]	56/73 (76.7)	(65.4, 85.8)	57/68 (83.8)	(72.9, 91.6)	86/131 (65.6)	(56.9, 73.7)	53/78 (67.9)	(56.4, 78.1)	252/350 (72.0)	(67.0, 76.6)
After 1st booster dose	31/31 (100.0)	(88.8, 100.0)	29/30 (96.7)	(82.8, 99.9)	82/84 (97.6)	(91.7, 99.7)	58/58 (100.0)	(93.8, 100.0)	200/203 (98.5)	(95.7, 99.7)
1 month after year 3 booster	25/25 (100.0)	(86.3, 100.0)	23/24 (95.8)	(78.9, 99.9)	75/77 (97.4)	(90.9, 99.7)	47/47 (100.0)	(92.5, 100.0)	170/173 (98.3)	(95.0, 99.6)
1 month after year 4 booster	6/6 (100.0)	(54.1, 100.0)	6/6 (100.0)	(54.1, 100.0)	7/7 (100.0)	(59.0, 100.0)	10/10 (100.0)	(69.2, 100.0)	29/29 (100.0)	(88.1, 100.0)
1 month after year 5 booster	N/A	N/A	N/A	N/A	N/A	N/A	1/1 (100.0)	(2.5, 100.0)	1/1 (100.0)	(2.5, 100.0)
NT										
1 month after 3rd dose (study 209)	75/75 (100.0)	(95.2, 100.0)	69/70 (98.6)	(92.3, 100.0)	133/133 (100.0)	(97.3, 100.0)	78/79 (98.7)	(93.1, 100.0)	355/357 (99.4)	(98.0, 99.9)
2 years	75/75 (100.0)	(95.2, 100.0)	69/70 (98.6)	(92.3, 100.0)	129/133 (97.0)	(92.5, 99.2)	78/79 (98.7)	(93.1, 100.0)	351/357 (98.3)	(96.4, 99.4)
3 years	73/73 (100.0)	(95.1, 100.0)	67/68 (98.5)	(92.1, 100.0)	129/133 (97.0)	(92.5, 99.2)	76/78 (97.4)	(91.0, 99.7)	345/352 (98.0)	(95.9, 99.2)
4 years[a]	70/73 (95.9)	(88.5, 99.1)	66/68 (97.1)	(89.8, 99.6)	124/132 (93.9)	(88.4, 97.3)	68/77 (88.3)	(79.0, 94.5)	328/350 (93.7)	(90.6, 96.0)
5 years[a]	62/73 (84.9)	(74.6, 92.2)	65/68 (95.6)	(87.6, 99.1)	114/133 (85.7)	(78.6, 91.2)	56/76 (73.7)	(62.3, 83.1)	297/350 (84.9)	(80.7, 88.4)
After 1st booster dose	31/31 (100.0)	(88.8, 100.0)	30/30 (100.0)	(88.4, 100.0)	83/83 (100.0)	(95.7, 100.0)	58/58 (100.0)	(93.8, 100.0)	202/202 (100.0)	(98.2, 100.0)
1 month after year 3 booster	25/25 (100.0)	(86.3, 100.0)	24/24 (100.0)	(85.8, 100.0)	76/76 (100.0)	(95.3, 100.0)	47/47 (100.0)	(92.5, 100.0)	172/172 (100.0)	(97.9, 100.0)
1 month after year 4 booster	6/6 (100.0)	(54.1, 100.0)	6/6 (100.0)	(54.1, 100.0)	7/7 (100.0)	(59.0, 100.0)	10/10 (100.0)	(69.2, 100.0)	29/29 (100.0)	(88.1, 100.0)
1 month after year 5 booster	N/A	N/A	N/A	N/A	N/A	N/A	1/1 (100.0)	(2.5, 100.0)	1/1 (100.0)	(2.5, 100.0)

Abbreviation: N/A = Not Applicable.
[a] For subjects who received a booster and for drop outs this analysis is based on the extrapolated result.

cut-off, there were still a large proportion of subjects (130/358, 36%) who completed the 5 years post- primary immunization follow-up without requiring a first booster. Of the 205 subjects (57%) who received a first booster, only 8 subjects had a prebooster NT titer <10 and only 12 subjects had and ELISA $\leq$ 126 VIE U/mL.

High geometric mean fold rises (GMFRs) after the first booster by either NT or ELISA were demonstrated for subjects boostered at year 3 or year 4. At year 3, GMFRs for subjects aged 1–2, 3–6, 7–11 or 12–15 years old at first dose were 8.2, 3.8, 5.4 and 8.0, respectively, by NT. At year 4, GMFRs for subjects aged 1–2, 3–6, 7–11 or 12–15 years at first dose were 10.1, 7.3, 11.6 and 9.3, respectively, by NT. Only one subject (age 12–15 years at first dose) was boosted at 5 years with a GMFR of 11.4 by NT (Table 2).

3.2. Seropersistence and booster response up to 10 years after first booster (4th dose) (NCT00894686)

Seropositivity rates for subjects in the PP population as measured by NT and ELISA from 1 month until 10 years after the first booster vaccination are presented in Table 3, respectively. Seropositivity rates as measured by NT remained at or above 96.6% for all age groups through 5 years. After 5 years, seropersistence gradually declined over the years for all age groups except for subjects 3 to 6 years of age who remained stable until year 10. At 10 years, seropositivity rates were 86.2% (1 to 2 years), 92.0% (3 to 6 years), 93.4% (7 to 11 years), and 87.5% (12 to 15 years). Data measured by ELISA were comparable to that of the NT. Seropositivity rates as measured by NT and ELISA for all subjects who received the second booster vaccination were 100% for all age groups at 1 month after the second booster.

