Supplementary Material
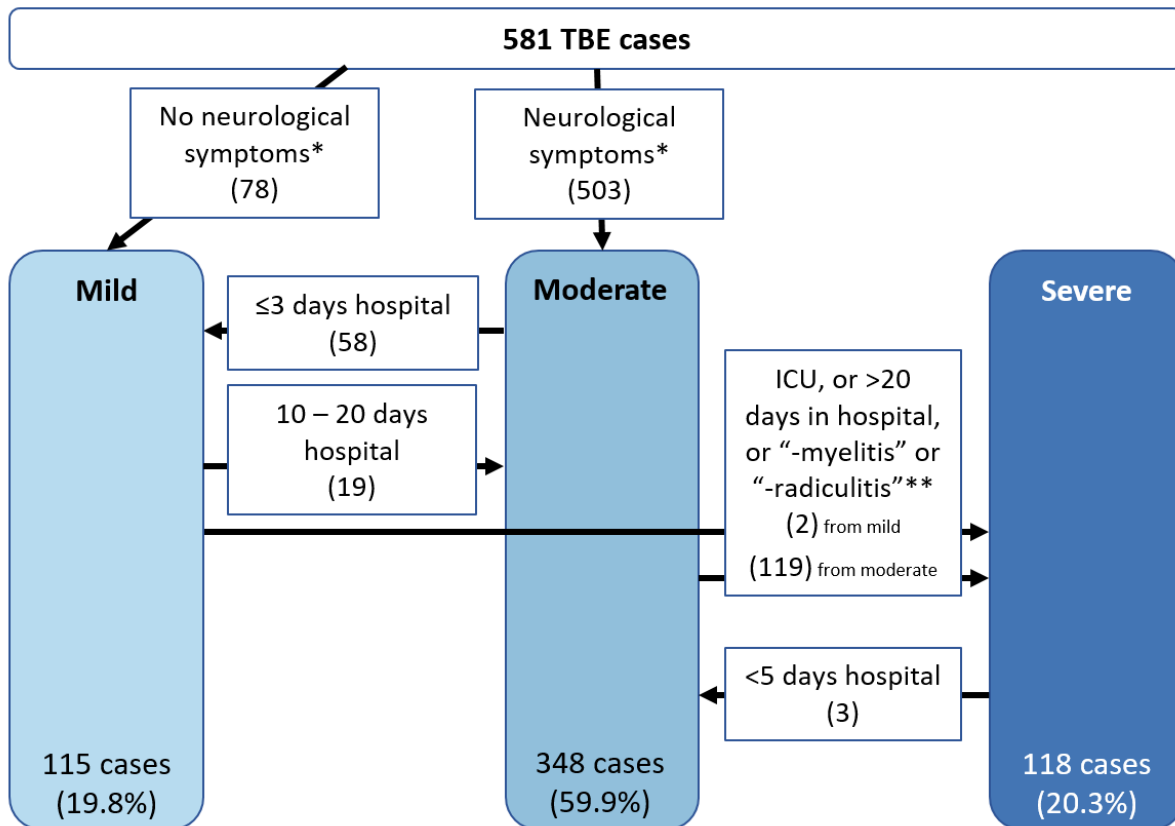
Article: Tick-Borne Encephalitis: Acute Clinical Manifestations and Severity in 581 cases from Germany, 2018–2020

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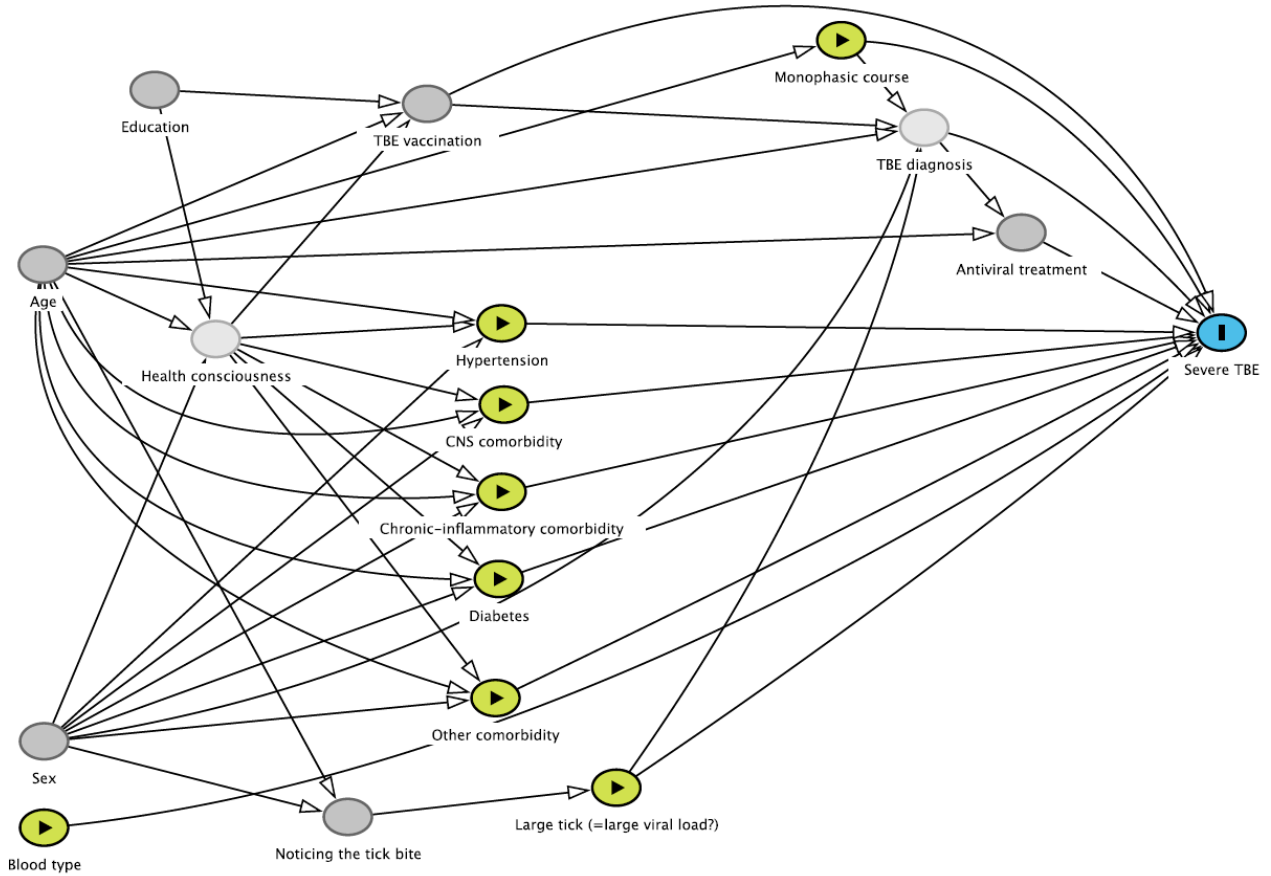**Appendix 1 (Figure).** Definition of acute TBE disease severity

