

Tick-borne encephalitis (TBE) vaccination: Applying the most suitable vaccination schedule

I. Schöndorf^{a,*}, J. Beran^b, D. Cizkova^b, V. Lesna^b, A. Banzhoff^a, O. Zent^a

^a Novartis Vaccines and Diagnostics GmbH & Co. KG, Clinical Research & Medical Affairs, Emil-von-Behring-Str. 76, 35041 Marburg, Germany

^b Vaccination and Travel Medicine Centre, Poliklinika II., Bratři Stefanu 895, 50003 Hradec Kralove, Czech Republic

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Abstract

Tick-borne encephalitis (TBE) is caused by an arthropod-borne virus, belonging to the family of Flaviviridae. In case of disease, which can lead to neurological sequelae or even fatal outcomes, only symptomatic treatment is available. TBE can be prevented by vaccination. Various primary immunization schedules have been developed. To identify the most suitable schedule, the present randomised, controlled study was designed to provide data on the immune response elicited by four different immunization schedules obtained by ELISA and by neutralization test (NT). A total of 398 healthy subjects aged ≥ 12 years were randomised to vaccination according to either the rapid schedule (Group R, vaccination on days 0, 7 and 21), the conventional schedule (Group C, vaccination on days 0, 28 and 300), the modified conventional schedule (Group M, vaccination on days 0, 21 and 300) or the accelerated conventional schedule (Group A, vaccination on days 0, 14 and 300). Within 3 weeks (i.e. by day 21) antibody levels were higher in Group R and Group A than in Group M and Group C. Group R and Group C both had higher titres on days 42, 180 and 300, than Group A and Group M. The rapid schedule thus combines the advantages of fast protection and of high titres over the observation period of 300 days.

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1. Introduction

Tick-borne encephalitis (TBE) is endemic in a broad region ranging from Alsace-Lorraine and Scandinavia to north-eastern regions of China and North Japan. In case of TBE disease, only symptomatic treatment is available. Affections of the central nervous system include meningitis, meningoencephalitis and myelomeningoencephalitis, which may result in death or long-term neurological sequelae.

Vaccination is the most effective means of preventing TBE and its unfavourable outcome [1]. Vaccines against TBE have been used for decades, showing a favourable safety profile and high immunogenicity. However, there is debate as to what constitutes the most suitable vaccination schedule. Demands made on a TBE vaccine are high: not only

should it be safe and induce high titres of protective antibodies but also – at least under certain circumstances – provide protection within a short timeframe [2,3]. The two classical examples for the need for fast protection are people travelling from non-endemic to TBE-endemic areas, and inhabitants of endemic areas during the tick-season. A fourth requirement for TBE vaccine is lasting protection where risk of infection persists, as in people living in, or often visiting, endemic areas.

For TBE vaccination, various schedules have been proposed. The “classical” one is the conventional schedule, in which the first two doses are given 1–3 months apart, and the third dose 9–12 months later [4]. A rapid schedule has been approved for one TBE vaccine, which was developed along the lines of the schedule for other vaccines [5]. Other proposed schedules are similar to the conventional schedule, but with a shorter interval between the first two doses, reduced from 4 weeks to 3 or even 2 weeks.

* Corresponding author. Tel.: +49 6421 39 6831; fax: +49 6421 39 4667.
E-mail address: ines.schoendorf@chiron.com (I. Schöndorf).

The present study provides comparable immunogenicity data from four different immunization schedules in a mixed adult and adolescent population.

2. Material and methods

2.1. Design

The study was designed as a controlled, randomised, open, single-centre study involving a planned 400 subjects. The day of first immunization is designated day 0. Blood samples for immunogenicity analysis were taken on day 0, and days 21, 42, 180 and 300. An additional blood sample was obtained on day 321 from all subjects vaccinated on day 300 (i.e. only subjects of Group R were excluded). The study was conducted in accordance with Good Clinical Practice (ICH-GCP), the Declaration of Helsinki, and local rules and regulations of the country. Approval by the appropriate local Ethics Committee was obtained before starting the study.