GMCs (ELISA) and GMTs (NT) for the PP population after the first booster are presented in Fig. 3A and B, respectively. GMTs dropped significantly between approximately one month following the first booster vaccination (380.7) and year 3 (162.1) for all age groups (total PP population). Some slight increases in GMT were seen at various time points for most age groups throughout the study most likely due to small sample sizes and test variations. An overall gradual decline in GMTs was seen for all ages after year 3 through year 10 (53.9). GMCs correlated well with the NT results.

Twenty-six (26) children/adolescents/young adults received a second booster dose (5th dose) during the 10 years follow-up period which induced a significant increase (>5 fold rise) in GMTs. GMTs and GMFRs from prebooster to postbooster as measured by NT for the per-protocol population (n = 26) are presented in Table 4.

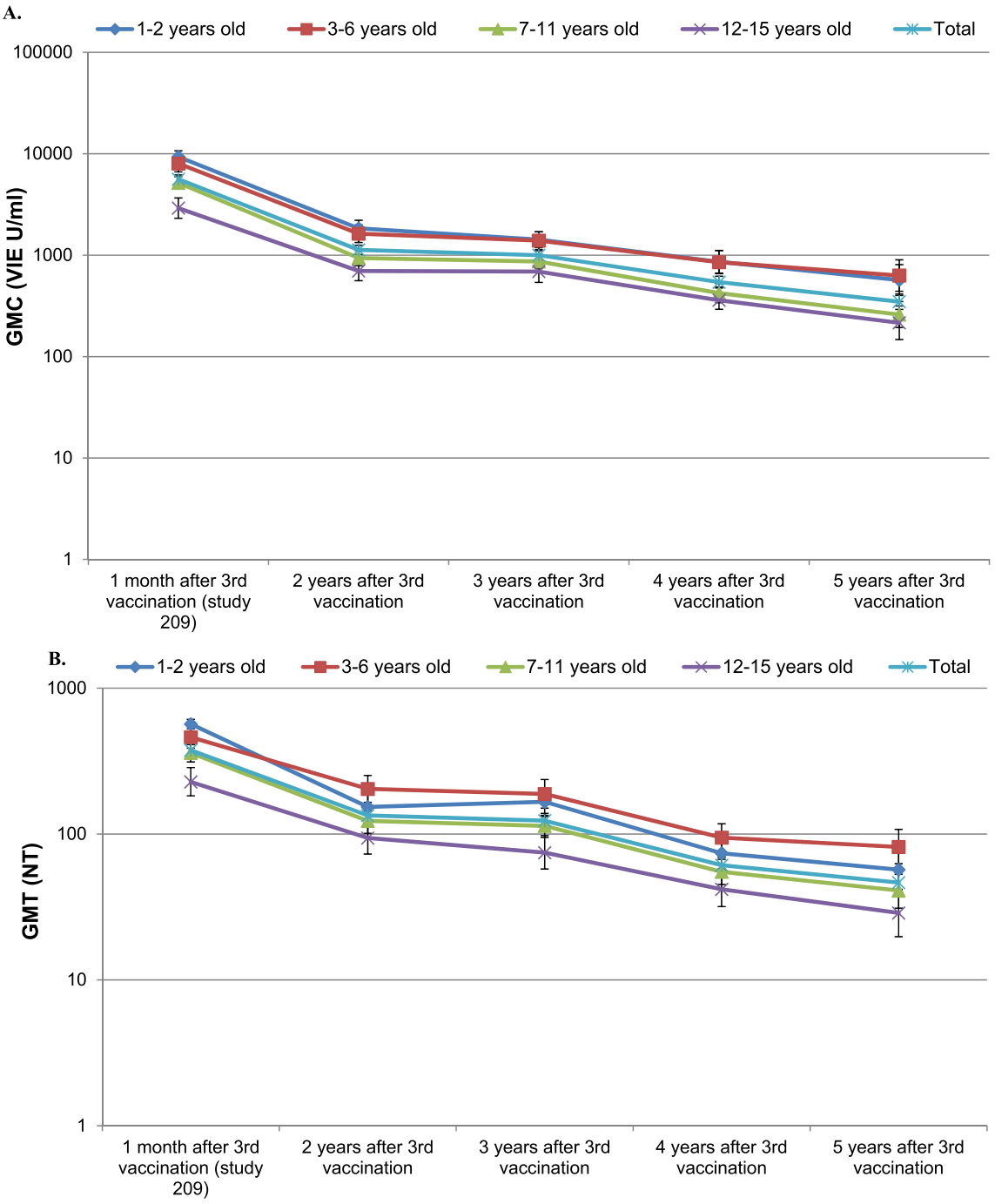

Fig. 2. Geometric mean concentration results of ELISA (A) and geometric mean titer results of NT assay (B) after 3rd vaccination in study 209.

3.3. Safety

No deaths occurred, no vaccine-related serious adverse events were reported, and no subjects were withdrawn due to an unrelated serious adverse event in these studies.

