Chapter 8

TBE in children

Malin Veje, Zane Freimane, Dace Zavadska

Key points

- TBE follows a similar clinical course in children and adults, manifesting mainly as meningitis. However, a broader clinical picture is seen in children, especially in preschool age.
- Laboratory evaluation may show elevated blood inflammatory indices, but cerebrospinal fluid analysis and anti-TBEV serology are still crucial for establishing the TBE diagnosis.
- The case fatality in pediatric TBE is overall very low. However, severe cases also occur in the pediatric population.
- Long-term somatic sequelae occur also after childhood TBE. Yet, long-term symptoms and neurodevelopmental/cognitive deficits are seen in 10–40% of infected children.
- Protective immunity can be effectively elicited in children by TBE vaccines as of 1 year of age.

Children, ticks, and TBE

Compared to TBE in adults, data on TBE in children is relatively sparse. It used to be generally accepted that TBE in childhood was rare and followed a milder course compared to adults. However, during the past two decades, this notion has been challenged. Various European countries such as Sweden and Latvia have reported severe cases and neurological sequelae after TBE also in children.

In general, the clinical picture of children with TBE is similar to the one described in adults. In both children and adults, TBE manifests as a neurological illness, most commonly meningitis. However, children and adolescents as a group tend to have milder neurological symptoms, and the disease less frequently has severe and lethal consequences. Children have a better long-term prognosis, compared to adults.[1-3] The largest multicenter study performed in Europe, showed that meningitis is more common among children compared to adults.[4] A large retrospective study from Poland, comparing 68 pediatric to 601 adult TBE cases, concluded that the disease was milder in children.[5] In this cohort, 97% of the cases in children were classified as meningitis. A nationwide prospective study in Latvia identified 40 TBEV-infected children 1–15 years of age and 90% of children had symptoms of CNS inflammation and all were hospitalized. In this cohort, 83% of the cases in children were classified as meningitis and 17% as meningoencephalitis, 33% of them with a moderate clinical course.[6] Another recent large cohort study from Germany, including 66 pediatric and 515 adult cases, confirmed that children as a group have milder disease manifestations compared with adults.[7] However, the same study noted that 56% of the children had a moderate or severe disease.

Children with TBE initially present with non-specific symptoms such as headache, fever, malaise/fatigue and because of that, cases may be overlooked. This idea was substantiated by a prospective Swedish study on children seeking medical care for neurological complaints[8] and confirmed by a Swiss case series.[9] Initial clinical diagnosis of TBE in children can be challenging due to a lack of specific symptoms. TBE can disguise as other common infectious diseases. TBEV infection should therefore be considered in all children with or without tick bite history presenting with non-specific symptoms during tick activity season in endemic countries.

Although rare, cases in newborns and children a few months old have been published.[10-13] A case from Slovakia described TBEV transmitted via breastfeeding to an eight-month old infant.[14] As concluded in the recent review article by Parfut et al, the incidence of TBE in children seems to peak at around nine years of age and increases continually with age.[1,15-19] TBE in childhood naturally affects both boys and girls, but approximately twice as many cases are seen in boys. Boys also tend to have a more severe disease.[1-3,20,21]

Tick-bites have been recalled in 48-76% of childhood TBE cases.[2,8,16,17,19,22,23] A biphasic course is reported in around 70 (20-100) % of cases.[1,2,5,7,8,16,18,19,24,25] Cases presenting with only fever are rarely studied, but do exist.[19,26] In the majority of reports on pediatric TBE, fever is present in virtually all cases at diagnosis.[1,2,16,19] However, both retrospective data from a fairly large cohort[22] and prospective data from a study with broad inclusion criteria,[8] show that fever >38.5° C is not always observed in pediatric TBE. In addition to fever, headache and vomiting have been reported as central features of childhood TBE at rates of approximately 90–100% and 50–90%, respectively. Self-reported fatigue/malaise, behavioral changes, photophobia, muscle pain, etc. are commonly reported, but occur at varying frequencies.[1-3,7,8,16,17,19,22] Meningeal signs (nausea,

vomiting, and nuchal rigidity) are prevalent findings, noted in >80% of infected children,[1,2,7,16,19,23] but young children have a less-pronounced clinical presentation.[8]