2.2. Vaccine and vaccination schedules

Subjects were randomised in a 1:1:2:2 ratio in one of the following four groups:

- Group R: Primary immunization with the rapid schedule (RS) with vaccination on days 0, 7 and 21;
- Group C: Primary immunization with the conventional schedule (CS) with vaccination on days 0, 28 and 300;
- Group M: Primary immunization with the modified conventional schedule (MCS) with vaccination on days 0, 21 and 300;
- Group A: Primary immunization with the accelerated conventional schedule (ACS) with vaccination on days 0, 14 and 300.

All subjects received a single dose of *Encepur*TM adults i.m. on each vaccination day in accordance with the respective vaccination schedule. Each 0.5 mL dose of vaccine contained 1.5 µg of antigen (formalin-inactivated TBE virus strain K23) adjuvanted with 1.0 mg aluminium hydroxide, and sucrose (25 mg) as stabilizer. The vaccine is manufactured by Novartis Vaccines and Diagnostics GmbH & Co. KG; Marburg, Germany.

2.3. Study population

Healthy adults and adolescents of both sexes aged ≥ 12 years were enrolled in the study. Subjects were to be excluded if they had a known allergy to any component of the vaccine, had any severe chronic or acute disease or any other condition that might interfere with the evaluation of immunogenicity. In addition, subjects with known previous TBE infection, TBE or Yellow Fever vaccination were not enrolled into the study. All subjects or their legal representatives gave their written informed consent before participation.

2.4. Antibody assays

Serum samples were taken on day 0, prior to the first vaccination, and on days 21, 42, 180 and 300. With the exception of the subjects vaccinated in accordance with the rapid schedule, a sixth sample was obtained on day 321, i.e. 3 weeks after the third dose of the CS, MCS and ACS schedules. Antibody titres against the TBE virus were determined by the neutralization test (NT) as described elsewhere [6,7]. In brief, the NT titre is defined as the reciprocal dilution of sera, leading to complete protection of at least 50% of the cell cultures. Seropositivity was defined as a titre ≥ 2 , a stronger immune response was defined as a titre ≥ 10 . In addition, IgG antibody titres against the TBE virus were determined by a commercially available ELISA (*Enzygnost*TM, Dade Behring, Marburg, Germany) in accordance with the manufacturer's recommendations.

2.5. Safety

After each dose of vaccine all vaccinees were observed for 30 min for immediate postimmunization reactions. Solicited local and systemic reactions, adverse events and body temperature were recorded for 4 days after each vaccination. Adverse events leading to a visit to a physician, and all serious adverse events were documented throughout the study.

3. Results

A total of 398 subjects were enrolled, with 66, 66, 133 and 133 receiving vaccination in accordance with the rapid, conventional, modified conventional and accelerated conven-

Table 1
Demographic characteristics of the study groups, enrolled population

	Group R (rapid schedule)	Group C (conventional schedule)	Group M (modified conventional schedule)	Group A (accelerated conventional schedule)
Number of subjects	N=66	N=66	N=133	N=133
Age [years]: mean (range)	32.8 (13–61)	32.5 (12–61)	32.8 (12–64)	31.9 (12–64)
Sex: male [%]	45	38	46	46
Race: Caucasian [%]	100	100	100	100
Weight [kg]: mean	70.7	67.9	71.7	71.7
Height [cm]: mean	171.9	170.2	171.7	171.7

tional schedule, respectively. A total of 42 subjects were excluded from the immunogenicity analysis because of protocol violations, mainly failure to attend at the specified times for vaccination or blood sampling ($N=17$), being seropositive on day 0 ($N=13$), or lost to follow-up ($N=10$) resulting in a per protocol population of 356 subjects. All subjects for whom safety data were available were included in the safety analysis.

3.1. Demographics

The subjects of the four study groups were similar in terms of age, sex, race, weight and height (Table 1).

