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Irregular tick-borne encephalitis vaccination schedules: The effect of a single catch-up vaccination with FSME-IMMUN. A prospective non-interventional study

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ABSTRACT

Background: Intervals longer than recommended are frequently encountered between doses of tick borne encephalitis virus (TBE) vaccines in both residents of and travelers to endemic regions. In clinical practice the management of individuals with lapsed TBE vaccination schedules varies widely and has in common that the underlying immunological evidence is scarce.
Study purpose and methods: The aim of this study was to generate data reliable enough to derive practical recommendations on how to continue vaccination with FSME-IMMUN in subjects with an irregular TBE vaccination history. Antibody response to a single catch-up dose of FSME-IMMUN was assessed in 1115 adults (age ≥16 years) and 125 children (age 6–15 years) with irregular TBE vaccination histories.
Results: Subjects of all age groups developed a substantial increase in geometric mean antibody concentration after a single catch-up TBE vaccination which was consistently lower in subjects with only one previous TBE vaccination compared to subjects with two or more vaccinations. Overall, >94% of young adults and children, and >93% of elderly subjects with an irregular TBE vaccination history achieved antibody levels ≥25 U/ml irrespective of the number of previous TBE vaccinations.
Conclusion: We conclude that TBE vaccination of subjects with irregular vaccination histories should be continued as if the previous vaccinations had been administered in a regular manner, with the stage of the vaccination schedule being determined by the number of previous vaccinations. Although lapsed vaccination schedules may leave subjects temporarily with inadequate protection against TBE infection, adequate protection can quickly be re-established in >93% of the subjects by a single catch-up dose of FSME-IMMUN, irrespective of age, number of previous vaccinations, and time interval since the last vaccination.

1. Introduction

Tick-borne encephalitis (TBE) is endemic in large areas of Central, Northern and Eastern Europe as well as in Central and Northern Asia [1,2]. The disease is caused by the TBE virus (TBEV) and is transmitted by the bite of infected ticks. TBE is associated with considerable morbidity as well as mortality rates ranging from 0.5 to 2% (Central European strains) up to 40% (Far Eastern strains) in subjects with CNS involvement [1–3]. There is no causal therapy available. Vaccination is the most efficient means to prevent the disease.

FSME-IMMUN (Baxter AG, Vienna, Austria) is an inactivated whole virus vaccine against TBE. The primary immunization course consists of 3 vaccinations at day 0, 1–3 months, and 5–12 months after the preceding vaccination. A rapid immunization scheme is available for travelers comprising 2 vaccinations at days 0 and 14, followed by the regular 3rd dose after 5–12 months. According to the marketing authorization, the first booster should be given not

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later than 3 years after the third dose. Further booster vaccinations are recommended in 3- to 5-year intervals, depending on age [4,5]. The overall field effectiveness of the TBE vaccine has been estimated to range between 96% and 99% in regularly vaccinated persons, however irregularly vaccinated persons have been shown to have lower degrees of protection [4,5]. Besides FSME-IMMUN a second prophylactic TBE vaccine (Encepur®, Novartis Vaccines, Marburg, Germany) is available in several European countries. Vaccination schemes are similar for both TBE vaccines. In clinical studies in adults and children, subjects who received the 3 doses of the primary vaccination course with the same brand showed similar seropositivity rates compared to subjects who received the third dose of the other brand [6–9]. Clinical practice, as reflected by the queries of general practitioners and pediatricians to the marketing authorization holder (Baxter), has shown that incomplete and/or irregular vaccination histories are frequently encountered in both residents of and travelers to endemic geographies. Guidelines on how to proceed with the TBE vaccine FSME-IMMUN in subjects with an irregular and/or incomplete TBE vaccination history are therefore imperative but the body of evidence on the immunological effects of irregular TBE vaccination in both adults and children is scarce [10,11]. Different strategies are followed in current practice: (1) restart of the basic vaccination course, (2) measurement of the serum anti-TBE antibody concentration to support the decision on the further vaccination schedule, or (3) administration of one or more catch-up vaccinations followed by continuation of the recommended schedule.

The aim of this study was to generate a data basis reliable enough to derive practical recommendations on how to continue vaccination with FSME-IMMUN in subjects with an irregular TBE vaccination history. For this reason, the antibody response to a single catch-up dose of FSME-IMMUN in irregularly vaccinated subjects ≥6 years of age was assessed in an open manner.