4. Discussion

Although neutralizing antibodies are said to be the most important measure for assessing protective immunity against TBE, there is currently no standardized neutralization test and no quantitative neutralizing correlate of protection. FSME-IMMUN was initially approved based on induction of neutralizing antibodies in the sera of vaccinated subjects, with the intention of maintaining the antibody level over time above a certain "protective" threshold, as no efficacy data were available. Exact dosing and optimal booster intervals were unknown at that time, resulting in a 3-year booster interval recommendation for the 0.5 mL dose for all ages. The dose in children was subsequently reduced to 0.25 mL in 2001 following studies that indicated this dose was as effective in children, however with reduced reactogencity [8]. Subsequently, the Austrian vaccination board recommended the extension of booster intervals after the first booster to 3–5 years based on a retrospective investigation [9] and the FSME-IMMUN label was updated accordingly in 2004. Afterwards, based on data from prospective studies, the booster intervals after the first booster were extended to 5 years.

Table 2
GMFRs measured by ELISA (VIE U/ml) and NT from pre-first booster to post-first booster in the per-protocol population.

	Prebooster			Postbooster					
Visit Age Group	N	GM	(95% CI[a])	N	GM	(95% CI[a])	N	GMFR	(95% CI[a])
ELISA									
All Boostered	203	538.9	(485.77, 597.75)	203	4468.7	(3754.28, 5318.97)	203	8.3	(7.27, 9.46)
1–2 years	31	678.5	(606.82, 758.69)	31	8472.5	(6364.18, 11279.36)	31	12.5	(9.60, 16.25)
3–6 years	30	725.1	(539.34, 974.79)	30	5765.3	(3529.69, 9416.81)	30	8.0	(5.55, 11.40)
7–11 years	84	520.1	(442.84, 610.90)	84	4543.0	(3344.04, 6171.69)	84	8.7	(6.99, 10.92)
12–15 years	58	430.1	(345.52, 535.36)	58	2716.9	(2087.64, 3535.91)	58	6.3	(5.05, 7.91)
Boostered year 3	173	510.2	(453.27, 574.35)	173	4245.5	(3479.78, 5179.62)	173	8.3	(7.17, 9.65)
1–2 years	25	644.6	(566.10, 734.08)	25	8686.5	(6077.55, 12415.40)	25	13.5	(9.80, 18.53)
3–6 years	24	717.0	(492.82, 1043.05)	24	5867.5	(3195.38, 10774.24)	24	8.2	(5.33, 12.58)
7–11 years	77	507.2	(426.62, 603.07)	77	4272.7	(3076.72, 5933.57)	77	8.4	(6.62, 10.71)
12–15 years	47	382.4	(296.80, 492.69)	47	2433.5	(1805.70, 3279.61)	47	6.4	(4.92, 8.23)
Boostered year 4	29	764.6	(692.50, 844.10)	29	6387.5	(5003.27, 8154.57)	29	8.4	(6.44, 10.83)
1–2 years	6	839.9	(745.61, 946.19)	6	7636.3	(6165.75, 9457.60)	6	9.1	(6.70, 12.33)
3–6 years	6	758.5	(668.46, 860.62)	6	5373.8	(2600.90, 11103.16)	6	7.1	(3.11, 16.13)
7–11 years	7	685.6	(485.31, 968.44)	7	8919.4	(4693.09, 16951.68)	7	13.0	(8.47, 19.99)
12–15 years	10	783.7	(634.93, 967.27)	10	5038.6	(3066.06, 8280.31)	10	6.4	(3.58, 11.54)
Boostered year 5	1	267.0	NE	1	1001.0	NE	1	3.7	NE
12–15 years	1	267.0	NE	1	1001.0	NE	1	3.7	NE
NT									
All Boostered	202	57.8	(50.66, 65.86)	202	376.7	(335.63, 422.90)	202	6.5	(5.82, 7.31)
1–2 years	31	66.6	(53.08, 83.65)	31	565.9	(502.08, 637.90)	31	8.5	(6.81, 10.60)
3–6 years	30	86.8	(60.09, 125.42)	30	378.5	(272.52, 525.64)	30	4.4	(3.01, 6.32)
7–11 years	83	61.6	(49.90, 75.97)	83	356.8	(292.67, 434.98)	83	5.8	(4.90, 6.86)
12–15 years	58	39.6	(30.95, 50.59)	58	326.9	(262.40, 407.15)	58	8.3	(6.68, 10.21)
Boostered year 3	172	58.9	(50.80, 68.33)	172	359.4	(315.53, 409.41)	172	6.1	(5.39, 6.91)
1–2 years	25	69.3	(52.27, 91.78)	25	564.9	(490.70, 650.36)	25	8.2	(6.24, 10.67)
3–6 years	24	91.2	(57.91, 143.66)	24	349.1	(234.51, 519.76)	24	3.8	(2.50, 5.87)
7–11 years	76	62.9	(50.28, 78.74)	76	342.0	(276.34, 423.22)	76	5.4	(4.57, 6.46)
12–15 years	47	38.9	(29.35, 51.51)	47	310.8	(242.16, 398.94)	47	8.0	(6.35, 10.06)
Boostered year 4	29	55.3	(44.44, 68.71)	29	525.4	(444.24, 621.45)	29	9.5	(7.22, 12.53)
1–2 years	6	56.7	(46.53, 69.11)	6	570.2	(423.68, 767.32)	6	10.1	(7.02, 14.40)
3–6 years	6	71.3	(42.31, 120.04)	6	522.7	(310.68, 879.51)	6	7.3	(3.18, 16.90)
7–11 years	7	48.6	(24.52, 96.45)	7	565.5	(417.66, 765.58)	7	11.6	(7.03, 19.22)
12–15 years	10	51.1	(31.87, 81.87)	10	476.7	(315.27, 720.72)	10	9.3	(4.66, 18.69)
Boostered year 5	1	7.0	NE	1	80.0	NE	1	11.4	NE
12–15 years	1	7.0	NE	1	80.0	NE	1	11.4	NE

Abbreviation: NE = Not Estimable.
Note: Age group was age at first vaccination in Study 209.
[a] Confidence intervals (CIs) are back transformations of a confidence interval based on the Student t distribution for the mean logarithm of the titers, concentrations or the fold rises.