3.2. Immunogenicity

3.2.1. Neutralization test results

Seroconversion by day 21, defined as $NT \geq 2$, was achieved in 95% and 99% of the subjects in Group R and Group A, respectively, compared with 76% and 83% in Group C and Group M, respectively. With the exception of two subjects in Group M, all subjects had seroconverted by day 42 (Fig. 1). A stronger immune response, defined as $NT \geq 10$ was achieved by 56%, 29%, 28% and 53% of subjects by day 21 in Group R, Group C, Group M and Group A, respectively. By day 42, most of the subjects in Group R and Group C had achieved this threshold (92% and 95%, respectively), compared with 82% and 79% in Group M and Group A, respectively. On day 300, 74% and 71% of the subjects in Group R and Group C, respectively, still showed an $NT \geq 10$, while this was the case in only 60% and 59% of the subjects in Group M and Group A, respectively (Fig. 2).

The geometric mean titres (GMTs, Fig. 3) on day 21 were highest in Group R and Group A, with GMT-NT of 13 (95% confidence interval (CI): 9.71–16) and 12 (95% CI:

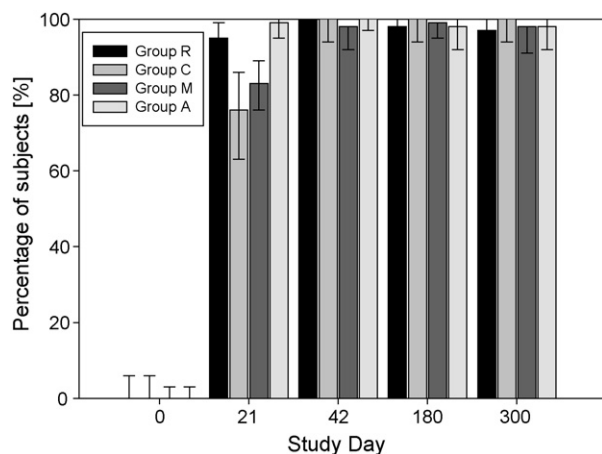


Fig. 1. Percentage of subjects with antibody titres determined by neutralization test ≥ 2 , Group R (vaccination on days 0, 7 and 21), Group C (vaccination on days 0, 28 and 300), Group M (vaccination on days 0, 21 and 300), Group A (vaccination on days 0, 14 and 300), lines indicating 95% confidence intervals, per protocol population.

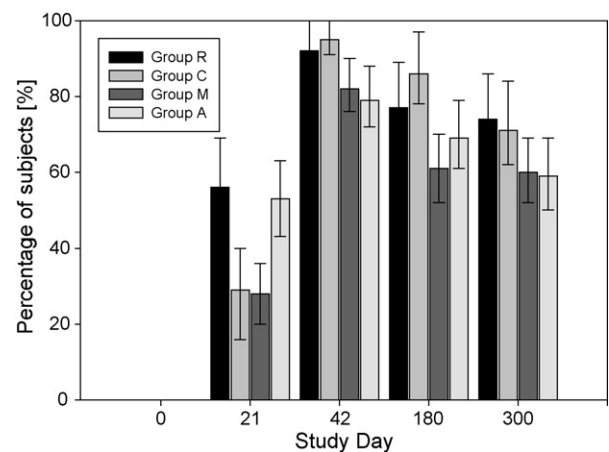


Fig. 2. Percentage of subjects with antibody titres as determined by neutralization test ≥ 10 , Group R (vaccination on days 0, 7 and 21), Group C (vaccination on days 0, 28 and 300), Group M (vaccination on days 0, 21 and 300), Group A (vaccination on days 0, 14 and 300), lines indicating 95% confidence intervals, per protocol population.

9.72–14), respectively. In comparison, GMT-NTs for Group C and Group M were 4.58 (95% CI: 3.52–5.96) and 4.79 (95% CI: 4.0–5.74), respectively. Thus, there was no 95% CI overlap of the GMT-NT in Group R and Group A in comparison with Group C and Group M. The differences between Group R and Group A to both Group M and Group C were highly significant ($p < 0.001$).