2. Material and methods

2.1. Study design and population

The study was conducted from May 1, 2005, to December 31, 2006 and was designed in accordance with the Recommendation on the Planning and Conduct of Post-authorization Observational Studies issued by the German Federal Institute for Drugs and Medical Devices [12] as a post-authorization multi-center open-label non-interventional study in individuals with irregularity patterns of their TBE vaccination histories. The study was carried out in accordance with the Declaration of Helsinki. The study protocol was reviewed and approved by five independent ethics committees.

Healthy subjects ≥6 years of age (for details of the inclusion/exclusion criteria see supplementary data) with an irregular TBE vaccination history as depicted in Table 1 were eligible. Participation in the study included two visits: At the first visit written informed consent was obtained. Then a blood sample was drawn and the catch-up vaccination was administered (FSME-IMMUN Junior 0.25 ml in subjects ≥6 to <16 years of age, FSME-IMMUN 0.5 ml in subjects ≥16 years of age). The second visit was scheduled 3–12 weeks after the catch-up vaccination to obtain a second blood sample.

2.2. Study objectives

The main objectives of the study were (1) to characterize irregularly vaccinated subjects in daily practice with respect to number and time intervals of TBE vaccinations, and (2) to determine the success of a single catch-up vaccination with FSME-IMMUN in subjects with an irregular TBE vaccination history by measurement of TBE IgG antibody concentrations in pre- and post-vaccination sera.

2.3. Antibody testing

The blood samples were tested for TBE IgG antibodies by a commercially available ELISA (Enzygnost® Anti-FSME-Virus, Dade Behring, Germany). The threshold was set to 25 U/ml for putative seroprotection. All TBE antibody concentrations below 10 U/ml were set to 9.99 for statistical analysis.

2.4. Statistical analysis

The data were analyzed by descriptive statistical methods. Mean ± SD or median ± quantiles were calculated as appropriate. Point estimates and 95% confidence intervals (CIs) were calculated for putative seroprotection rates. Geometric mean concentrations (GMC) with 95% CI and reverse cumulative distribution (RCD) plots were generated.

2.5. Safety analysis

Due to the extensive safety record of FSME-IMMUN vaccines [9,13] and the observational design of the study, no active safety measurements were performed. However, investigators were instructed to document and report any adverse reaction they become aware of during the conduct of the study. Safety analysis was limited to calculating the incidence of reported adverse reactions.

2.6. Role of the funding source

The study was designed and funded by Baxter. Baxter employees RS, AR and BU were responsible for study design, data collection, data analysis, data interpretation, and writing of the manuscript. Baxter independent co-authors UM, UH and RK served as the scientific advisory committee and were fully involved in the design of the study, data interpretation, and writing of the manuscript. UM was the responsible statistician and conducted the data management and analysis. The submission for publication was jointly decided by all authors. The corresponding author had full access to all data of the study. All study data were available to all authors on request.

3. Results

3.1. Demographic data

A total number of 2915 subjects were enrolled in 459 pediatric and general medical practices throughout Germany whereof 1240 (42.5%; 1115 adults and 125 children) fulfilled the criteria for inclusion in this analysis. Demographic attributes and their distribution in subgroups by number of previous vaccinations and time interval since the last vaccination are shown for adults in Tables 2a and 2b.

Adult study population: The median age was 34 years in young adults (16–50 years) and 61 years in the elderly (≥50 years). The median weight was 82.0 kg in males and 65.4 kg in females. As shown in Table 2b, 50% of the young adults presented with a minimum time interval between the last vaccination and the catch-up vaccination of 4.9–7.1 years, depending in the number of previous vaccinations, and 25% had an interval of at least 8.5–9.0 years. The respective figures for the elderly are 4.6–6.0 years (50%) and 7.3–8.8 years (25%). The maximum intervals ranged from 16.5–22.3 (young adults) and 17.4–23.0 years (elderly).

Pediatric study population: Due to the small sample size ($n = 125$), no further age stratification was applied. With regard to the TBE vaccination history, the most prominent group consisted of

Table 1
Definition of irregular TBE vaccination history. The conditions to be met for inclusion in the study are expressed in Boolean notation: AND = both conditions must apply, OR = one of both conditions must apply.

