

## ZünIK – Surveillance of Tick-Borne Neurological Infectious Diseases (TBE and Lyme Neuroborreliosis) in Children and Adolescents < 16 Years of Age in Germany and Switzerland

### Objectives and Research Questions

#### Aims

Comparative descriptive analysis of the differences and similarities in epidemiological, clinical, preventive (vaccination-related), and outcome-related characteristics among hospitalized children and adolescents under 16 years of age with confirmed or suspected tick-borne encephalitis (TBE) or Lyme neuroborreliosis (LNB) in Germany and Switzerland.

#### Project endpoints

Calculation of the incidence of confirmed or suspected LNB and TBE cases among hospitalized children and adolescents under 16 years of age in Germany and Switzerland, based on standardized and anonymized surveillance data collected during inpatient hospital stays. In addition, a comparative descriptive analysis will be conducted to identify differences and similarities with regard to clinical characteristics (diagnostics, treatment, and management), preventive measures (vaccination), and outcome-related characteristics.

### Study team

#### Project Initiator and Principal Investigator for Switzerland

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**Background:** Lyme borreliosis (LB) and tick-borne encephalitis (TBE) are the most reported tick-borne diseases in Germany and Switzerland. Due to climate change, both the epidemiology and the clinical manifestations of tick-borne diseases may change over time.

### Case definitions:

#### Tick-Borne Encephalitis (TBE)

At least one of the following clinical criteria and one of the following laboratory criteria must be fulfilled.

Clinical criteria: meningitis, encephalitis, meningoencephalitis, encephalomyelitis, or encephaloradiculitis. Laboratory criteria: detection of TBE-specific IgG and IgM antibodies in serum; detection of TBE-specific IgM antibodies in cerebrospinal fluid (CSF); seroconversion of TBE-specific antibodies in paired serum samples; detection of TBE virus nucleic acid in a laboratory specimen; isolation of TBE virus from a laboratory specimen; or detection of IgM antibodies in a single serum sample.

### LNB – Lyme Neuroborreliosis

#### Clinical criteria

Neurological symptoms without an alternative etiology, consistent with: meningitis; cranial nerve palsies; meningoradiculoneuritis (Bannwarth syndrome); myelitis; encephalomyelitis; acute hemiparesis; opsoclonus-mycoclonus syndrome; ataxia; or late neuroborreliosis (encephalomyelitis).

#### Laboratory criteria\*

Cerebrospinal fluid (CSF) pleocytosis **and** one of the following:

- demonstration of intrathecal production of *Borrelia burgdorferi* antibodies OR
- isolation of *Borrelia burgdorferi* sensu lato from CSF by culture OR
- detection of *Borrelia burgdorferi* nucleic acid in CSF by polymerase chain reaction (PCR).
- Detection of IgG antibodies against *Borrelia burgdorferi* in blood (applicable only to children under 18 years of age with facial nerve palsy or other cranial neuritis and a recent history of erythema migrans within the preceding two months).

#### Laboratory definitions:

\*Corresponds to the ECDC criteria for a confirmed case. (B.b. = *Borrelia burgdorferi*).

Pleocytosis is defined as  $> 5 \times 10^6$  cells/ $\mu$ L.

**Intrathecal *B. burgdorferi* antibody production:** a positive CSF-to-serum index (antibody index [AI]) for *B. burgdorferi*-specific IgG or IgM antibodies. An AI value exceeding a predefined cut-off (typically  $> 1.5$  or  $> 2.0$ , depending on the assay used) indicates that the concentration of *Borrelia*-specific IgG or IgM antibodies in the cerebrospinal fluid is higher than can be explained solely by blood-CSF barrier dysfunction (passive transfer from the blood).

**Positive *B. burgdorferi* IgM/IgG antibodies (immunoblot/Western blot):** an immunoblot is generally considered positive when a predefined number of specific bands, according to the laboratory methodology, are detected. These may include bands such as VlsE, flagellin p41, and OspC (early immune response), as well as p83, p39 (BmpA), p30, DbpA, and p14 (late immune response).

**CXCL13 in cerebrospinal fluid (CSF)** may be used as a supportive biomarker, particularly during the early phase of Lyme borreliosis; however, it is not an official ECDC laboratory criterion.

### Logistics:

This is an observational, multicenter, binational surveillance study involving the reporting of all children and adolescents under 16 years of age who are hospitalized with confirmed or suspected (according to the case definitions) tick-borne encephalitis (TBE) or Lyme neuroborreliosis (LNB) in a hospital participating in ESPED (Germany) or in a clinic/hospital participating in the Swiss Paediatric Surveillance Unit (SPSU) (Switzerland). In Switzerland, outpatient cases of LNB will also be reported. Data collection will be conducted anonymously using standardized electronic case report forms (REDCap), which are provided and managed by ESPED. In Switzerland, both disease entities are investigated through the SPSU in collaboration with the Swiss Federal Office of Public Health. The anonymized data collected in Switzerland are identical to those collected in Germany, enabling a comparative analysis at the conclusion of the surveillance period. The study is purely observational; no study-related diagnostic or therapeutic interventions will be performed. Data collection is fully anonymized. Participation in the study does not entail any additional risks or burdens for patients. In addition, a capture-recapture analysis in collaboration with the Robert Koch Institute (RKI) is planned. Furthermore, a comparison with data from the InEK Data Browser is envisaged.

### Literature:

1. RKI. Inzidenz der FSME in Kreisen und Kreisregionen, Anlage zum Epid Bull 9/2025. Available at: <https://www.rki.de/DE/Themen/Infektionskrankheiten/Infektionskrankheiten-A-Z/FSME/fsme-node.html>.
2. Danielova V, Kliegrova S, Daniel M, Benes C. Influence of climate warming on tickborne encephalitis expansion to higher altitudes over the last decade (1997-2006) in the Highland Region (Czech Republic). *Cent Eur J Public Health*. 2008;16(1):4-11.
3. Lukan M, Bullova E, Petko B. Climate warming and tick-borne encephalitis, Slovakia. *Emerg Infect Dis*. 2010;16(3):524-6.