On day 42, the highest GMT was seen in Group C (GMT-NT 66, 95% CI: 50–87), followed by Group R (GMT-NT 44, 95% CI: 34–58). While the differences between Group C and both Group A and Group M was highly significant ($p < 0.001$), the difference to Group R was less significant ($p = 0.39$). The GMT-NT of Group R was significantly higher than those of Group M ($p = 0.009$) and Group A ($p < 0.001$). A

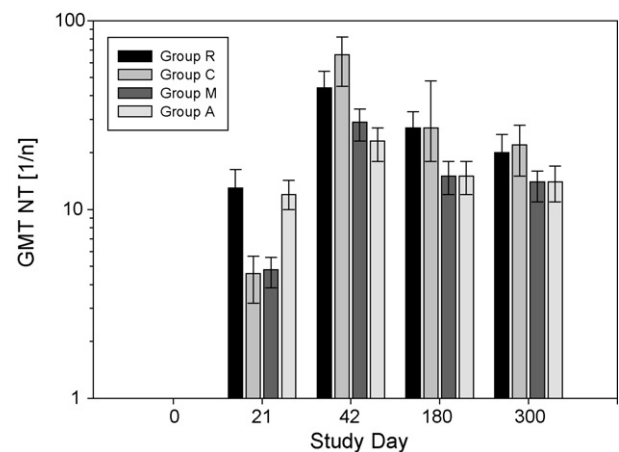


Fig. 3. Geometric mean antibody titres as determined by the neutralization test (GMT-NT) after vaccination in accordance with one of four different immunization schedules: Group R (vaccination on days 0, 7 and 21), Group C (vaccination on days 0, 28 and 300), Group M (vaccination on days 0, 21 and 300), Group A (vaccination on days 0, 14 and 300), lines indicating 95% confidence intervals, per protocol population.

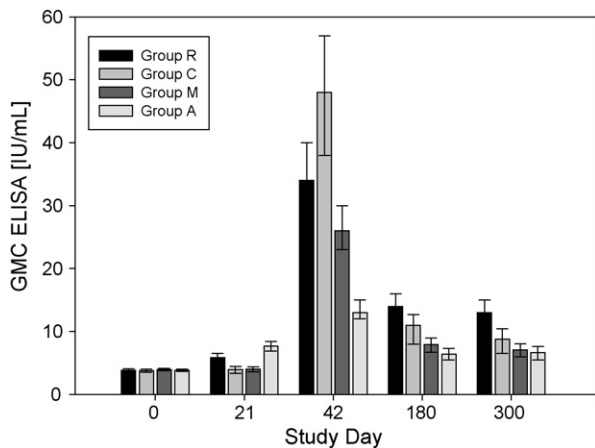


Fig. 4. Geometric mean antibody concentration as determined by ELISA (GMC-ELISA) after vaccination in accordance with one of four different immunization schedules: Group R (vaccination on days 0, 7 and 21), Group C (vaccination on days 0, 28 and 300), Group M (vaccination on days 0, 21 and 300), Group A (vaccination on days 0, 14 and 300), lines indicating 95% confidence intervals, per protocol population. (For day 0, ELISA was set to half of the detection limit, which is specific for each plate of the ELISA assay, which explains the slight differences in the values for day 0.)

similar picture was seen on day 180, with highly significantly higher GMT-NTs in both Group R and Group C compared to Group M and Group A ($p < 0.001$). No difference was seen between Group R and Group C, and between Group M and Group A.

On days 42, 180 and 300, the GMT-NT of Group M and Group A were below those of Group C and Group R (Fig. 3). There was no 95% CI overlap for of the GMTs in Group C and Group R with that of Group M and Group A on either day 42 or day 180. No difference was seen in the GMTs on day 321, 21 days after the third dose in Group C, Group M and Group A. From day 300 to day 321 GMT-NTs increased about 40-fold.

3.2.2. ELISA results

On day 21, the highest geometric mean concentrations (GMC) as determined by ELISA were achieved after immunization in accordance with the rapid and accelerated conventional schedules vis-à-vis the conventional and modified conventional schedules. The 95% confidence intervals (CIs) for the first two schedules did not overlap with the latter two. The differences between Group R and Group A compared to Group M and Group C were highly significant ($p < 0.001$). With a GMC of 7.69 IU/mL, titres were higher in Group A compared to Group R (GMC 5.83 IU/mL). Between day 42 and day 300, the highest geometric mean concentrations were calculated for Group R and Group C (Fig. 4). There was no overlapping of the 95% CI for the GMC-ELISA values of Group R and Group C versus Group A and Group M up to day 180. On day 300, GMC were highly significantly higher in Group R versus Group A and Group M ($p < 0.001$, both), and significantly higher compared to Group C ($p = 0.005$).