Number of previous vaccinations	Time interval				Conditions to be met for inclusion in the analysis
	Condition 1 1st → 2nd vacc.	Condition 2 2nd → 3rd vacc.	Condition 3 3rd vacc. → 1st booster or booster → booster	Condition 4 Last vacc. → catch-up vacc.	
1	N/A	N/A	N/A	≥123 days	4
2	≥123 days	N/A	N/A	≥457 days	1 OR 4
3	≥123 days	≥457 days	N/A	≥1278 days	(1 OR 2) AND 4
≥4	≥123 days	≥457 days	≥1278 days	≥1278 days	(1 OR 2 OR 3) AND 4

Table 2a
Demographic data. Overweight was defined as body weight of ≥80 kg in adult females and ≥100 kg in adult males. Body height was not documented, therefore the BMI could not be calculated. Since overweight assessment in children would have required comparison with age-dependent percentile nomograms, no attempt was made to calculate the proportion of children with overweight.

Demographic attributes	Adults		Children	
	N	%	*N*	%
Total number of subjects	1115	100	125	100
Gender				
Male	496	44.5	59	47.2
Female	619	55.5	66	52.8
Age				
Young adults (≥16 to <50 years)	704	63.1	N/A	N/A
Elderly (≥50 years)	411	36.9	N/A	N/A
Weight				
Underweight or normal weight	970	87.0	N/A	N/A
Overweight	145	13.0	N/A	N/A
Number of previous vaccinations				
1	132	11.8	12	9.6
2	346	31.0	80	64.0
3	145	13.0	19	15.2
≥4	492	44.1	14	11.2

subjects with 2 vaccinations (64.0%) (Table 2c). The distribution of gender was not homogeneous in the subgroups (data not shown).

3.2. Antibody concentration

3.2.1. Adults

GMC before catch-up vaccination (Tables 3a and 3b). After 1 or 2 previous vaccinations, the GMC before the catch-up vaccination was low in both age groups. With 3 or more previous vaccinations, the GMC before the catch-up vaccination was above the putative seroprotection threshold (≥25 U/ml) in both age groups, but young adults had a distinctly higher antibody concentration as compared to the elderly (3 vaccinations subgroup: 61.8 vs. 29.7 U/ml, ≥4 vaccinations subgroup: 94.3 vs. 36.1 U/ml).

GMC after catch-up vaccination (Tables 3a and 3b). The GMC clearly depends on age and the number of previous vaccinations. Young adults achieved a substantially higher GMC, ranging from 171.8 U/ml (1 previous vaccination) to 392.8 U/ml (≥4 previous vaccinations), as compared to the elderly whose values ranged from 135.8 U/ml (1 previous vaccination) to 196.9 U/ml (≥4 previous vaccinations).

Overall effect of the catch-up vaccination in adult subjects (Fig. 1a). The RCD curves before catch-up vaccination demonstrate that 1 or 2 previous vaccinations were insufficient to generate long-term antibody levels above the putative protective threshold whereas a

Table 2b
Time interval since last vaccination in adult subjects. The upper panel shows the proportion of subjects in various time intervals since the last vaccination, stratified by the number of previous vaccinations. The lower panel indicates the minimum time interval being exceeded by 50%/25% of the subjects with the longest intervals, and the maximum time interval observed in young adults and the elderly.

Interval	Number of previous vaccinations			
	1	2	3	≥4
≥4 to <15 months	25.0% (*n* = 33)	2.3% (*n* = 8)	N/A	N/A
≥15 months to <3.5 years	18.1% (*n* = 24)	33.8% (*n* = 117)	N/A	N/A
≥3.5 to <5 years	7.6% (*n* = 10)	14.7% (*n* = 51)	20.0% (*n* = 29)	29.5% (*n* = 145)
≥5 to <10 years	31.1% (*n* = 41)	28.9% (*n* = 100)	61.4% (*n* = 89)	55.7% (*n* = 274)
≥10 years	18.1% (*n* = 24)	20.2% (*n* = 70)	18.6% (*n* = 27)	14.8% (*n* = 73)
Total	*n* = 132	*n* = 346	*n* = 145	*n* = 492
Time intervals [years] exceeded by 50%/25% of the subjects				
Young adults	≥4.9/≥8.5	≥5.1/≥9.0	≥7.1/≥9.0	≥6.7/≥8.8
Elderly	≥4.6/≥8.6	≥4.7/≥8.8	≥6.0/≥8.1	≥5.7/≥7.3
Maximum interval [years]				
Young adults	18.0	22.3	16.6	16.5
Elderly	23.0	20.6	17.4	18.0

Table 2c
Distribution of children/adolescents by number of vaccinations. Due to the small sample size, no attempt was made to stratify the subjects by time since last vaccination.