The clinical picture of pediatric TBE usually manifests as meningitis in 63–79% of cases, meningoencephalitis in 21–38%, and meningoencephalomyelitis in 0–4%. A study from Latvia reported that a mild disease course was seen more often in children than adults: 67% in 1-15 years of age and 60.5% in adults. However, none of the children had severe disease compared to 9% of the adults6. A recent Lithuanian study showed that milder disease manifestations were more common in children aged 1-8 years than in those 9-17 years old.[1,4,16,17,23] Clinical findings in childhood TBE include tremor, ataxia, impaired general appearance, somnolence, lymphadenopathy, apatheia, hyperesthesia, speech disorders, sensation disorders, and confusion/cognitive dysfunction.[1,2,5,8,16,17,19,22,24] Though uncommon, some children present with seizures, hemiparesis, paresis of the limbs, or cranial nerve pareses.[1,5,7,22,27] The largest clinical studies on TBE in children report median hospital stays ranging between 5-18 days, similar numbers or slightly shorter than what is described in the adult population.[1-3,7,16,19,22,28,29]

TBE without signs of CNS inflammation are not mandatorily reported and included in official surveillance, therefore the non-CNS TBE form is not well recognized and investigated. In the literature this TBE clinical picture has been described as “fever form”, “non-CNS cases of TBE” or “Febrile illness” and is characterized by the presence of fever and constitutional symptoms, and the absence of clinical signs of CNS involvement at the time of illness. According to the published data, up to 50% of symptomatic TBEV infections manifest without CNS involvement.[30,31] However, a recent population-based study reported less frequent non-CNS TBE cases among children than in adults, 8.7% and 18.7%, respectively.[6] This may indicate higher TBE awareness in children, especially towards excluding neurological involvement of the disease.

Diagnosis

For TBE diagnosis, detection of TBEV-specific IgM and IgG is required to prove TBEV infection, see ECDC criteria.[32] Lumbar puncture should be performed to confirm CNS inflammation and shows an elevated leukocyte count with predominantly mononuclear cells[1-3,16,19,22,24]. Increased CSF protein/ albumin levels seem to be more common in adults than in children with TBE.[2,5,22] CRP and leukocyte counts are often elevated, but in analogy with the adult population, no laboratory tests can discriminate TBE from other viral infections.[1-3,5,16,19,22]

Electroencephalogram (EEG) results can help confirm the diagnosis, but are not specific for TBE. The EEG abnormalities seen include mild to moderate, generalized, slowing background activity, but also sharp waves in contrast, though seldom generalized spike wave activity.[1,3,11,16,18,24] Magnetic resonance imaging (MRI) has been used infrequently in children with TBE. Similar to findings in adults, the most commonly reported finding is alterations in the thalami.[3,24,27,33-35] MRI changes have also been detected in cerebellar structures, putamen, and caudate nucleus, as well as the cortex. Of note, some children present with a normal MRI.[24,27] In a review of the spectrum of MRI findings in childhood TBE, von Stülpnagel et al reported poor outcomes, i.e., long-term neurologic disabilities and death, in children with MRI changes.[27] However, these data were retrospective and there might be a selection bias towards more severe cases undergoing MRI. Nonetheless, it can be concluded that pronounced CNS damage in pediatric TBE exists.

Short and long-term consequences of childhood TBE

Although most cases have a favorable outcome, a large proportion of children with TBE still have symptoms at discharge,[14,17,23] which contrasts with children with some other CNS infections.[36] Engman et al. reported significantly more days of acute illness in childhood TBE compared to children with neuroborreliosis or other infections with CNS symptoms. Additionally, they found a prolonged period of convalescence and more days of sick leave in the TBE cases.[37] Reported rates of admission into intensive care units range from 0 % to the very high 22% of TBE cases in children.[1,7,16,19,21] Compared with adults, fatal cases of TBE are reported only infrequently.[4,21,22,38]

While the occurrence of long-term neurologic and neuro-psychological sequelae in adults after TBE infection now is well-established,[3,4] the literature is inconsistent when it comes to the risk for long-term residua of childhood TBE. There are also considerable methodology differences between studies, both regarding methods and time-point for evaluation.[15]

For many years, but also recently, some studies have concluded that pediatric TBE has a more favorable outcome.[7,16,17,19] However, defining the complications of TBE is important. Only determining the gross neurologic status and a superficial assessment of health and cognitive functioning, leads to the conclusion that childhood TBE is not a long-term problem for most patients. But emerging data support the premise that pediatric TBE carries a risk of incomplete recovery, especially in terms of well-being and cognitive functions.

