EFFECTIVENESS OF PRIMARY VACCINATION AGAINST TICK-BORNE ENCEPHALITIS IN EMPLOYEES OF THE ARMED FORCES

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SUMMARY

Objective: The aim of our study is to evaluate immune response after receiving the primary vaccination against tick-borne encephalitis (TBE), and to establish a link between seropositivity and selected factors in soldiers.

Methods: Blood samples, questionnaires and vaccination records were obtained. TBE antibodies were detected using both ELISA and a neutralization test (NT). We used logistic regression for statistical analysis.

Results: Overall, seropositivity (presence of IgG) was detected in 88% of participants. The proportion of seropositive subjects in relation to the number of doses of vaccine was 69% (2 doses) and 91% (3 doses). A statistically significant relationship was found between seropositivity and the number of vaccine doses. No statistical significance was identified in relation to age and sex. There was no statistical significance of seropositivity, depending on the time of the last dose of the vaccine.

Conclusions: TBE immunisation should be targeted at individuals in the most affected locations and those at highest risk of exposure according to lifestyle and occupation.

Key words: tick-borne encephalitis, vaccination, immune response, soldiers

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INTRODUCTION

Over the past decades, tick-borne encephalitis (TBE) has become a growing public health problem, as the number of risk areas and reported cases across Europe, Russia and parts of Asia continues to increase (1, 2).

Because there is no specific antiviral agent available for treating TBE and treatment is based solely on symptomatic measures, prevention of the disease via vaccination is the best strategy (3–5).

Active immunisation remains the most effective protective measure against TBE for people living in risk zones, those exposed at work and travelers to endemic areas (6, 7).

Two TBE vaccines – FSME-IMMUN® (Pfizer, Austria) and Encepur® (GSK Vaccines GmbH, Germany) – are registered in Europe (2, 3, 8–12).

In Slovakia, FSME-IMMUN® vaccines for immunisation of adults and children are available on the market. FSME-IMMUN®, which is based on the Neudoerfl strain, has been approved for the vaccination of risk groups since 1976 (6). Based on the manufacturer's recommendations, the conventional schedule for primary vaccination course consists of 3 doses of the vaccine administered intramuscularly (0.5 mL for adults and 0.25 mL for children aged 1–15 years) at 0, 1–3 and 5–12 months (6, 11). Immunity is maintained with booster doses: the first booster dose is administered 3 years after completion of the primary vaccination, then later on one dose is needed every 5 years (3-year interval for individuals aged > 60 years) (3, 13). Accelerated schedules can be implemented in emergency situations (vaccination on days 0 and 14, followed by a third dose 5–12 months following the second) (6).

Heinz et al. calculated that the field effectiveness for regularly vaccinated subjects is ≈99% under best-case assumptions and 96% under worst-case assumptions (9).

The World Health Organization (WHO) and the European Centre for Disease Prevention and Control (ECDC) recommend TBE vaccination for whole populations in highly endemic areas (> 5 cases/100,000/year) and vaccination of risk groups in low to moderate endemic areas (< 5 cases/100,000/year) (13, 14).

In Slovakia, TBE vaccination is voluntary. According to Section 8 of Decree No. 585/2008 Coll. of the Ministry of Health of the Slovak Republic on the Prevention and Control of Communicable Diseases, vaccination is compulsory for virology laboratory employees who work with tick-borne encephalitis virus (TBEV). Based on the Section 10 of this regulation vaccination is recommended for subjects who are professionally exposed to an increased risk of selected diseases (i.e. forest workers, agricultural workers, police officers and customs officers, soldiers, etc.) (15).

The aim of our study is to evaluate immune response after receiving primary TBE-vaccination in soldiers of the Army of the Slovak Republic.

MATERIALS AND METHODS

Blood samples, questionnaires and vaccination records were obtained from all study participants. We have chosen group of professional soldiers because they are classified as a high-risk group to obtain a TBE.

Serum Samples

Blood samples were centrifuged for 10 minutes at 2,500 rpm in order to separate the serum from the clot within 2 h of collection. Serum samples were kept in a freezer at a temperature of −70 °C until analyzed.

Questionnaires

All participants completed a questionnaire on demographic (age, sex, occupation, residence), epidemiological (tick-bites, pet-ownership, time spent in an endemic region, previous travels/mission, outdoor activities) and clinical data (type of TBE vaccine received and number of vaccine doses, vaccination against other flaviviruses, previous tick-borne infections, general health status, chronic illness).