	Number of previous vaccinations			
	1	2	3	≥4
Number of subjects (*n* = 125)	9.6% (*n* = 12)	64.0% (*n* = 80)	15.2% (*n* = 19)	11.2% (*n* = 14)

Table 3a
Antibody concentration (GMC in U/ml) in young adults before, and GMC and putative seroprotection rates after the catch-up vaccination. Data are stratified by number of previous vaccinations. 95% C.I. = 95% confidence interval (lower and upper bound).

No. of prev. vacc.	*N*	Antibody concentration *before* the catch-up vaccination		Antibody concentration *after* the catch-up vaccination		Putative seroprotection rate *after* the catch-up vaccination		
		GMC	95% C.I.	GMC	95% C.I.	*n*/*N*	%	95% C.I.
1	87	21.4	[16.3; 28.1]	171.8	[136.6; 216.1]	82/87	94.3%	[87.1%; 98.1%]
2	231	22.4	[19.5; 25.7]	295.4	[262.3; 332.7]	229/231	99.1%	[96.9%; 99.9%]
3	86	61.8	[49.0; 77.9]	365.0	[317.4; 419.8]	86/86	100.0%	[95.8%; 100.0%]
≥4	300	94.3	[83.3; 106.9]	392.8	[358.6; 430.3]	299/300	99.7%	[98.2%; 100.0%]

3rd vaccination added substantially to antibody persistence. After the catch-up vaccination, individuals with 1 previous vaccination showed generally lower antibody levels compared to individuals with 2, 3, or ≥4 previous vaccinations whose distribution curves were comparable.

3.2.2. Pediatric population

Table 3c shows the GMC before and after the catch-up vaccination by number of previous vaccinations. The GMC before the catch-up vaccination was similar to those of young adults, with the exception of the GMC after 1 previous vaccination which was considerably lower in children (11.2 vs. 21.4 U/ml). The GMC after the catch-up vaccination increased with the number of previous vaccinations from 259.3 U/ml (1 vaccination) to 435.3 U/ml (≥4 vaccinations). As compared to young and elderly adults, the GMC levels were higher in children. The RCD curves before and after the catch-up vaccination (Fig. 1b) are largely similar to the respective curves in adults.

3.3. Putative seroprotection rates (≥25 U/ml) after catch-up vaccination

3.3.1. Adults

The majority of subjects with an irregular TBE vaccination history achieved antibody levels ≥25 U/ml after the catch-up vaccination with FSME-IMMUN (Tables 3a and 3b): After 1 previous vaccination, antibody levels ≥25 U/ml were reached by 94.3% of the young adults and 93.3% of the elderly. After ≥2 previous vaccinations, antibody concentrations ≥25 U/ml were achieved in >99% of the young adults and in >96% of the elderly irrespective of the number of previous vaccinations. Young adults accomplished a slightly higher putative seroprotection rate than the elderly. The putative seroprotection levels of subjects with an extended time interval of more than 10 years since last TBE vaccination ($n = 194$) were comparable to the ones with a shorter vaccination interval (data not shown).

3.3.2. Pediatric population

After the catch-up vaccination, all except one of the 125 subjects reached an antibody level of ≥25 U/ml, corresponding to a putative overall seroprotection rate of 99.2% irrespective of the number of previous vaccinations (Table 3c).

3.4. Post vaccination fold increases of antibody concentrations

The GMC fold increases are strongly dependent on the number of previous vaccinations (Fig. 2). In adults of both age groups the highest fold increase was observed in subjects with 2 previous vaccinations (14.8-fold in the young adults and 17.1-fold in the elderly), followed by those with only 1 previous vaccination (9.1-fold in young adults and 8.3-fold in the elderly). After 3 or more vaccinations, the fold increase drops to about 4–6 (range: 3.7-fold to 5.8-fold). Due to the small sample size no such analysis was done for children.