One of the first studies addressing the issue of incomplete neurocognitive recovery was published in 2005 by Schmolck et al. Over a mean of 3.2 years (range 6 months–11 years) after acute TBE illness, 19 pediatric subjects were evaluated

in comparison with healthy controls. Children who had suffered from TBE displayed lower scores in a structured neurologic examination and had significantly impaired attention and psycho-motor speed. Additionally, only 1/14 children in the TBE group had a normal EEG during hospitalization, whereas the remaining children were found to display pathological symptoms (mainly background slowing) without clinical disease. At follow-up, 8/19 EEGs were normal.[24] Later, in a Swiss study, researchers concluded that permanent residua (i.e., severe mental and physical handicap) after pediatric TBE were rare (1 child out of 55, approximately 2%), but no specific assessment of cognitive functions was performed.[17]

By administering validated questionnaires, Fowler et al. showed that 4 out of 6 children had residual symptoms, not always obvious, several years after TBE was diagnosed.[39] The occurrence of residual symptoms was later confirmed by Engman et al. Pediatric TBE patients, recruited from a previous prospective study, followed up 1 year after their acute disease, reported significantly more fatigue, headache, and irritability than did children after neuroborreliosis or control subjects. Additionally, the children were screened for neuro-developmental problems (e.g., executive functions, memory, motor skills, behavior, etc.) using a validated questionnaire. Children in the TBE group had significantly more difficulties (5 out of 7), mainly with memory, executive function, and perception.[37]

In a larger study by Fowler et al., the findings of residual symptoms and neurodevelopmental/cognitive problems in childhood TBE were consolidated. Of note, the severity of the acute phase of disease did not influence the risk of long-term disease burden. More than three residual symptoms (e.g., headache, fatigue, memory problems, irritability, concentration problems, etc.) were seen in approximately 70% of the children at follow-up on average 4.2 years after the acute disease. Clinically significant problems with executive functioning were noted in approximately 40% of the children. Additionally, a significant decrease in working memory index, but not global IQ, was seen using the Wechsler Intelligence Scale for Children-IV.[18]

Prominent deficits in working memory capacity and increased task-related functional MRI signal in working memory-related cortical areas during working memory testing have been shown in pediatric patients after TBE. These functional MRI abnormalities suggest diffuse neuronal damage behind the development of neurodevelopmental/cognitive problems seen in childhood TBE.[40]

Krbková et al. also described cognitive problems (memory problems and lowered school grades) at follow-up in a large study; however, they found such deficits to a somewhat lower extent (11%).[19] Fatigue is a common residual symptom after TBE. A recent Swiss review on sleep-related symptoms concluded that 73,9% of children suffer from fatigue at long-term follow up (≥12 months) after TBE,[41] and sleep disorders have also been reported after TBE in adults.[42] Using phone interviews at 18 months post TBE, a recently published German cohort study including 59 children concluded a more favorable outcome for children compared to adults. The most common remaining self-reported symptom in the whole cohort consisting of both children and adults at 18 months´ follow-up was fatigue.[43]

Long-term sequelae of a more somatic nature are less frequently reported in childhood TBE. However, such cases occur. Fritsch et al. reported severe neurologic residua (hemiparesis and epilepsia) at a rate of 1.7% in their large pediatric cohort[1]. Others have also reported on neurologic sequelae, mainly hemiparesis, in children with TBE.[11,19,21,33] However, the frequency of paralysis and paresis in pediatric TBE is only reported up to approximately 2%, which is lower than the rate seen in adults.[2-4,16,17,21,33] While rare, such neurologic residua constitute a significant handicap in those affected, disrupting quality of life for many years. That TBE in childhood can be associated with altered cerebral electrophysiologic processes, i.e., pathologic EEGs and development of epilepsia,[1,11,19,24,33] is further substantiated by a report by Mukhin et al. Rather treatment-resistant epilepsia partialis continua was seen in 10 Russian children (predominantly boys) days to years after TBE. This cohort also suffered from oculomotor dysfunction, varying degree of paresis, dysarthria, cerebellar signs, and cognitive dysfunction.[44]

To conclude, pediatric TBE carries a high risk for subjective sequelae, which to some extent can be objectively assessed by using structured questionnaires and interviews.[18,21,36] The early findings by Schmolck et al[24] that TBE in childhood can be associated with neurodevelopmental/cognitive difficulties have now been verified.[18,19,37] As summarized in a review by R. Steffen; Although larger studies may be required to determine the incidence of these sequelae, the individual child's long-term disease burden cannot be neglected.[45] In contrast to somatic residua and epilepsy, which of course are rare but more easily diagnosed, neurodevelopmental/cognitive problems may elude diagnosis due to young children's difficulties in verbalizing their problems and for their parents to recognize them. Hence, an opportunity exists to advocate for structured follow-up of children diagnosed with TBE so that early actions can be taken.

