Vaccine 30 (2012) 499–502

Contents lists available at SciVerse ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Brief report

Immunogenicity of delayed TBE-vaccine booster

H.H. Askling[a,b,*], S. Vene[c], L. Rombo[a,d], L. Lindquist[e,f]

[a] Karolinska Institutet, Department of Medicine/Solna, Unit for Infectious Diseases, Stockholm, Sweden
[b] Department of Infectious Diseases, Karolinska University Hospital, SE 17176 Solna, Sweden
[c] Swedish Institute for Communicable Disease Control, Nobels väg 18, SE 17182 Solna, Sweden
[d] Centre for Clinical Research, Sormland County Council, Drottninggatan 16 B, SE 632 20 Eskilstuna, Sweden
[e] Department of Infectious Diseases, Karolinska University Hospital, SE 14186 Huddinge, Sweden
[f] Karolinska Institutet, Department of Medicine/Huddinge, Stockholm, Sweden

ARTICLE INFO

Article history:
Received 5 August 2011
Received in revised form
11 November 2011
Accepted 15 November 2011
Available online 26 November 2011

Keywords:
TBE
Vaccination
Booster dose
Neutralizing antibodies

ABSTRACT

Information is scarce regarding the antibody response when TBE-vaccine booster doses are delayed, which is a common situation in daily life. We have investigated the immune response after a delayed booster dose compared to a normal booster interval in an every-day setting. Overall, 250/260 (96%) of the study participants had neutralizing antibodies post-booster, with no significant difference between normal and delayed booster intervals. Based on our findings we propose that healthy individuals who have failed adherence to the recommended schedule of TBE-vaccination can be given a delayed dose without concern of immunogenicity.

1. Introduction

Tick-borne encephalitis (TBE) is a notifiable disease according to the Swedish Communicable Diseases Act. In recent years, a rising number of TBE-cases have been reported to the Swedish Institute of Communicable Disease Control. This includes cases from areas in Sweden where TBE has previously not been seen [1] and has occurred despite an increasing number of distributed doses for vaccination in exposed areas. Cases have also recently been reported in patients with documented TBE-vaccinations according to the recommended schedule [2]. The information regarding the immunogenicity of delayed TBE-vaccine booster is scarce, although these delays constitute a common situation in daily life. We have investigated the immune response after a delayed booster dose compared to a normal booster interval in an every-day setting. Our aim was to evaluate further recommendations regarding TBE-booster to those individuals who have not been vaccinated according to the recommended schedule.

2. Materials and methods

2.1. Study population and design

We conducted an open, uncontrolled, open-label, single centre study. The study population consisted of previously TBE-immunized (FSME-Immune® or Encepur®) healthy adults (>18 years), who consecutively and by their own initiative attended a vaccination clinic for a booster with TBE-vaccine during 2007–2009 in Stockholm, Sweden. The vaccine used was FSME-Immune® 0.5 ml, given intramuscularly in the deltoid region. All subjects gave informed consent and had documented TBE-immunisations with at least one dose. Study performance was in accordance with the International Conference on Harmonisation-Good Clinical Practice (ICH-GCP) guidelines as well as local regulatory requirements and was approved by the regional ethics committee in Stockholm.

2.2. Definitions of intervals between doses

A normal interval (*N*) to a booster dose was defined as 3 years after 3 doses within 1 year (0, 1, 5–12 months) and subsequent doses every 5 years. A delayed interval (*D*) to a booster dose was defined as >1 to <2 year after one or two doses, >3 to <10 years after three doses or >6 to <10 years after ≥4 doses. A very delayed interval (VD) to a booster dose was defined as >2 years after one or two doses and ≥10 years after ≥3 doses.

* Corresponding author at: Department of Communicable Diseases Control and Prevention, Stockholm Box 17533, SE-11891 Stockholm, Sweden.
Tel.: +46 8 737 3922; fax: +46 8 31 57 67; mobile: +46 70 227 1545.
E-mail addresses: helena.hervius-askling@sll.se (H.H. Askling), sirkka.vene@smi.se (S. Vene), lars.rombo@dll.se (L. Rombo), lars.lindqvist@karolinska.se (L. Lindquist).

0264-410X/$ – see front matter © 2011 Elsevier Ltd. All rights reserved.
doi:10.1016/j.vaccine.2011.11.061

Table 1
Number of individuals with neutralizing antibodies ≥5 ED_{50} after a booster dose, in relation to the number of previous doses, age at first dose and interval since last dose, $n = 260$. For definitions of intervals see Section 2.2.