3.5. Safety

Altogether 6 adverse reactions, 5 in adults and 1 in children/adolescents, were reported in temporal relationship with the catch-up vaccination during the study: Of the adverse reactions observed in adults, 3 were local reactions at the injection site, 1 was a systemic reaction with flu-like symptoms with onset 2–3 days after immunization, and 1 was a combination of a local reaction and flu-like symptoms 12 h after immunization. The adverse reaction in the pediatric population was a local reaction at the injection site. All 6 adverse reactions were classified as non-serious and labeled in the summary of product characteristics. The incidence was 0.48% overall, thereof 0.45% in the adult subpopulation and 0.80% in the pediatric subpopulation.

4. Discussion

With 1115 adult and 125 pediatric subjects analyzed, this is the largest study on incomplete and/or irregular TBE vaccination schedules conducted so far and the first study which also included children. The results presented here clearly demonstrate that a catch-up vaccination with a single dose of FSME-IMMUN was able to elicit high antibody levels in most of the previously irregularly TBE vaccinated subjects over a broad age range.

This finding is corroborated by a recently published study where FSME-IMMUN was administered in healthy young adults with regular or delayed TBE vaccination histories and substantial booster responses were noted in the majority of subjects [10]. However, whereas our study clearly indicates that the antibody response to a further dose of TBE vaccine correlates with the number of previous TBE vaccinations, the booster responses in the study conducted by

Table 3b
Antibody concentration (GMC in U/ml) in elderly adults before, and GMC and putative seroprotection rates after the catch-up vaccination. Data are stratified by number of previous vaccinations. 95% C.I. = 95% confidence interval (lower and upper bound).

No. of prev. vacc.	*N*	Antibody concentration *before* the catch-up vaccination		Antibody concentration *after* the catch-up vaccination		Putative seroprotection rate *after* the catch-up vaccination		
		GMC	95% C.I.	GMC	95% C.I.	*n*/*N*	%	95% C.I.
1	45	18.8	[13.9; 25.5]	135.8	[97.0; 190.1]	42/45	93.3%	[81.7%; 98.6%]
2	115	13.7	[11.8; 16.0]	193.1	[159.5; 233.8]	111/115	96.5%	[91.3%; 99.0%]
3	59	29.7	[23.0; 38.3]	180.3	[142.9; 227.4]	58/59	98.3%	[90.9%; 100.0%]
≥4	192	36.1	[31.1; 41.8]	196.9	[174.6; 222.0]	187/192	97.4%	[94.0%; 99.1%]

Table 3c
Antibody concentration (GMC in U/ml) in children before, and GMC and putative seroprotection rates after the catch-up vaccination. Data are stratified by number of previous vaccinations. 95% C.I. = 95% confidence interval (lower and upper bound).

No. of prev. vacc.	*N*	Antibody concentration *before* the catch-up vaccination		Antibody concentration *after* the catch-up vaccination		Putative seroprotection rate *after* the catch-up vaccination		
		GMC	95% C.I.	GMC	95% C.I.	*n*/*N*	%	95% C.I.
1	12	11.2	[8.5; 14.6]	259.3	[182.3; 368.9]	12/12	100.0%	[73.5%; 100.0%]
2	80	25.3	[20.1; 31.7]	342.3	[281.8; 415.8]	79/80	98.8%	[93.2%; 100.0%]
3	19	61.4	[35.6; 106.0]	321.2	[245.4; 420.5]	19/19	100.0%	[82.4%; 100.0%]
≥4	14	95.4	[53.4; 170.6]	435.3	[284.4; 666.3]	14/14	100.0%	[76.8%; 100.0%]