3.2.3. Safety results

No differences in local and systemic reactions were observed among the study groups. The safety results were similar to those previously described for this type of vaccine [8]. The rate of at least moderate local and systemic reactions across all study groups was highest for local pain (9%, 5%, 6%, after the first, second and third dose, respectively), followed by myalgia (4%, <1%, 2%, after the first, second and third dose, respectively), and headache (2%, <1%, <1%, after the first, second and third dose, respectively). Fever, defined as temperature $\geq 38^\circ\text{C}$ (oral measurement), was seen in 0.25%, 0.25% and 0.5% of the subjects after the first, second and third dose, respectively.

4. Discussion

Various different schedules have been proposed for vaccination against TBE, of which the conventional schedule with three vaccinations given 1–3 and 9–12 months apart is regarded as the first choice. The rapid schedule was developed for the TBE vaccine *Encepur*TM to meet the need for urgent protection. It was developed along the lines of well-established schedules for other vaccines, for example for pre-exposure rabies vaccination (vaccination on days 0, 7 and 28) [9], or Japanese encephalitis [10].

A number of studies have been published, each applying only one schedule: either the conventional schedule with vaccination on days 0, 28 and at 9–12 months, or the rapid schedule with vaccination on days 0, 7 and 21. These studies focused on dose-finding in children [11] and adults [12,13], persistence of antibodies [14,15], or efficacy [16]. After the third dose, almost all subjects had seroconverted, irrespectively of the schedule used. With the conventional schedule, 100% and 97% of the subjects receiving the full adult dose seroconverted as determined by ELISA after two doses by day 42 [17]. The rapid immunization schedule leads to seroconversion in 90% of subjects as early as day 21. By day 35, all the subjects had seroconverted, as measured by ELISA [17,18]. Only limited data are available on further schedules. To our knowledge, only a single study investigating the immune response elicited by an accelerated conventional schedule has been published. With this schedule, the time interval between the first two doses was reduced from 28 to 10–13 days [19]. On study days 17–20, 28.6% of the subjects had seroconverted (ELISA). This percentage had increased to 92.9% 14 days after the second dose (i.e. study days 24–27).

Immunogenicity results across these studies are, however, difficult to compare, since the results were generated in different populations. In addition, titres against TBE virus were determined by different laboratories using different assays. To our knowledge, only one study directly comparing two different immunization schedules has so far been published. In that study, the immune response to the rapid immunization schedule (vaccination on days 0, 7 and 21) was compared with that of the conventional schedule (vaccination on days

0, 28, 300) [17]. After immunization with the rapid schedule, antibodies as measured by both ELISA and neutralization test increased earlier, were higher on day 28 and remained at a higher level throughout the 10-month observation period.

The present study focuses on the immune response elicited during the first year of primary immunization. Any differences in and the strengths of the fast-protection schedules should become obvious within this time frame, since the study evaluates not only the response within the first weeks, but also the persistence of antibodies throughout the year. This is important, as exposure to the virus often extends over the entire tick-season. The following discussion therefore emphasizes early immune response (day 21), first peak antibody levels (day 42), and persistence of antibodies (day 300).

As pointed out above, the main objective of the study was to compare immunogenicity after different primary immunization schedules. To ensure that schedule-specific differences between the groups were maintained, while avoiding variance due to protocol violations of blood-sampling dates, all subjects violating time windows, who were seropositive at day 0 or who were lost to follow-up were excluded from the immunogenicity analysis.

4.1. Early immune response: day 21

With the rapid schedule for *Encepur*TM, all three primary immunization doses are given within 3 weeks. It has been shown that after TBE vaccination in accordance with the rapid schedule, 100% and 90% of the subjects (as determined by NT and ELISA, respectively) had seroconverted already by day 21 [17]. For the accelerated conventional schedule, seroconversion rates of 96.4% and 28.6% as measured by NT and ELISA, respectively, on days 17–20 (i.e. 7 days after the second vaccination) have recently been reported [19]. On day 28, 92.9% of subjects were seropositive as determined by ELISA. In view of differences in populations, vaccines and laboratory assays, a true comparison of the data reported in different studies is not possible.