Study data presented here show that seropositivity remained high 5 years after the 3-dose primary immunization in a big proportion of children and adolescents (84.9%), as well as up to 10 years following the first booster (at or above 86.2% for all age groups).

Moreover, after receiving either a first or second booster all subjects were seropositive by NT with a fold rise ranging from 4.4 to 12.5 across all age groups, indicating the establishment of a strong immune memory. These results are consistent with other studies in adults demonstrating the stability of anti-TBEV antibody levels as well as the immune memory response years after multiple booster immunizations [9–15]. Importantly, in this age group of children who received their 3-dose primary immunization between 1 and 15 years of age, no demographic factors (age, BMI, and gender) were found to have a significant effect on the probability of remaining TBE seropositive up to 118 months after the first booster vaccination.

A direct comparison of these studies must be undertaken with care. The setting and serological data from our recent childhood study are directly comparable only with the adult study as published by Konior et al 2017 (same NT performed), which clearly shows the age dependence of the seropositivity rates and GMT values [14]. Nonetheless, competent immune memory response has clearly been demonstrated even in the older age groups and after extended time intervals [14].

An age dependent decline of GMT and seropositivity values has been demonstrated in a similar way in another adult study by Paulke-Korinek et al. [10]. However, the study setting was quite different, and there was a change in the serological test system (switch from Novartis in-house NT to NT of Institute of Virology at the University of Vienna) performed up to 8 years after the first booster. Additionally, the study published by Konior is a prospective investigation of TBE antibodies seropersistence after the first booster in subjects, most of whom received FSME-IMMUN throughout the complete 3-dose primary immunization and first booster. The study published by Paulke-Korinek represents a retrospective investigation of a sample of healthy subjects with documented 3-dose primary immunization against TBE with FSME-IMMUN and the last vaccination given at least 3 years before study entry, stratified according to age and boosted once with Encepur® adults (irrespective of the antibody titer before vaccination).

In the third study [15] healthy adults and adolescents 12 years of age and older who had received 3 different primary vaccination schedules and a booster dose with Encepur were included. The testing system used in this study was the Novartis in-house NT, thus a direct comparison of the serological results between the studies is not possible. Immune response to a second booster after an extended time interval was also not tested in that study.

Although all of these studies demonstrate age dependent GMT and seropositivity rates clearly decline over time, field

Table 3
Seropositivity rates measured by ELISA and NT in the per-protocol population.