Previous doses/interval	Normal interval (*N*), $n = 132$		Delayed interval (*D*), $n = 74$		Very delayed interval (VD), $n = 54$	
Age at first dose	<50 years $n = 88$	≥50 years $n = 44$	<50 years $n = 38$	≥50 years $n = 36$	<50 years $n = 43$	≥50 years $n = 11$
1 dose	NA	NA	3/4	1/1	6/7	NA
2 doses	NA	NA	3/3	1/1	25/25	3/5
3 doses	21/24	24/24	20/20	26/27	9/9	6/6
≥ 4 doses	63/64	19/20	11/11	7/7	2/2	NA

2.3. Sample analysis

Blood-samples were drawn immediately before and 1–3 months after booster vaccination. Tick-borne encephalitis neutralizing antibodies were assessed by a rapid fluorescent focus inhibition test, essentially as previously described with minor modifications [3]. Sera were analyzed at two dilutions (1:5 and 1:20). ED_{50} (50% effective dose) values were calculated. Reciprocal titres of ≥5 were considered positive.

2.4. Safety

All participants were asked to report any kind of adverse event possibly related to the TBE-vaccination. This was done on a separate form which was distributed to the participant at the time of vaccination and returned at the time of the second blood-sample.

3. Results

3.1. Demographics

We included 313 individuals of which 53 were lost at follow-up with the second blood-sample 1–3 months after vaccination. The remaining study population consisted of 260 patients with a median age of 54 years (range 18–80) whereof 105 (40%) were males. With respect to the number of previous TBE-vaccine doses, the study participants were distributed as follows: one dose $n = 12$, two doses $n = 34$, three doses $n = 110$ and ≥4 doses $n = 104$.

3.2. Immunogenicity

Overall, 250/260 (96%) of the study participants were positive for neutralizing antibodies post-booster. There was no significant difference ($p = 0.96$) between the group with normal (*N*) ($n = 132$) and delayed (*D*) or very delayed (VD) booster interval ($n = 128$). In the group with two previous doses of TBE-vaccine, 4/4 with delayed intervals (*D*) and 28/30 with very delayed intervals (VD) were positive for neutralizing antibodies post booster dose. The corresponding numbers after three doses were 45/48 (*N*), 46/47 (*D*) and 15/15 (VD), respectively. After at least 4 doses, ED_{50} titres ≥5 were present in 82/84 (*N*), 18/18 (*D*) and 2/2 (VD). Considering the waning immune response above the age of 50, the study population was divided into two groups with respect to that age and the first dose of TBE-vaccine. The results are shown in Tables 1 and 2.

3.3. Pre- and post booster neutralizing antibodies

In the group of participants with ≥3 previous TBE-vaccine doses, we analyzed the pre- and post-booster levels of neutralizing antibodies. The results showed that the pre-booster level was ≥5 ED_{50} in more than 80% of the participants when ≥4 doses had been given, irrespective of the interval between doses, compared to 46% (*N*) and 57% (VD), respectively, when only three doses had been given. This is graphically illustrated in Figs. 1 and 2.

3.4. Study participants with one previous dose only

Twelve individuals (8 males) had only one documented dose of TBE-vaccine. The time since this dose ranged from 1 to 11 years. Ten individuals had a pre-booster level of neutralizing antibodies below detection level, but only 2/12 did not respond adequately after the booster dose. The two non-responders were both young males and the time since the TBE-vaccination was 1 year and 9 years, respectively.

3.5. Non-responders

Ten individuals (4%) did not have detectable antibodies before dose and did not elicit detectable immune response after booster doses. In this group, 7/10 were males and the number of previous

Table 2
Number of individuals with corresponding neutralizing titres (ED_{50}) pre- and post booster dose, in relation to interval since last dose, $n = 260$. For definitions of intervals see Section 2.2.

Neutralizing titres (ED50)	Normal $n = 132$	Delayed $n = 74$	Very delayed $n = 54$
	Prebooster[a]	Prebooster[a]	Prebooster[a]
<5	38	26	23
5	5	1	2
5–10	57	32	18
20	2	1	3
>20	29	13	7
	Postbooster	Postbooster	Postbooster
<5	5	2	3
5	0	1	0
5–10	32	21	9
20	4	0	1
>20	90	50	41

[a] Three individuals had missing pre-booster titres.