TBE immunity and vaccination in children

Children, from the age of 1 year, as well as adults, can elicit highly effective protective immunity to TBEV (i.e., response to the viral E protein) by immunization with the two TBE vaccines available in the EU46. These vaccines are based on the European TBEV strains Neudörfl (FSME-IMMUN® Junior)

and K23 (Encepur® Children).[47] The field effectiveness in children less than 15 years of age is reported to be 97% after immunization with either of the two vaccines; however, it should be noted that the vaccine based on the Neudörfl strain had a higher market share at the time of the study (>96%).[48] TBE vaccination effectiveness has also been demonstrated by the nearly complete disappearance of TBE in a highly endemic area with implementation of a general vaccination program.[49]

Vaccination breakthroughs, although rare, occur in children. In the multicenter study by Kohlmaier et al, 16 of the 546 patients where data could be obtained were previously vaccinated, and 9 of these 16 patients where younger than 20 years.[4] Among the many publications on immunization in children, it is important to note that the vaccines marketed within the EU have been shown to be safe and effective in eliciting antibody titers, that the booster interval can be expanded, and that rapid immunization schedules have worked well.[50] Previous recommendations stated that the primary TBE vaccination (i.e., the first 3 doses) preferably should be accomplished with the same vaccine because of differences in each vaccine's immunologic properties.[50-52] However, more recent data suggest that the vaccines may be interchangeable and even point out advantages with administration of vaccine shots from the two different brands.[53,54]

Natural immunity to TBE seems to persist over time and as children age, according to Baldovin et al., but with the reservation that their cohort was small.[55] Truly long-term data on natural immunity (for example, follow-up of now-older adults after TBE in childhood years) have not yet been reported.

Contact: malin.veje@gu.se

Citation:

Veje M, Freimane Z, Zavadska D. TBE in children. Chapter 8. In: Dobler G, Erber W, Bröker M, Chitimia-Dobler L, Schmitt HJ, eds. *The TBE Book*. 7th ed. Singapore: Global Health Press; 2024. doi: 10.33442/26613980_8-7