Vaccination Records

We acquired vaccination records of all study participants, including the date of each vaccine dose and time since the last vaccine dose. Only the FSME-IMMUN vaccine had been administered. Written informed consent was obtained from all participants prior to enrollment.

Antibody Assays

TBE antibodies were detected centrally using both ELISA and a neutralization test (NT). Serum samples were analyzed for IgG and IgM antibodies to TBEV using a commercial ELISA (TBE/FSME IgG and IgM – ELISA NovaLisa™, NovaTec, Germany) according to the manufacturer's instructions. Serum IgG levels > 110 NTU/mL are considered positive, 55–110 NTU/mL borderline and <55 NTU/mL negative, while serum IgM levels > 11 NTU/mL are considered positive, 9–11 NTU/mL borderline and < 9 NTU/ml negative. Antibody concentrations in NTU/mL were interpreted according to the manufacturer's instructions. Borderline values were considered negative in the statistical analysis. Antibodies to the TBEV were assayed by a NT. An individual is considered to have seropositive levels if their TBEV antibody titer is ≥ 1 : 10 (10–12, 16, 17).

Statistical Analysis

The data collected using the questionnaire method and laboratory tests were processed with the help of the IBM SPSS 21.0 statistical programme. Demographic data were described using descriptive statistics as medians with standard deviations, medians with interquartile range (IQR) for the serial variables and as percentages for categorical variables. The chi-square test was used for comparison of the difference of seropositivity among selected groups of the set (by gender, age categories, according to doses of administered vaccine against TBE). In the analyses, logistic regression was used to determine the impact between the selected variables. Seropositivity was considered to be a dependent variable. The independent variables were the number of vaccine doses, time since the last dose of the vaccine against TBE, gender and age. This analysis was done by regressing seropositivity separately with each independent variable (crude associations) and thereafter in a multivariable model that includes all variables contributing to the model with statistical significance. The value $p < 0.05$ was considered to be of statistical significance.

Demography

We analyzed serum samples received from 101 individuals. The set of respondents consisted of 88.1% (n = 89) men, mean age of 33.4 (SD 4.9), and 11.9% (n = 12) women, mean age of 33.6 (SD 7.7). The mean age of the soldiers was 33.4 years (SD 5.3); 53 (52.5%) subjects live in cities and 48 (47.5%) live in rural areas.

Table 1. *Characteristics of demography, epidemiology and clinic data in study group (N = 101)*

	n	%
Demography		
Gender		
Men	89	88.1
Women	12	11.9
Residence		
Urban	53	52.5
Rural	48	47.5
Epidemiology		
Tick bite/other insects	84/97	83.2/96.1
Pet owners	63	62.4
Staying abroad	57	56.4
Raw milk consumed	51	50.5
Clinical data		
Flu and fever	84	83.2
Skin illnesses	10	9.9
Rheumatic illnesses	3	3.0
Lyme disease	4	4.0

Epidemiology

A total of 84/97 (83.2%/96.1%) subjects reported being bitten by a tick and other insects; 63 (62.4%) subjects reported ownership of pets/contact with animals; 57 (56.4%) subjects reported staying abroad/in endemic area/mission, and 51 (50.5%) subjects reported consumption of raw milk, 37 of whom consumed cow′s milk, 8 sheep′s milk and 6 goat′s milk. A full 100% of the study participants took part in activities outdoors, whether related to their profession or as part of their leisure activities in nature (e.g., work in the garden, in the field, in the woods, hiking, hunting, fishing, sports, and others) (Table 1).

Clinical Data

Flu and fever illnesses were reported by 84 (83.2%) respondents, skin illnesses by 10 (9.9%) respondents and rheumatic illnesses by 3 (3%) respondents from the entire set. In addition, 4 respondents reported Lyme disease. Vaccination against other flaviviral infections was not found.

Vaccination (vaccination rate) of the respondents against tick-borne encephalitis by 3 or 2 doses was 100% (n = 101). At the time of blood collection 88 (87.1%) subjects had received 3 doses of the vaccine (i.e. primary vaccination), 13 (12.9%) subjects had received 2 doses, and none of the subjects had received only a single dose of the vaccine (Table 1).

***Table 2**. Vaccination of study participants (N = 101)*

Status	Number of women	Number of men	Age, median (IQR)	Months since last vaccination, median (IQR)
2 doses	–	13	36 (24–42)	7 (2–9)
3 doses	12	76	33 (22–49)	8 (0.5–34)
Total	12	89	33 (22–49)	8 (0.5–34)

IQR – interquartile range

RESULTS

Seropositivity

Overall, seropositivity (IgG) was detected in 89 subjects (88.1%). No antibody response (i.e. negative samples) was found in 12 soldiers. Data on the respondents regarding vaccinations are given in Table 2. IgM antibodies were detected in three soldiers, after 8 months, 7 months and 14 days after administration of the third dose of the primary vaccination.