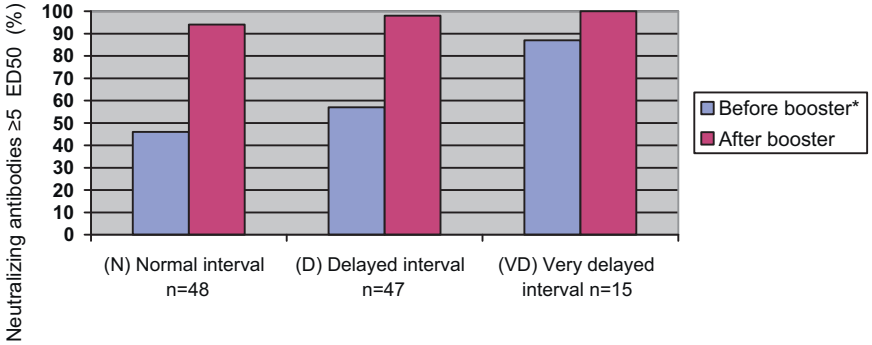

Fig. 1. Neutralizing antibodies ≥5 ED_{50} (%) before and after booster doses, with 3 previous doses of TBE-vaccine. $N = 110$. *Prebooster N vs. D, $p = 0.26$; N vs. VD, $p = 0.005$; D vs. VD, $p = 0.04$.

doses was distributed as follows: 1 ($n = 2$), 2 ($n = 2$), 3 ($n = 4$) and 4 ($n = 2$). The median age was 54 years (range 30–68), excluding an outlier of 18 years old, and 4/10 had been given their first dose at age ≥50 years old. Half of the non-responders (5/10) had a documented normal interval between previous doses, 3/10 had previously received three doses and 2/10 four doses or more, respectively.

3.6. Age

In the group with VD and age ≥50 at first dose, 2/5 (both males) lacked post-booster antibody responses. On the other hand, in the group with normal intervals between doses and aged <50 years, 3/24 lacked post-booster antibody responses. With respect to pre-booster neutralizing antibodies there was a predominance of study participants ≥50 years old at first dose (17/20) with levels below the detection limit in the group with delayed intervals. The antibody response post-booster was, however, adequate. The median age was the same in the non-responder group and the whole group of study participants.

3.7. Safety

No serious adverse events were reported. Mild adverse events were reported in 25/260 (10%) study participants, the most common of which was pain or tenderness at the injections site (22/25).

4. Discussion

This prospective every-day setting study, contributes to the question on how to deal with individuals who do not follow the recommended schedule of TBE-vaccination. To our knowledge there is no similar data published. Overall, 96% of the study participants had adequate levels of neutralizing antibodies post-booster, independent of the number of previous doses and intervals. Based on these results, the key-message is that the booster interval is of minor clinical importance to the protection of TBEV. This finding is consistent with yet unpublished data of the long-lasting immunological memory after two or more TBE vaccinations [4], as well as by the assumption of field effectiveness for irregularly vaccinated individuals [5]. In the group of individuals with ≥4 doses all but two had adequate serological responses, independent of age at first dose and previous intervals. We are not able to draw any firm conclusions with the respect to antibody response and age or gender from the small group of non-responders. The immunological responsiveness to vaccination decreases with age and recent studies regarding TBE-vaccination of persons aged >50 years have confirmed this [6–9]. In our study, 87/91 study participants aged ≥50 years at first dose had an adequate immune response independent of booster intervals. This finding highlights the fact that other individual factors (e.g. weight, smoking), of which we had no information, may be of importance for immunogenicity. The pre-booster antibody results indicate that the longevity of protection is dependent on the number of previously given doses, rather than the interval to the last dose given. The fact that the study participants could have been previously vaccinated with either of the two TBE-vaccines (FSME-Immune® or Encepur®) demonstrates a well accepted cross-immunogenicity [10], which can be useful for the recommendations in an every-day setting. Considering the potential cross-reactions with other flavivirus antibodies (yellow fever, Japanese encephalitis, dengue fever) we want to point out that the methodology used [3] is specific for TBEV. Also, the majority