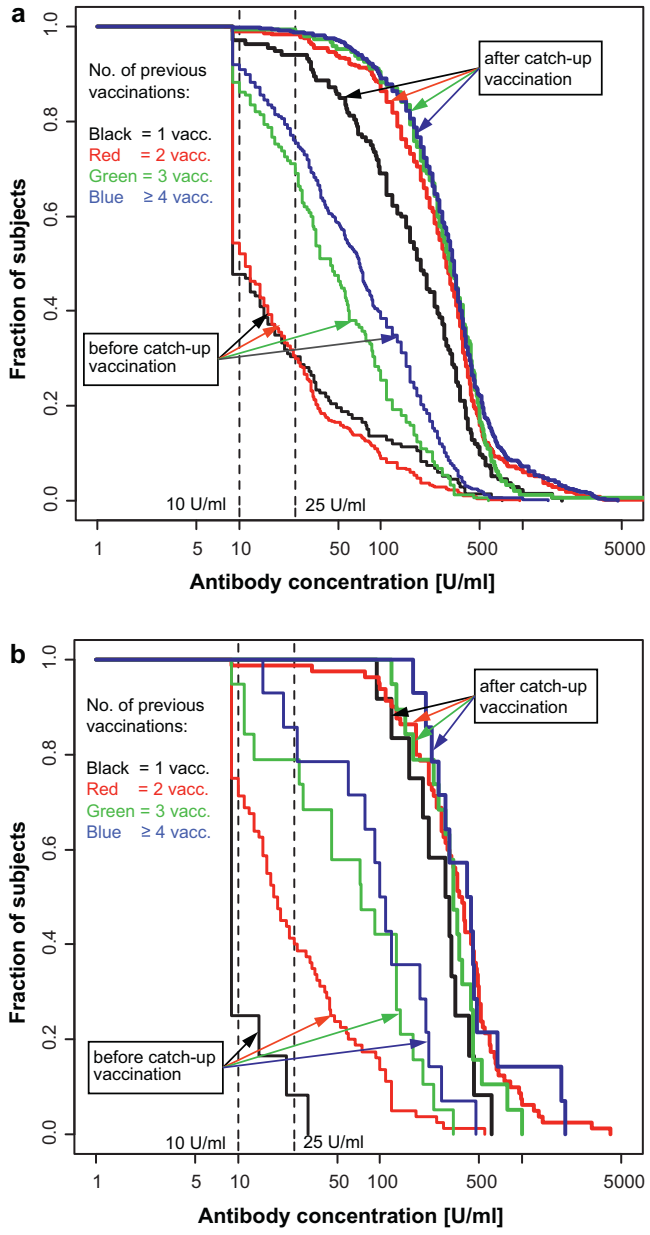

Fig. 1. (a) Reverse cumulative distribution plot of the overall effect of the catch-up vaccination on the TBE antibody response in adults. Shown are the fractions of adult subjects with specific TBE antibody concentrations measured by ELISA before and after the catch-up vaccination stratified by number of previous vaccinations. (b) Reverse cumulative distribution plot of the overall effect of the catch-up vaccination on the TBE antibody response in children and adolescents. Shown are the fractions of children and adolescents with specific TBE antibody concentrations measured by ELISA before and after the catch-up vaccination stratified by number of previous vaccinations.

Askling et al. were independent of the number of previous doses. This discrepancy could be explained by differences in the study design and/or the small sample size of various vaccination subgroups in the study of Askling et al.

In our study, putatively seroprotective anti-TBE antibody levels (≥25 U/ml) in response to the catch-up vaccination were reached by 99–100.0% of the children, 94–100% of the young adults, and 93–98% of the elderly, irrespective of the number of previous TBE vaccinations. However, the absolute values of the TBE antibody GMCs after the catch-up FSME-IMMUN vaccination were for all age groups consistently lower in subjects with only one previous TBE vaccination as compared to subjects with two or more vaccinations, suggesting a shorter period of protection after only one TBE vaccination. This pattern of increasing antibody responses with increasing number of previous vaccinations is similar to the pattern seen during a regular vaccination course [9,13]. Here also, substantial protection can only be expected after the second vaccination. A third vaccination 5–12 months after the second vaccination is crucial for the completion of the primary vaccination course and for obtaining a long-lasting antibody response. The pooled seroconversion rates – defined as ≥126 VIEU/ml (Immunozym ELISA assay) and a titer of ≥1:10 (neutralization assay) – of all clinical studies with FSME-IMMUN in subjects with regular vaccination schedules [13] lie in a similar range as those which we obtained in subjects with an irregular vaccination schedule in this study. This finding supports the conclusion that, similar to many other inactivated vaccines, the number of vaccinations is most important for the mounting of a long-lasting antibody response after a TBE catch-up or booster dose, regardless of the time intervals between previous TBE vaccinations. This is in accordance with national recommendations which emphasize that extended vaccination intervals usually do not reduce the antibody response to subsequent vaccinations [14,15].

