Anti-TBE Virus ELISA 2.0 (IgG)

- **Semiquantitative or quantitative determination of IgG antibodies against TBE virus to aid in the diagnosis of TBE virus infections**
- **Based on native, purified TBE virus antigens**
- **Fully automated processing and evaluation**

Technical data

Antigen	The reagent wells are coated with native, purified TBEV antigens.
Calibration	Quantitative, in relative units per millilitre (RU/ml) Calibration serum 1: 200 RU/ml Calibration serum 2: 50 RU/ml Calibration serum 3: 20 RU/ml Calibration serum 4: 2 RU/ml Recommended upper threshold for non-infected individuals (cut-off): 20 RU/ml
Sample dilution	Serum or plasma, 1:101 in sample buffer
Reagents	Ready for use, with the exception of the wash buffer (10x); colour-coded solutions, in most cases exchangeable with those in other EUROIMMUN ELISA kits
Test procedure	60 min (37 °C) / 30 min / 15 min, room temperature (sample/conjugate/substrate incubation), fully automatable
Measurement	450 nm, reference wavelength between 620 nm and 650 nm
Test kit format	96 break-off wells; kit includes all necessary reagents
Order number	**EI 2661-9601-2 G**

Clinical significance

Tick-borne encephalitis virus (TBEV) has three known subtypes: European (TBEV-Eu), Siberian (TBEV-Sib) and Far Eastern (TBEVFE). TBEV is transmitted via tick bites or, less commonly, by consumption of raw milk and raw milk products of infected goats, sheep and cows. Most TBEV infections in humans are asymptomatic. Symptomatic courses are mono- or biphasic with varying severity depending on the subtype. Biphasic illness begins with unspecific flu-like symptoms. Viraemia occurs in this first phase lasting from day 1 to 8. After an asymptomatic interval of approximately one week, around a third of patients enter the second phase, in which the virus reaches the central nervous system. Typical symptoms include high fever and neurological manifestations such as meningitis, encephalitis and myelitis. The mortality rate is 1 % to 2 % (TBEV-Eu), 6 % to 8 % (TBEV-Sib) and 40 % (TBEV-FE).

Due to the mostly unspecific symptoms of TBE, differential diagnostics is particularly challenging. The diagnostic method of choice is the determination of TBEV-specific IgM and IgG antibodies in serum or CSF using ELISA. Specific antibodies in serum or CSF can usually be measured in the second phase of the disease. IgM is detectable for 6 to 7 weeks or longer. IgG persists lifelong and protects against reinfection with TBEV. TBEV infection is diagnosed based on simultaneous detection of TBEV-specific IgM and IgG or based on a significant increase in the IgG concentration between two samples collected 2 to 4 weeks apart. The sole detection of IgM is not sufficient. In cases with CNS involvement, determination of specific, intrathecally produced IgM and IgG antibodies in the CSF is indicated. Cross reactivity of anti-TBEV antibodies (especially IgG) with other flaviviruses (yellow fever, dengue, Japanese encephalitis and West Nile virus, including following vaccination) must be taken into account.

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Prevalences

The levels of anti-TBEV antibodies were determined with the ELISA in a panel of healthy blood donors (n = 500, origin: Schleswig-Holstein, Germany, 2022). With a cut-off value of 20 RU/ml, 23.6 % of the blood donors were anti-TBEV positive (IgG). This result is within the expected range of prevalence for this region in Germany. In a panel of apparently healthy blood donors from 2012 (n = 500, origin: Schleswig-Holstein, Germany), the positive rate was still 14.8 %. This development is consistent with the expected increase in the prevalence of anti-TBEV IgG antibodies in the German population.

Cross-reactivity (analytical specificity)

To investigate the cross-reactivity of the test system, samples positive for IgG antibodies against dengue, yellow fever, hepatitis C, Japanese encephalitis, West Nile or Zika virus were analysed using the Anti-TBE Virus ELISA 2.0 (IgG). It was shown that cross-reactions with antibodies against yellow fever and hepatitis C virus are unlikely, whereas cross-reactions with antibodies against dengue, Japanese encephalitis, West Nile and Zika virus are likely. It should be noted that double infections may occur, particularly in endemic areas, or that infection with another flavivirus may have occurred at an earlier time. In these cases, positive findings do not result from a cross-reaction of the respective antibodies.

Antibodies against	n	Positive rate in % in the Anti-TBE Virus ELISA 2.0) (IgG)
Dengue virus (DENV)	27	85,2
Yellow fever virus (YFV)	12	0,0
Hepatitis C virus (HCV)	6	0,0
Japanese encephalitis virus (JEV)	12	58,3
West Nile virus (WNV)	30	50,0
Zika virus (ZIKV)	22	86,4

Method comparison

28 precharacterised patient samples and 92 samples from healthy blood donors (origin: Europe) were investigated using EUROIMMUN's Anti-TBE Virus ELISA 2.0 (IgG) and a commercial ELISA from another manufacturer as reference. The positive agreement was 100 % (95 % CI: 91.4 – 100) and the negative agreement 94.4 % (95% CI: 86.4 – 98.5) with a mean concordance of 96.5 %. Borderline results were not included in the calculation.

n = 120		Other commercial ELISA		
		positive	borderl.	negative
Anti-TBE Virus ELISA 2.0 (IgG), EUROIMMUN	positive	41	7	4
	borderline	0	0	0
	negative	0	0	68

Clinical performance

In total, 271 samples were analysed with the Anti-TBE Virus ELISA 2.0 (IgG). The sensitivity was determined by analysing samples from patients with acute or past TBEV infection and from TBEV-vaccinated individuals. The specificity was determined by analysing samples from healthy blood donors in addition to samples from patients with other diseases relevant for differential diagnostics such as anaplasmosis, herpes simplex virus infections and SARS-CoV-2 infections.

n = 271		Clinical characterisation	
		positive	negative
Anti-TBE Virus ELISA 2.0 (IgG), EUROIMMUN	positive	144	5
	borderline	1	0
	negative	0	121

Without borderline results, the following performance parameters were obtained (see table).

Evaluation	n = 270	
	Value in %	95 % CI
Specificity	96.0	91.0 – 98.7
Sensitivity	100.0	97.5 – 100.0

Positive likelihood ratio: >10, negative likelihood ratio: <0.1

Literature

1. Robert-Koch Institute. **RKI-Ratgeber Frühsommer-Meningoenzephalitis (FSME) und verwandte Virusenzephalitiden (TBE, tick-borne encephalitis).** Epidemiological Bulletin 16:3-8 (2022) [in German].
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