Number of Vaccine Doses and Seropositivity

The proportion of seropositive subjects in terms of the number of doses of the vaccine was as follows: 69.2% (2 doses) and 90.9% (3 doses). None of the subjects received only a single dose of the

***Table 3**. Background characteristics of the sample – gender, age categories, number of doses (N = 101)*

		Total n (%)	Seropositivity n (%)	Seronegativity n (%)	Seropositivity vs. seronegativity p-value
Total number		101 (100.0)	89 (88.1)	12 (11.9)	
Gender	Men	89 (88.1)	78 (87.6)	11 (91.7)	0.69 n.s.
	Women	12 (11.9)	11 (12.4)	1 (8.3)	
Age categories	< 30 years	22 (21.8)	19 (86.4)	3 (13.6)	0.95 n.s.
	30–40 years	69 (68.3)	61 (88.4)	8 (11.6)	
	≥ 41 years	10 (9.9)	9 (90.0)	1 (10.0)	
Number of doses	2 doses	13 (12.9)	9 (69.2)	4 (30.8)	0.02*
	3 doses	88 (87.1)	80 (90.9)	8 (9.1)	

n.s. – non significant, *p < 0.05

***Table 4.** Association between number of doses, time since last dose of vaccine, gender, age and seropositivity; odds ratios (OR) and 95% confidence intervals (CI) in parentheses*

		Model 1		Model 2	
		OR (95% CI)	p-value	OR (95% CI)	p-value
Number of doses	2 (doses)	1 (ref.)		1 (ref.)	
	3 (doses)	4.44 (1.11–17.74)	0.04*	4.80 (1.10–20.91)	0.04*
Time since last dose↑		0.93 (0.70–1.22)	0.58	0.88 (0.64–1.20)	0.41
Gender	Men	1 (ref.)		1 (ref.)	
	Women	1.55 (0.18–13.21)	0.69	0.94 (0.10–8.72)	0.96
Age↑		0.96 (0.85–1.07)	0.44	0.96 (0.85–1.09)	0.55

Model 1: Crude effect of number of doses, time since last vaccine dose, gender, age separately on seropositivity
Model 2: Combined effect of number of doses, time since last vaccine dose, gender and age on seropositivity
Logistic regression, OR: odds ratio, CI 95%: confidence interval, *p < 0.05

vaccine. As the Table 3 shows, the percentage of seronegative subjects after 3 doses of the vaccine is lower compared to seronegative subjects after 2 doses of the vaccine (9.1% vs. 30.8%). Using logistic regression we found a statistically significant relationship between seropositivity and dose of the vaccine in the group of subjects vaccinated (OR = 4.44, 95% CI = 1.11–17.74, p = 0.04). Adding the time since the last dose of the vaccine, gender and age to the model did not affect the strength of the association of seropositivity with the examined factor (OR = 4.8, 95% CI = 1.10–20.91, p = 0.04) (Table 4).

Age, Gender and Seropositivity

The youngest participant in the study was 22 years old and the oldest 49 years old. The studied population was divided into three age groups. Seropositivity was about the same in all age categories: 86.4% in subjects of ≤ 30 years of age, 88.4% in subjects between 30–40 years of age, and 90.0% in subjects of ≥ 41 years of age without statistical significance; however, the level of antibody titer was the highest in the group of subjects age 41 year or older (Fig. 1). Using logistic regression we found no statistically significant relationship between seropositivity and the age and gender of subjects vaccinated (p > 0.05) (Table 4).

Time since the Last Dose of the Vaccine and Seropositivity

There was no statistical significance of seropositivity, depending on the time of the last dose of the vaccine (p > 0.05) (Table 4).

DISCUSSION

According to our knowledge, most studies deal with seropersistence of TBE antibodies after re-vaccination (booster vaccination), unlike this study, the purpose of which was the detection of antibodies after primary vaccination in relation to individual factors.