	Age at First Vaccination in Study 209									
	1–2 Years		3–6 Years		7–11 Years		12–15 Years		Total	
Assay Visit	% (n/N)	(95% CI[a])	% (n/N)	(95% CI[a])	% (n/N)	(95% CI[a])	% (n/N)	(95% CI[a])	% (n/N)	(95% CI[a])
ELISA (>126 (VIE U/ml)										
After 1st Booster Vaccination (Study 700401)										
1 month	100.0 (30/30)	(88.4, 100.0)	96.2 (25/26)	(80.4, 99.9)	98.6 (68/69)	(92.2, 100.0)	100.0 (46/46)	(92.3, 100.0)	98.8 (169/171)	(95.8, 99.9)
3 years	100.0 (30/30)	(88.4, 100.0)	100.0 (25/25)	(86.3, 100.0)	93.9 (62/66)	(85.2, 98.3)	97.8 (44/45)	(88.2, 99.9)	97.0 (161/166)	(93.1, 99.0)
4 years	100.0 (29/29)	(88.1, 100.0)	100.0 (23/23)	(85.2, 100.0)	100.0 (54/54)	(93.4, 100.0)	100.0 (40/40)	(91.2, 100.0)	100.0 (146/146)	(97.5, 100.0)
5 years[b]	100.0 (29/29)	(88.1, 100.0)	100.0 (25/25)	(86.3, 100.0)	98.4 (60/61)	(91.2, 100.0)	92.9 (39/42)	(80.5, 98.5)	97.5 (153/157)	(93.6, 99.3)
6 years[b]	96.6 (28/29)	(82.2, 99.9)	100.0 (25/25)	(86.3, 100.0)	98.4 (60/61)	(91.2, 100.0)	92.7 (38/41)	(80.1, 98.5)	96.8 (151/156)	(92.7, 99.0)
7 years[b]	93.1 (27/29)	(77.2, 99.2)	100.0 (25/25)	(86.3, 100.0)	98.4 (60/61)	(91.2, 100.0)	92.7 (38/41)	(80.1, 98.5)	96.2 (150/156)	(91.8, 98.6)
8 years[b]	93.1 (27/29)	(77.2, 99.2)	100.0 (25/25)	(86.3, 100.0)	98.4 (60/61)	(91.2, 100.0)	92.7 (38/41)	(80.1, 98.5)	96.2 (150/156)	(91.8, 98.6)
9 years[b]	82.8 (24/29)	(64.2, 94.2)	92.0 (23/25)	(74.0, 99.0)	95.1 (58/61)	(86.3, 99.0)	92.7 (38/41)	(80.1, 98.5)	91.7 (143/156)	(86.2, 95.5)
10 years[b]	82.8 (24/29)	(64.2, 94.2)	88.0 (22/25)	(68.8, 97.5)	93.3 (56/60)	(83.8, 98.2)	82.9 (34/41)	(67.9, 92.8)	87.7 (136/155)	(81.5, 92.5)
After 2nd Booster Vaccination (Study B9371021)										
1 mo. after year 3 booster	(0/0)	N/A	100.0 (1/1)	(2.5, 100.0)	100.0 (5/5)	(47.8, 100.0)	100.0 (3/3)	(29.2, 100.0)	100.0 (9/9)	(66.4, 100.0)
1 mo. after year 4 booster	100.0 (1/1)	(2.5, 100.0)	(0/0)	N/A	100.0 (1/1)	(2.5, 100.0)	100.0 (3/3)	(29.2, 100.0)	100.0 (5/5)	(47.8, 100.0)
1 mo. after year 6 booster	100.0 (1/1)	(2.5, 100.0)	(0/0)	N/A	(0/0)	N/A	100.0 (1/1)	(2.5, 100.0)	100.0 (2/2)	(15.8, 100.0)
1 mo. after year 8 booster	100.0 (2/2)	(15.8, 100.0)	100.0 (1/1)	(2.5, 100.0)	(0/0)	N/A	(0/0)	N/A	100.0 (3/3)	(29.2, 100.0)
1 mo. after year 9 booster	(0/0)	N/A	100.0 (2/2)	(15.8, 100.0)	100.0 (1/1)	(2.5, 100.0)	100.0 (1/1)	(2.5, 100.0)	100.0 (4/4)	(39.8, 100.0)
1 mo. after year 10 booster	100.0 (2/2)	(15.8, 100.0)	(0/0)	N/A	100.0 (1/1)	(2.5, 100.0)	(0/0)	N/A	100.0 (3/3)	(29.2, 100.0)
All Boostered	100.0 (6/6)	(54.1, 100.0)	100.0 (4/4)	(39.8, 100.0)	100.0 (8/8)	(63.1, 100.0)	100.0 (8/8)	(63.1, 100.0)	100.0 (26/26)	(86.8, 100.0)
NT										
After 1st Booster Vaccination (Study 700401)										
1 month	100.0 (30/30)	(88.4, 100.0)	100.0 (26/26)	(86.8, 100.0)	100.0 (69/69)	(94.8, 100.0)	100.0 (46/46)	(92.3, 100.0)	100.0 (171/171)	(97.9, 100.0)
3 years (Visit 1)	100.0 (30/30)	(88.4, 100.0)	100.0 (25/25)	(86.3, 100.0)	100.0 (67/67)	(94.6, 100.0)	100.0 (45/45)	(92.1, 100.0)	100.0 (167/167)	(97.8, 100.0)
4 years (Visit 2)	100.0 (29/29)	(88.1, 100.0)	100.0 (23/23)	(85.2, 100.0)	100.0 (55/55)	(93.5, 100.0)	100.0 (40/40)	(91.2, 100.0)	100.0 (147/147)	(97.5, 100.0)
5 years (Visit 3)[b]	96.6 (28/29)	(82.2, 99.9)	100.0 (25/25)	(86.3, 100.0)	100.0 (61/61)	(94.1, 100.0)	100.0 (41/41)	(91.4, 100.0)	99.4 (155/156)	(96.5, 100.0)
6 years (Visit 6)[b]	96.6 (28/29)	(82.2, 99.9)	100.0 (25/25)	(86.3, 100.0)	98.4 (61/62)	(91.3, 100.0)	97.6 (40/41)	(87.1, 99.9)	98.1 (154/157)	(94.5, 99.6)
7 years (Visit 7)[b]	93.1 (27/29)	(77.2, 99.2)	100.0 (25/25)	(86.3, 100.0)	98.4 (61/62)	(91.3, 100.0)	95.0 (38/40)	(83.1, 99.4)	96.8 (151/156)	(92.7, 99.0)
8 years (Visit 8)[b]	93.1 (27/29)	(77.2, 99.2)	100.0 (25/25)	(86.3, 100.0)	96.8 (60/62)	(88.8, 99.6)	92.5 (37/40)	(79.6, 98.4)	95.5 (149/156)	(91.0, 98.2)
9 years (Visit 9)[b]	93.1 (27/29)	(77.2, 99.2)	100.0 (25/25)	(86.3, 100.0)	96.8 (60/62)	(88.8, 99.6)	90.0 (36/40)	(76.3, 97.2)	94.9 (148/156)	(90.1, 97.8)
10 years (Visit 10)[b]	86.2 (25/29)	(68.3, 96.1)	92.0 (23/25)	(74.0, 99.0)	93.4 (57/61)	(84.1, 98.2)	87.5 (35/40)	(73.2, 95.8)	90.3 (140/155)	(84.5, 94.5)
After 2nd Booster Vaccination (Study B9371021)										
1 mo. after year 3 booster	(0/0)	N/A	100.0 (1/1)	(2.5, 100.0)	100.0 (5/5)	(47.8, 100.0)	100.0 (3/3)	(29.2, 100.0)	100.0 (9/9)	(66.4, 100.0)
1 mo. after year 4 booster	100.0 (1/1)	(2.5, 100.0)	(0/0)	N/A	100.0 (1/1)	(2.5, 100.0)	100.0 (3/3)	(29.2, 100.0)	100.0 (5/5)	(47.8, 100.0)
1 mo. after year 6 booster	100.0 (1/1)	(2.5, 100.0)	(0/0)	N/A	(0/0)	N/A	100.0 (1/1)	(2.5, 100.0)	100.0 (2/2)	(15.8, 100.0)
1 mo. after year 8 booster	100.0 (2/2)	(15.8, 100.0)	100.0 (1/1)	(2.5, 100.0)	(0/0)	N/A	(0/0)	N/A	100.0 (3/3)	(29.2, 100.0)
1 mo. after year 9 booster	(0/0)	N/A	100.0 (2/2)	(15.8, 100.0)	100.0 (1/1)	(2.5, 100.0)	100.0 (1/1)	(2.5, 100.0)	100.0 (4/4)	(39.8, 100.0)
1 mo. after year 10 booster	100.0 (2/2)	(15.8, 100.0)	(0/0)	N/A	100.0 (1/1)	(2.5, 100.0)	(0/0)	N/A	100.0 (3/3)	(29.2, 100.0)
All Boostered	100.0 (6/6)	(54.1, 100.0)	100.0 (4/4)	(39.8, 100.0)	100.0 (8/8)	(63.1, 100.0)	100.0 (8/8)	(63.1, 100.0)	100.0 (26/26)	(86.8, 100.0)