The GMC before and after the catch-up vaccination was consistently lower in the elderly as compared to young adults or children. This observation was also made in the study by Askling et al. and in many other TBE vaccine studies, and has regularly been attributed to immunosenescence [11,16–23]. However, recent studies suggest

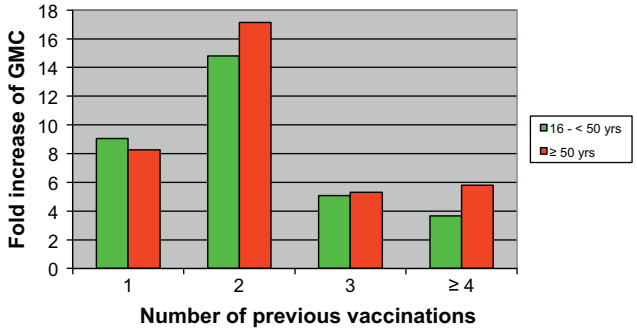

Fig. 2. Fold increase of TBE antibody concentration (ELISA) after catch-up vaccination in young and elderly adults.

that the quality of antibodies in terms of avidity and functional activity (neutralization assay/ELISA ratio) is not different between young adults and the elderly [24]. Furthermore, it has been shown in our study as well as in other investigations that the fold increase of the anamnestic antibody response in the elderly is comparable to that of young adults [11,25]. This indicates that the quantity of antibodies is the only difference between young adults and the elderly which could be explained by the competition model of Radbruch [26,27]. According to this hypothesis the number of survival niches for long-lived plasma cells in the bone marrow is constant throughout life-time. The long-lived plasma cells producing various antibody specificities have to share the limited number of survival niches. As a subject acquires more and more antibody specificities due to infection or vaccination over the course of a life-time, the number of survival niches per antibody specificity and, as a consequence, also the antibody production will decrease with increasing age. Thus, the age-dependent reduction of antibody levels produced by long-lived plasma cells may not be a pathological, but rather a physiological process, resembling the adaptation to an increasing number of antibody specificities.

The inequality of the group sizes after stratification by the number of previous vaccinations possibly reflects the real distribution of the irregularity patterns in the German population. Discontinuation of travel-associated TBE vaccination (subgroup with 2 previous vaccinations) or after one or several booster vaccinations (subgroup with ≥4 previous vaccinations) is apparently more likely to occur than discontinuation after the 1st dose or after completion of the basic immunization course (subgroup with 3 previous vaccinations), thus explaining why the subgroups with 1 or 3 previous vaccinations were considerably smaller than those with 2 or ≥4 previous vaccinations. Although each of the two smaller subgroups contained more than 130 subjects, the number of subjects drops below 100 when it comes to subgroup analysis, e.g. by age. The pediatric population was altogether small ($n = 125$), resulting in very small sample sizes of only 12–19 subjects in the subgroups with 1, 3 and ≥4 previous vaccinations. As a consequence, care should be taken when interpreting the results of the adult population derived from small subgroups, and great caution should be exercised when interpreting the results of the pediatric population except for the subgroup with 2 previous vaccinations.

5. Conclusions

From the results of our study it can be concluded that irregular and/or incomplete TBE vaccination series should be continued as if the previous vaccinations had been given according to a regular schedule. This can be translated into practice as follows:

- 1 previous vaccination: Administer the 2nd dose and complete the primary vaccination course by a 3rd dose 5–12 months later, followed by the 1st booster after 3 years and subsequent booster doses every 3 or 5 years (according to age).
- 2 previous vaccinations: Administer the 3rd dose to complete the primary course, followed by the 1st booster 3 years later and subsequent booster doses every 3 or 5 years (according to age).
- 3 previous vaccinations: Administer the 1st booster dose followed by subsequent booster doses every 3 or 5 years (according to age).
- ≥4 previous vaccinations: Administer the next and subsequent booster doses every 3 or 5 years (according to age).

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.vaccine.2014.01.072.

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