In the present study, both the rapid (Group R) and the accelerated conventional schedule (Group A) led to seroconversion, as determined by NT, already by day 21 in most subjects. Over half of the subjects in these groups even showed a strong immune response ($NT \geq 10$). Not surprisingly, up to day 42, the antibody levels as determined by NT and ELISA increased much more strongly in Group R than in Group A, since subjects in Group R received a third dose of the vaccine on day 21.

In Group C and Group M, 24% and 17% of subjects, respectively, had not seroconverted by day 21, and fewer than 30% showed a strong immune response ($NT \geq 10$) on that day. This can easily be explained by the fact that these subjects had received only one dose of the vaccine by that time. These last two schedules may thus not seem suitable to provide rapid protection within 3 weeks, and are therefore not appropriate for travellers about to leave for endemic

regions, or as primary immunization during tick-season in such regions.

4.2. Antibody levels: day 42

For the evaluation of the strength of the immune response, both GMT-NT and GMC-ELISA are more suitable parameters than the percentage of seropositive subjects (whether by ELISA or NT) for revealing group differences in the strength of the immune response in terms of peak titres. Few data are available on the timing of peak titre after TBE vaccination. In a study applying the accelerated conventional schedule with an interval of 10–13 days between the first two doses, antibody levels had already declined by about 40% and 30% as measured by NT and ELISA, respectively, between day 33 (21 days after the second dose) and day 56 (42 days after the second dose) [19]. In the rapid immunization schedule, titres determined by NT declined between day 42 and day 56, but only marginally [20].

In the present study, the highest titres were measured on day 42 in all groups, thus emphasizing the importance of the results obtained on this day. With reference to the groups receiving only two vaccinations by day 42, the results of the study underscore the importance of longer time intervals between the first two doses, since both GMC-ELISA and GMT-NT were higher, the longer the interval between the first and second dose. The exception to this rule is the rapid immunization schedule, in which the subjects had already received all three doses of the primary immunization schedule (by day 42). For subjects in Group R, both GMC-ELISA and GMT-NT were clearly above those in Group M and Group A, with no overlapping of the 95% CIs. A comparison of Group R and Group C showed that higher antibody levels were achieved with the conventional schedule, but that the 95% CIs widely overlapped.

Both the rapid immunization schedule and the conventional schedule led to higher antibody titres (GMT-NT) and concentrations (GMC-ELISA), and may therefore be recommended over other schedules.

4.3. Persistence of antibodies: day 300

While a fast immune response is most important for travellers leaving at short notice, persistence of antibodies is critical for subjects exposed to the virus throughout the entire tick-season. Importance therefore also attaches to the persistence of antibodies during the first year. This period is of special interest, since the immune response has not yet been boosted. It is known that the first booster increases the NT by about 40-fold [20].

In the present study, in all three schedules, 97–100% of subjects were still positive, as determined by NT, up to day 300. Using the more stringent criterion of $NT \geq 10$, differences between the schedules become more obvious. The highest percentage was achieved in Group R (74%), followed by Group C (71%). In Group R and Group C, higher mean

antibody levels were maintained up to day 300 than in Group M and Group A. The highest GMT-NT and GMC-ELISA levels were maintained up to day 300 after vaccination with the rapid immunization schedule, as has been described earlier [17]. If higher antibody titres are required during the first year after initiation of primary immunization, both the rapid and conventional schedules are superior to the other two schedules.

In conclusion, this study for the first time compares four different vaccination schedules for primary immunization against TBE. The conventional schedule (vaccination on days 0, 28 and 300) achieves the highest titres on day 42. The rapid immunization schedule with vaccination on days 0, 7 and 21 provides fast protection, as with the accelerated conventional schedule, it provides high antibody titres and concentrations on day 42 that are almost as high as with the conventional schedule, and the highest level of antibodies, similar to the conventional schedule (both as determined by NT and ELISA) is maintained throughout the first 300 days of follow-up.

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