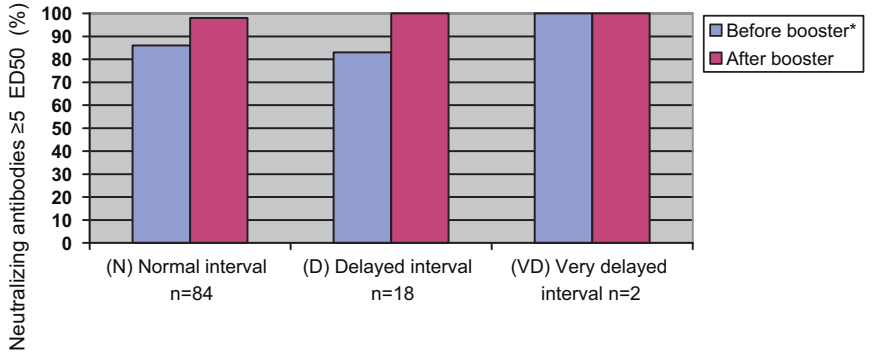

Fig. 2. Neutralizing antibodies ≥5 ED_{50} (%) before and after booster doses, with ≥4 previous doses of TBE-vaccine. $N = 104$. *Prebooster N vs. D, $p = 0.8$; N vs. VD, $p = 0.2$; D vs. VD, $p = 0.3$.

of the patients did not receive any concomitant vaccination nor did they travel to a dengue endemic area before the post booster sample.

5. Conclusions

There is an adequate immune response regardless of booster delay in the majority of the adults irrespective of the number of doses of TBE-vaccine previously given, even though the post-booster response was best in the group with ≥4 previous doses. Our results support the Swedish practice to extend the booster interval to 5 years after the fourth dose. We propose that otherwise healthy individuals who have failed adherence to the recommended schedule of TBE-vaccination can be given a delayed dose without concern of immunogenicity.

Acknowledgements

Erik Ekwall for economical and practical support.

Charlotta Rydgård Andersson for administrative support.

Wasa vaccination nurses Anna Moberg, Pia Hallin, Lena Ihr, Elizabeth Kozlic and Catharina Rizell.

Conflict of interest statement: LR has participated in advisory boards for Novartis and Crucell and given lectures arranged by Crucell.

LL is a member of the International Scientific TBE working group organized by Baxter and has been reimbursed for lectures arranged by Baxter.

HHA and SV declare no conflict of interest.

Funding source: Centre for Clinical Research, Sormland County Council, Eskilstuna, Sweden.

Baxter Sweden kindly provided vaccine doses but did not have any input in study design, or collection, analysis and interpretation of data.

References

[1] Swedish Institute for Infectious Diseases Control. Available at: http://www.smittskyddsinstitutet.se/statistik/viral-meningoencefalit/?t=com&p=17529#statistics-nav [accessed on 01.08.11].

[2] Andersson CR, Vene S, Insulander M, Lindquist L, Lundkvist A, Günther G. Vaccine failures after active immunisation against tick-borne encephalitis. Vaccine 2010;28(April (16)):2827–31.

[3] Vene S, Haglund M, Lundkvist A, Lindquist L, Forsgren M. Study of the serological response after vaccination against tick-borne encephalitis in Sweden. Vaccine 2007;25(January (2)):366–72.

[4] Schosser R, Kaiser R, Mansmann U, Heininger U. Seropositivity before and seroprotection after a booster vaccination with FSME-Immun Adults in subjects with a time interval of ≥4.5 years since the last tick-borne encephalitis (TBE) vaccination. In: 10th International Jena symposium on tick-borne diseases. 2009.

[5] Heinz FX, Holzmann H, Essl A, Kundi M. Field effectiveness of vaccination against tick-borne encephalitis. Vaccine 2007;25(October (43)):7559–67.

[6] Weinberger B, Keller M, Fischer KH, Stiasny K, Neuner C, Heinz FX, et al. Decreased antibody titers and booster responses in tick-borne encephalitis vaccines aged 50–90 years. Vaccine 2010;28(April (20)):3511–5.

[7] Hainz U, Jenewein B, Asch E, Pfeiffer KP, Berger P, Grubeck-Loebenstein B. Insufficient protection for healthy elderly adults by tetanus and TBE vaccines. Vaccine 2005;23(May (25)):3232–5.

[8] Rendi-Wagner P, Zent O, Jilg W, Plentz A, Beran J, Kollaritsch H. Persistence of antibodies after vaccination against tick-borne encephalitis. Int J Med Microbiol 2006;296(Suppl. 40):202–7.

[9] Jílková E, Vejvalková P, Stiborová I, Skorkovský J, Král V. Serological response to tick-borne encephalitis (TBE) vaccination in the elderly—results from an observational study. Expert Opin Biol Ther 2009;(7):797–803.

[10] Bröker M, Schöndorf I. Are tick-borne encephalitis vaccines interchangeable? Expert Rev Vaccines 2006;5(August (4)):461–6.