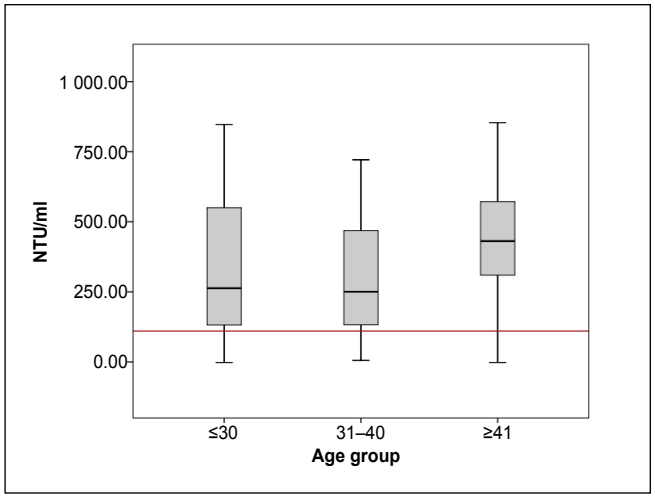

Fig. 1. *Concentration of IgG antibodies against TBEV in relation to age group.*

NTU – NovaTec Units

The authors of previous studies have found that after a one-booster dose circulating antibodies persisted in 96–99% subjects (1, 9, 18). These data cannot be compared to our results, because we only analyzed the presence of antibodies after 2 and 3 doses of primary vaccination. We found that in study participants with the full primary vaccination (3 doses) IgG antibodies were detected in 90.9% of the participants and in 69.2% participants with 2 doses. We did not have blood samples of the same studied population following re-vaccination, but it would be very interesting to compare the seropersistence after the primary vaccination vs. re-vaccination.

In three cases, IgM antibodies were also confirmed. IgM antibodies may persist for many weeks after TBEV infection or after TBE vaccination. Without information on the history of TBE vaccinations, positive serological findings caused by recent vaccination may lead clinicians to suspect TBE even in cases of non-TBEV related CNS manifestations. Therefore, confirmation of the diagnosis of TBE by detection of IgG antibodies is recommended, but it is necessary to monitor increased IgG titers for 1–2 weeks or even longer, which is rarely performed (19).

We studied seropositivity in relation to age. The studied set consisted only of people under 50 years of age, who were divided into three groups (≤ 30 years of age, 30–40 years of age, ≥ 41 years of age). No statistically significant difference was found between the different age groups, since, according to other studies, significantly lower antibody levels were detected not only in patients aged > 60 years but also in the age group between 50 and 60 years of age (19).

The antibody response to TBEV vaccination declines with age, resulting in a significantly higher proportion of individuals over 50 years of age being seronegative after the last vaccine dose. The antibody response to TBEV vaccination appears to decline linearly throughout adult life (10, 11).

No statistical significance of seropositivity in relation to sex (man vs. woman) was found. The reason might be a low number of women (n = 12) in the examination set. Age and number of vaccine doses are the most important factors determining the immunological response to vaccination. Whereas the antibody response to immunization declines linearly during life, to compensate for the declining antibody response to each single dose of vaccine, older individuals needs to take additional vaccine doses in order to reach the same antibody titers as younger individuals (10).

Data on any failures in the field of vaccination are limited. According to published reports, a breakthrough disease after proper basic vaccination and/or timely boosters appears to be rare and tends to occur in higher age groups, but also in children (7, 20).

In Slovakia, according to the Annual Reports of the Public Health Authority for the period 2012–2016, no diseases were reported after vaccination against the TBE (21).

The efficacy of TBE vaccines is determined based on their immunogenicity, as measured by the induction of protective antibodies. Protective antibodies appear after TBE vaccination, and serological tests, such as ELISA, NT or hemagglutination inhibition tests, are used for antibody detection (19).

We used ELISA for the detection of antibodies. The major limitation of the ELISA test is that cross-reacting antibodies in IgG ELISA might be shown in persons who were previously exposed to other flaviviruses through infections or vaccination, potentially leading to false-positive results (19). Our respondents were not vaccinated against diseases caused by flaviviruses.

As this study was carried out on a population of deployable soldiers, exposure to other flaviviruses and vaccination against flaviviruses is high. Therefore, the NT was used, which is the most specific assay for checking immunity against TBEV (1).

CONCLUSION

The increased spreading of TBEV into new regions of Europe and a general increase in TBE cases serve to stress the need for effective prevention strategies. TBE vaccination offers very high protection against TBE.

TBE immunisation should be targeted at individuals in the most affected locations and those at highest risk of exposure in connection with lifestyle and occupation.

The relatively low positivity after a full primary vaccination showed the need for a booster vaccination, particularly in the group of persons at risk, who often carry out various activities in the outdoor environment related to their profession, such as professional soldiers.

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Conflict of Interests

None declared

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