Abbreviations: ELISA = enzyme-linked immunosorbent assay; NT = neutralization test; N/A = not applicable; VIE U/ml = Vienna units per milliliter.
[a] Exact 2-sided confidence interval (Clopper and Pearson) based upon the observed proportion of subjects.
[b] For subjects who received a booster, or subjects with early withdrawals, extrapolated results from regression were used.

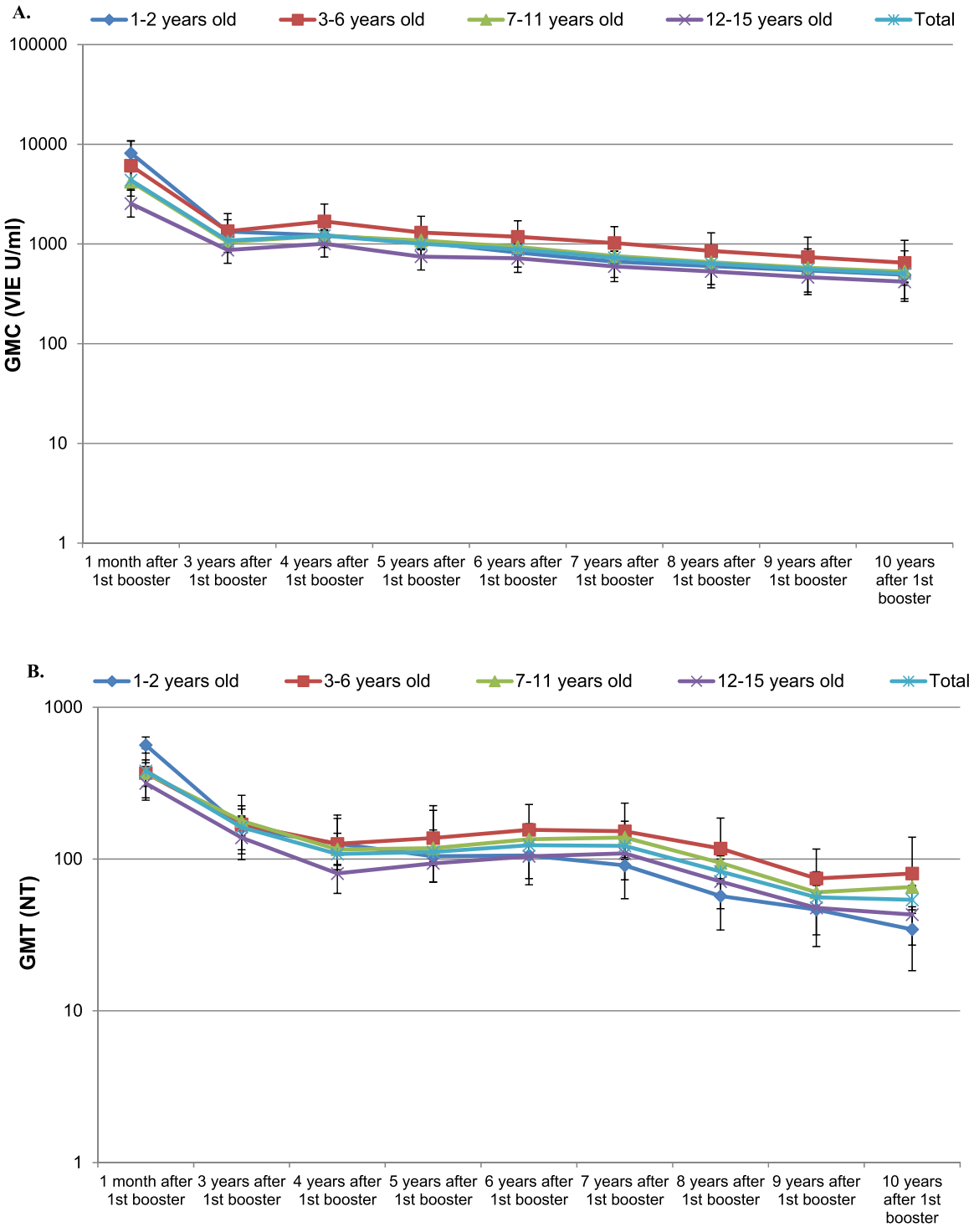

Fig. 3. Geometric mean concentration results of ELISA (A) and geometric mean titer results of NT assay (B) after first booster.

effectiveness data as well as population impact data convincingly show high protection rates [16] even after extended time intervals [17–19]. A study conducted in Sweden based on documented patient vaccination history showed that vaccine failures are most common in elderly [20]. The vaccine effectiveness analysis of the Austrian data [16] on the contrary, which also was based on documented patient vaccination history and the vaccination coverage in the respective age cohorts, showed that the vaccine failure rate was comparable among all age groups, and not significantly increased among elderly persons. This was true for both subjects with a regular or irregular/overdue vaccination interval.