References

1. Fritsch P, Gruber-Sedlmayr U, Pansi H, et al. Tick-borne encephalitis in Styrian children from 1981 to 2005: a retrospective study and a review of the literature. *Acta Paediatr*. 2008;97(5):535-8. doi:10.1111/j.1651-2227.2008.00763.x
2. Logar M, Arnez M, Kolbl J, Avsic-Zupanc T, Strle F. Comparison of the epidemiological and clinical features of tick-borne encephalitis in children and adults. *Infection*. 2000;28(2):74-7. doi:10.1007/s150100050050
3. Kaiser R. The clinical and epidemiological profile of tick-borne encephalitis in southern Germany 1994-98: a prospective study of 656 patients. Brain. 1999;122(11):2067-78.
4. Kohlmaier B, Schweintzger NA, Sagmeister MG, et al. Clinical Characteristics of Patients with Tick-Borne Encephalitis (TBE): A European Multicentre Study from 2010 to 2017. *Microorganisms.* Jun 30 2021;9(7)doi:10.3390/microorganisms9071420
5. Krawczuk K, Czupryna P, Pancewicz S, Ołdak E, Moniuszko-Malinowska A. Comparison of tick-borne encephalitis between children and adults-analysis of 669 patients. *J Neurovirol*. Aug 2020;26(4):565-571. doi:10.1007/s13365-020-00856-x
6. Zavadska D, Freimane Z, Karelis G, et al. Effectiveness of Tick-borne Encephalitis Vaccines in Children, Latvia, 2018–2020. *Pediatr Infect Dis J*. 2023;42(10):927-931. doi:10.1097/inf.0000000000004034
7. Nygren TM, Pilic A, Böhmer MM, et al. Tick-borne encephalitis: Acute clinical manifestations and severity in 581 cases from Germany, 2018–2020. *J Infection*. 2023;86(4):369-375. doi:10.1016/j.jinf.2023.02.018
8. Sundin M, Hansson ME, Engman ML, et al. Pediatric tick-borne infections of the central nervous system in an endemic region of Sweden: a prospective evaluation of clinical manifestations. *Eur J Pediatr*. 2012;171(2):347-52. doi:10.1007/s00431-011-1542-2
9. Meyer PM, Zimmermann H, Goetschel P. Tick-borne encephalitis presenting as fever without localising signs—a case series. *Eur J Pediatr.* 2010/06/01 2010;169(6):767-769. doi:10.1007/s00431-009-1097-7
10. Grubbauer HM, Dornbusch HJ, Spork D, Zobel G, Trop M, Zenz W. Tick-borne encephalitis in a 3-month-old child. *Eur J Pediatr*. 1992;151(10):743-4. doi:10.1007/bf01959081
11. Jones N, Sperl W, Koch J, Holzmann H, Radauer W. Tick-borne encephalitis in a 17-day-old newborn resulting in severe neurologic impairment. *Pediatr Infect Dis J*. 2007;26(2):185-6. doi:10.1097/01.inf.0000253056.34894.5f
12. Kosina P, Plisek S, Krausova J, Kracmarova R. Tick-borne encephalitis virus – a rare cause of encephalitis in infants. *Wien Klin Wochenschr*. 2008;120(21):710-711. doi:10.1007/s00508-008-1069-3
13. Iff T, Meier R, Olah E, Schneider JFL, Tibussek D, Berger C. Tick-borne meningo-encephalitis in a 6-week-old infant. *Eur J Pediatr*. 2005;164(12):787-788. doi:10.1007/s00431-005-1753-5
14. Kerlik J, Avdičová M, Musilová M, Bérešová J, Mezencev R. Breast Milk as Route of Tick-Borne Encephalitis Virus Transmission from Mother to Infant. *Emerg Infect Dis.* 2022;28(5):1060-1061. doi:10.3201/eid2805.212457
15. Parfut A, Laugel E, Baer S, et al. Tick-borne encephalitis in pediatrics: An often overlooked diagnosis. *Infect Dis Now*. 2023;53(2):104645. doi:10.1016/j.idnow.2023.01.005
16. Lesnicar G, Poljak M, Seme K, Lesnicar J. Pediatric tick-borne encephalitis in 371 cases from an endemic region in Slovenia, 1959 to 2000. *Pediatr Infect Dis J*. 2003;22(7):612-7. doi:10.1097/01.inf.0000073202.39700.a0
17. Stähelin-Massik J, Zimmermann H, Gnehm HE. Tick-Borne Encephalitis in Swiss Children 2000–2004: Five-Year Nationwide Surveillance of Epidemiologic Characteristics and Clinical Course. *Pediatr Infect Dis J.* 2008;27(6):555-557. doi:10.1097/INF.0b013e318165c195