The discrepancy between serological results of clinical studies and population impact data may be explained by the excellent boostability with FSME-IMMUN after a 3-dose primary immunization even after prolonged intervals [21], and the rapid induction of high antibody titers already 7 days after the 3rd dose as documented in adults [22,23]. Thus, one can speculate that the anamnestic immune response, i.e. the levels of neutralizing

Table 4
GMFRs measured by ELISA and NT from pre-second booster to post-second booster in the per-protocol population.

	Prebooster			Postbooster					
Booster Visit Age Group	N	GM	(95% CI[a])	N	GM	(95% CI[a])	N	GMFR	(95% CI[a])
ELISA									
All Boostered	26	214.0	(172.36, 265.74)	26	1844.1	(1305.54, 2604.91)	26	8.6	(6.69, 11.10)
1–2 years	6	348.5	(243.03, 499.68)	6	2383.2	(937.88, 6055.79)	6	6.8	(3.49, 13.42)
3–6 years	4	281.1	(169.56, 466.10)	4	3829.8	(743.35, 19731.61)	4	13.6	(4.08, 45.53)
7–11 years	8	150.5	(91.88, 246.65)	8	1608.1	(766.97, 3371.85)	8	10.7	(6.86, 16.64)
12–15 years	8	184.2	(135.28, 250.74)	8	1210.7	(815.84, 1796.67)	8	6.6	(4.23, 10.21)
Boostered year 3	9	125.9	(94.70, 167.27)	9	1184.4	(857.66, 1635.69)	9	9.4	(6.69, 13.24)
3–6 years	1	182.0	(NE, NE)	1	1288.0	(NE, NE)	1	7.1	(NE, NE)
7–11 years	5	109.0	(67.89, 174.96)	5	1044.2	(547.28, 1992.33)	5	9.6	(4.89, 18.78)
12–15 years	3	141.5	(60.54, 330.58)	3	1420.9	(732.70, 2755.65)	3	10.0	(3.80, 26.52)
Boostered year 4	5	197.4	(122.80, 317.26)	5	1251.4	(472.45, 3314.57)	5	6.3	(3.16, 12.71)
1–2 years	1	378.0	(NE, NE)	1	4465.0	(NE, NE)	1	11.8	(NE, NE)
7–11 years	1	148.0	(NE, NE)	1	1230.0	(NE, NE)	1	8.3	(NE, NE)
12–15 years	3	175.0	(125.56, 243.77)	3	823.7	(305.62, 2219.80)	3	4.7	(1.31, 16.86)
Boostered year 6	2	335.3	(18.58, 6051.39)	2	1422.7	(65.81, 30755.61)	2	4.2	(3.54, 5.08)
1–2 years	1	421.0	(NE, NE)	1	1812.0	(NE, NE)	1	4.3	(NE, NE)
12–15 years	1	267.0	(NE, NE)	1	1117.0	(NE, NE)	1	4.2	(NE, NE)
Boostered year 8	3	241.8	(170.61, 342.62)	3	1275.5	(234.01, 6952.94)	3	5.3	(1.07, 26.05)
1–2 years	2	227.9	(67.00, 775.53)	2	890.9	(24.78, 32030.32)	2	3.9	(0.03, 478.10)
3–6 years	1	272.0	(NE, NE)	1	2615.0	(NE, NE)	1	9.6	(NE, NE)
Boostered year 9	4	339.2	(306.80, 375.10)	4	4848.1	(1411.94, 16647.00)	4	14.3	(4.58, 44.60)
3–6 years	2	355.2	(211.48, 596.59)	2	7992.2	(3.03, 21105701)	2	22.5	(0.01, 35377.01)
7–11 years	1	321.0	(NE, NE)	1	3355.0	(NE, NE)	1	10.5	(NE, NE)
12–15 years	1	327.0	(NE, NE)	1	2578.0	(NE, NE)	1	7.9	(NE, NE)
Boostered year 10	3	427.6	(295.79, 618.16)	3	6292.3	(2652.92, 14924.27)	3	14.7	(4.41, 49.08)
1–2 years	2	465.4	(349.39, 619.87)	2	5341.7	(415.38, 68693.80)	2	11.5	(0.67, 196.61)
7–11 years	1	361.0	(NE, NE)	1	8731.0	(NE, NE)	1	24.2	(NE, NE)
NT									
All Boostered	26	24.4	(14.68, 40.66)	26	126.8	(94.76, 169.64)	26	5.2	(2.78, 9.67)
1–2 years	6	15.9	(12.13, 20.83)	6	123.7	(71.69, 213.28)	6	7.8	(3.67, 16.51)
3–6 years	4	16.1	(9.57, 27.24)	4	207.4	(52.26, 823.39)	4	12.8	(4.54, 36.36)
7–11 years	8	80.1	(18.12, 354.26)	8	128.9	(63.78, 260.49)	8	1.6	(0.24, 10.68)
12–15 years	8	12.7	(10.34, 15.49)	8	99.4	(57.58, 171.43)	8	7.8	(4.53, 13.59)
Boostered year 3	9	56.6	(13.13, 243.83)	9	89.8	(60.26, 133.76)	9	1.6	(0.35, 7.28)
3–6 years	1	10.0	(NE, NE)	1	80.0	(NE, NE)	1	8.0	(NE, NE)
7–11 years	5	211.6	(32.09, 1395.70)	5	85.8	(40.44, 182.04)	5	0.4	(0.06, 2.78)
12–15 years	3	11.2	(6.90, 18.13)	3	100.6	(25.18, 402.07)	3	9.0	(1.78, 45.50)
Boostered year 4	5	11.5	(9.64, 13.73)	5	95.2	(39.30, 230.74)	5	8.3	(3.06, 22.39)
1–2 years	1	12.0	(NE, NE)	1	226.0	(NE, NE)	1	18.8	(NE, NE)
7–11 years	1	10.0	(NE, NE)	1	160.0	(NE, NE)	1	16.0	(NE, NE)
12–15 years	3	11.9	(7.82, 18.06)	3	60.1	(20.39, 176.89)	3	5.1	(1.13, 22.60)
Boostered year 6	2	16.7	(1.74, 161.32)	2	190.6	(2.39, 15215.26)	2	11.4	(0.01, 8766.14)
1–2 years	1	20.0	(NE, NE)	1	135.0	(NE, NE)	1	6.8	(NE, NE)
12–15 years	1	14.0	(NE, NE)	1	269.0	(NE, NE)	1	19.2	(NE, NE)
Boostered year 8	3	20.0	(NE, NE)	3	95.4	(20.46, 444.58)	3	4.8	(1.02, 22.23)
1–2 years	2	20.0	(NE, NE)	2	73.6	(0.32, 16962.10)	2	3.7	(0.02, 848.11)
3–6 years	1	20.0	(NE, NE)	1	160.0	(NE, NE)	1	8.0	(NE, NE)
Boostered year 9	4	19.2	(16.87, 21.85)	4	246.7	(86.84, 700.71)	4	12.8	(4.54, 36.36)
3–6 years	2	18.4	(6.57, 51.78)	2	380.3	(0.51, 283270.2)	2	20.6	(0.08, 5470.82)
7–11 years	1	20.0	(NE, NE)	1	160.0	(NE, NE)	1	8.0	(NE, NE)
12–15 years	1	20.0	(NE, NE)	1	160.0	(NE, NE)	1	8.0	(NE, NE)
Boostered year 10	3	15.0	(7.81, 28.72)	3	240.0	(28.79, 2000.69)	3	16.0	(3.62, 70.97)
1–2 years	2	13.0	(4.87, 34.51)	2	147.0	(49.94, 432.51)	2	11.3	(10.26, 12.53)
7–11 years	1	20.0	(NE, NE)	1	640.0	(NE, NE)	1	32.0	(NE, NE)