18. Fowler Å, Forsman L, Eriksson M, Wickström R. Tick-borne encephalitis carries a high risk of incomplete recovery in children. *J Pediatr.* 2013;163(2):555-60. doi:10.1016/j.jpeds.2013.01.037
19. Krbková L, Štroblová H, Bednářová J. Clinical course and sequelae for tick-borne encephalitis among children in South Moravia (Czech Republic). *Eur J Pediatr*. 2015;174(4):449-58. doi:10.1007/s00431-014-2401-8
20. Zöldi V, Juhász A, Nagy C, Papp Z, Egyed L. Tick-borne encephalitis and Lyme disease in Hungary: the epidemiological situation between 1998 and 2008. *Vector Borne Zoonotic Dis*. 2013;13(4):256-65. doi:10.1089/vbz.2011.0905
21. Cizman M, Rakar R, Zakotnik B, Pokorn M, Arnez M. Severe forms of tick-borne encephalitis in children. *Wien Klin Wochenschr*. 1999;111(12):484-7.
22. Hansson ME, Orvell C, Engman ML, et al. Tick-borne encephalitis in childhood: rare or missed? *Pediatr Infect Dis J*. 2011;30(4):355-7. doi:10.1097/INF.0b013e3181fe3b5a
23. Bogdanavičienė K, Gudavičiūtė G, Šeškutė M. A Retrospective Analysis of Tick-borne Encephalitis in Children Treated in Kaunas Hospital During 2012 to 2019. *Pediatr Infect Dis J*. 2022;41(9):702-705. doi:10.1097/INF.0000000000003595
24. Schmolck H, Maritz E, Kletzin I, Korinthenberg R. Neurologic, Neuropsychologic, and Electroencephalographic Findings After European Tick-borne Encephalitis in Children. *J Child Neurol*. 2005;20(6):500-508. doi:10.1177/088307380502000606
25. Kaiser R. Frühsommermeningoenzephalitis im Kindes- und Jugendalter. Monatsschrift Kinderheilkunde. 2006;154(11):1111-1116. doi:10.1007/s00112-005-1184-4
26. Meyer PM, Zimmermann H, Goetschel P. Tick-borne encephalitis presenting as fever without localising signs–a case series. *Eur J Pediatr*.2010;169(6):767-9. doi:10.1007/s00431-009-1097-7
27. von Stülpnagel C, Winkler P, Koch J, et al. MRI-imaging and clinical findings of eleven children with tick-borne encephalitis and review of the literature. *Eur J Paediatr Neurol*. Jan 2016;20(1):45-52. doi:10.1016/j.ejpn.2015.10.008
28. Bogovič P, Stupica D, Rojko T, et al. The long-term outcome of tick-borne encephalitis in Central Europe. *Ticks Tick Borne Dis*. 2018;9(2):369-378. doi:10.1016/j.ttbdis.2017.12.001
29. Günther G, Haglund M, Lindquist L, Forsgren M, Sköldenberg B. Tick-bone encephalitis in Sweden in relation to aseptic meningo-encephalitis of other etiology: a prospective study of clinical course and outcome. *J Neurol*. 1997;244(4):230-238. doi:10.1007/s004150050077
30. Bogovič P, Kastrin A, Lotrič-Furlan S, et al. Clinical and Laboratory Characteristics and Outcome of Illness Caused by Tick-Borne Encephalitis Virus without Central Nervous System Involvement. *Emerg Infect Dis*. 2022;28(2):291-301. doi:10.3201/eid2802.211661
31. Dumpis U, Crook D, Oksi J. Tick-Borne Encephalitis. *Clinical Infectious Diseases*. 1999;28(4):882-890. doi:10.1086/515195
32. ECDC Meeting Report 2011. Second expert consultation on tick-borne diseases with emphasis on Lyme borreliosis and tick-borne encephalitis. 2012. Accessed 28 March, 2024. https://www.ecdc.europa.eu/sites/default/files/media/en/publications/Publications/Tick-borne-diseases-meeting-report.pdf.
33. Kluger G, Schöttler A, Waldvogel K, et al. Tickborne encephalitis despite specific immunoglobulin prophylaxis. *Lancet*. 1995;346(8988):1502. doi:10.1016/s0140-6736(95)92527-9
34. Zawadzki R, Garkowski A, Kubas B, et al. Evaluation of Imaging Methods in Tick-Borne Encephalitis. *Pol J Radiol*. 2017;82:742-747. doi:10.12659/pjr.903940
35. Palyga-Bysiecka I, Kręcisz B, Szczepańska B. Clinical course and neurological sequels after tick-borne encephalitis in children – case report. journal article. *Ann Agric Environ Med*. 2022;29(1):162-167. doi:10.26444/aaem/133206
36. Fowler A, Stödberg T, Eriksson M, Wickström R. Childhood encephalitis in Sweden: etiology, clinical presentation and outcome. *Eur J Paediatr Neurol*. 2008;12(6):484-90. doi:10.1016/j.ejpn.2007.12.009
37. Engman ML, Lindström K, Sallamba M, et al. One-year follow-up of tick-borne central nervous system infections in childhood. *Pediatr Infect Dis J*. 2012;31(6):570-4. doi:10.1097/INF.0b013e31824f23c0
38. Varnaitė R, Gredmark-Russ S, Klingström J. Deaths from Tick-Borne Encephalitis, Sweden. *Emerg Infect Dis.* 2022;28(7):1471-1474. doi:10.3201/eid2807.220010
39. Fowler Å, Stödberg T, Eriksson M, Wickström R. Long-term Outcomes of Acute Encephalitis in Childhood. *Pediatrics*. 2010;126(4):e828. doi:10.1542/peds.2009-3188
40. Henrik U, Åsa F, Ronny W. Increased working memory related fMRI signal in children following Tick Borne Encephalitis. *Eur J Paediatr Neurol*. 2016;20(1):125-30. doi:10.1016/j.ejpn.2015.09.004
41. Chiffi G, Grandgirard D, Sendi P, Dietmann A, Bassetti CLA, Leib SL. Sleep-Wake and Circadian Disorders after Tick-Borne Encephalitis. *Microorganisms*. 2022;10(2)doi:10.3390/microorganisms10020304
42. Veje M, Studahl M, Thunström E, et al. Sleep architecture, obstructive sleep apnea and functional outcomes in adults with a history of Tick-borne encephalitis. *PloS one*. 2021;16(2):e0246767. doi:10.1371/journal.pone.0246767
43. Nygren TM, Pilic A, Böhmer MM, Wagner-Wiening C, Wichmann O, Hellenbrand W. Recovery and sequelae in 523 adults and children with tick-borne encephalitis in Germany. *Infection*. 2023;51(5):1503-1511. doi:10.1007/s15010-023-02023-w
44. Mukhin KY, Mameniškienė R, Mironov MB, et al. Epilepsia partialis continua in tick-borne Russian spring-summer encephalitis. *Acta Neurol Scand*. 2012;125(5):345-52. doi:10.1111/j.1600-0404.2011.01575.x
45. Steffen R. Tick-borne encephalitis (TBE) in children in Europe: Epidemiology, clinical outcome and comparison of vaccination recommendations. *Ticks Tick Borne Dis*. 2019;10(1):100-110. doi:10.1016/j.ttbdis.2018.08.003
46. Angulo FJ, Zhang P, Halsby K, et al. A systematic literature

review of the effectiveness of tick-borne encephalitis vaccines in Europe. *Vaccine*. 2023;41(47):6914-6921. doi:10.1016/j.vaccine.2023.10.014
47. Heinz FX, Holzmann H, Essl A, Kundi M. Field effectiveness of vaccination against tick-borne encephalitis. *Vaccine*. 2007;25 (43):7559-7567. doi:10.1016/j.vaccine.2007.08.024
48. Pöllabauer EM, Pavlova BG, Löw-Baselli A, et al. Comparison of immunogenicity and safety between two paediatric TBE vaccines. *Vaccine*. Jun 23 2010;28(29):4680-5. doi:10.1016/j.vaccine.2010.04.047
49. Zenz W, Pansi H, Zoehrer B, et al. Tick-borne encephalitis in children in Styria and Slovenia between 1980 and 2003. *Pediatr Infect Dis J*. Oct 2005;24(10):892-6. doi:10.1097/01.inf.0000180506.76201.43
50. Wittermann C, Petri E, Zent O. Long-term persistence of tick-borne encephalitis antibodies in children 5 years after first booster vaccination with Encepur Children. *Vaccine*. 2009;27 (10):1585-8. doi:10.1016/j.vaccine.2008.12.057
51. Prymula R, Pöllabauer EM, Pavlova BG, et al. Antibody persistence after two vaccinations with either FSME-IMMUN® Junior or ENCEPUR® Children followed by third vaccination with FSME-IMMUN® Junior. *Hum Vaccin Immunother*. 2012;8(6):736-42. doi:10.4161/hv.20058
52. Wittermann C, Schöndorf I, Gniel D. Antibody response following administration of two paediatric tick-borne encephalitis vaccines using two different vaccination schedules. *Vaccine*. 2009;27(10):1661-6. doi:10.1016/j.vaccine.2008.10.003
53. Bestehorn-Willmann M, Girl P, Greiner F, Mackenstedt U, Dobler G, Lang D. Increased Vaccination Diversity Leads to Higher and Less-Variable Neutralization of TBE Viruses of the European Subtype. *Vaccines*. 2023;11(6):1044. doi:10.3390/vaccines11061044
54. Vaccines against tick-borne encephalitis: WHO position paper – 2011. Accessed 28 March, 2024. https://www.who.int/teams/immunization-vaccines-and-biologicals/policies/position-papers/tick-borne-encephalitis
55. Baldovin T, Mel R, Bertoncello C, et al. Persistence of immunity to tick-borne encephalitis after vaccination and natural infection. *J Med Virol*. 2012;84(8):1274-1278. doi:10.1002/jmv.23313