Abbreviations: ELISA = enzyme-linked immunosorbent assay; NT = neutralization test; GMC = geometric mean concentration; GMFR = geometric mean of fold increase; NE = not estimable; VIE U/ml = Vienna units per milliliter.
Note: Age group was age at first vaccination in Study 209.
Note: Age groups that are not present indicate all zeros for the counts.
[a] Confidence intervals (CIs) are back transformations of a confidence interval based on the Student t distribution for the mean logarithm of the titers, concentrations or the fold rises.

antibodies after an encounter with the antigen, are being built up fast enough in most instances to control infection to an extent that can prevent the disease. Nonetheless, we do not have any information on the immunological status of the patients at the time of infection, their individual immune responsiveness at the time of the 3-dose primary vaccination course, nor the time interval from exposure to onset of CNS-symptoms. Immune responses being too slow or not effective enough, and exceptionally short incubation periods therefore might be a reason for the rare occurrence of vaccine failure despite a secondary immune response having been documented [23].

Taken together, these results demonstrate a long-term seropersistence of TBEV antibodies in children after the 3rd dose and after first booster (4th dose) with FSME-IMMUN. A robust immune memory response was shown in all subjects who received a first or second booster (4th or 5th dose) at any time point over a 5 or

10 year follow up period, respectively. These data may support the conclusion that at least in young individuals with adequate and documented priming with three doses, an extension of the FSME-IMMUN booster interval up to 10 years seems to be warranted. Moreover, data from the adult studies on seropersistence [14], boostability [21] and population impact [16] indicate that this may also hold true for subjects who started primary vaccination at a later time in life.

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Conflicts of interest

This study was sponsored by Pfizer, Inc. P. Zhang, L. Harper, H.J. Schmitt and W. Erber are employees of Pfizer and may hold stock/stock options in the company.

Data sharing

Upon request, and subject to certain criteria, conditions and exceptions (see https://www.pfizer.com/science/clinical-trials/trial-data-and-results for more information), Pfizer will provide access to individual de-identified participant data from Pfizer-sponsored global interventional clinical studies conducted for medicines, vaccines and medical devices (1) for indications that have been approved in the US and/or EU or (2) in programs that have been terminated (i.e., development for all indications has been discontinued). Pfizer will also consider requests for the protocol, data dictionary, and statistical analysis plan. Data may be requested from Pfizer trials 24 months after study completion. The de-identified participant data will be made available to researchers whose proposals meet the research criteria and other conditions, and for which an exception does not apply, via a secure portal. To gain access, data requestors must enter into a data access agreement with Pfizer.

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