ICU: intensive care unit

* at least 1 of: ataxia, sensory impairment, dysphasia, dysphagia, pareses, impaired consciousness, seizures, hearing impairment, respiratory difficulty/paralysis

** according to hospital discharge summaries

Appendix 2 (Figure). Directed acyclic graph (DAG) of the causal structure underlying the mechanisms connecting potential exposures to the outcome severe TBE, as determined by subject-specific knowledge. Created with Dagitty (1).

Blue node = outcome. Green nodes = exposures of interest. One exposure was selected at a time to identify the minimal sufficient adjustment set of covariates to estimate the adjusted total causal effect of that exposure on the outcome (for minimal adjustment sets see Appendix 3).

Appendix 3. Factors associated with TBE severity: Frequency of covariates and covariate-specific minimal adjustment sets, as determined with a directed acyclic graph (Appendix 2)

Exposure of interest		Cases with data	Cases with outcome	Minimal adjustment sets
General exposures and comorbidities	Age	581	581	None
	Monophasic course	579	242	Age
	Hypertension	581	122	Age, Other comorbidity, Sex, TBE vaccination
	Diabetes	581	23	Age, Other comorbidity, Sex, TBE vaccination, Hypertension
	CNS comorbidity	581	177	Age, Sex
	Chronic-inflammatory comorbidity	581	93	Age, Sex
	Other comorbidity	581	32	Age, Diabetes, Hypertension, Sex, TBE vaccination
Size of tick at removal	Smaller than pepper grain (reference)	581	271	Age, Sex
	Pepper grain-/pea-sized	581	154	
	Size unknown	581	156	
Blood type	A (reference)	581	105	
	B	581	29	
	O	581	105	None
	AB	581	20	
	Unknown	581	322	

Appendix 4 (Table). Factors associated with severe acute TBE: Results of univariable logistic regression analyses.

Covariates		OR	Lower 95% CI	Upper 95% CI	p-value
General exposures and comorbidities	Age	1.04	1.02	1.05	<0.001
	Monophasic course	2.25	1.49	3.40	<0.001
	Hypertension	3.42	2.20	5.34	<0.001
	Diabetes	3.86	1.66	8.99	0.002
	CNS comorbidity	1.86	1.22	2.83	0.004
	Chronic inflammatory comorbidity	2.45	1.51	3.99	<0.001
	Other comorbidity	0.90	0.36	2.24	0.822
Size of tick at removal	Smaller than pepper grain (reference)	1.00			
	Pepper grain-/pea-sized	0.80	0.47	1.35	0.401
	Size unknown	1.64	1.03	2.61	0.037
Blood group	A (reference)	1.00			
	B	1.35	0.48	3.81	0.570
	O	1.07	0.52	2.21	0.853
	AB	0.58	0.12	2.71	0.484
	Unknown	1.57	0.88	2.81	0.126
Covariates used for adjustment and other individual comorbidities	Male	1.01	0.67	1.54	0.956
	TBE vaccination	2.57	1.53	4.30	<0.001
	Immunosuppressive therapy	1.51	0.53	4.33	0.442
	Neuropathy	2.01	0.74	5.48	0.171
	Arthritis	2.03	0.85	4.87	0.112
	Autoimmune disease	1.03	0.38	2.83	0.948
Laboratory parameters	Elevated c-reactive protein	1.10	0.63	1.91	0.744
	CSF pleocytosis	0.16	0.03	0.98	0.047
	CSF elevated lactate	2.35	1.19	4.63	0.014
	CSF elevated glucose	1.24	0.44	3.54	0.681
	CSF elevated protein	0.77	0.37	1.61	0.487
	CSF leucocytes	1.21	0.70	2.07	0.498
CT result	Pathological CT result	2.60	1.03	6.58	0.044

OR = odds ratio; CI = confidence interval; CNS comorbidity = comorbidities of the central and peripheral nervous system; CSF = cerebrospinal fluid; CT = computed tomography

Appendix 5 (Table). Characteristics of 1,220 TBE cases from Bavaria and Baden-Wuerttemberg notified between 2018–2020 and eligible for the study according to parameters in routine surveillance data, by participation status.

	Participants n = 581	Non-participants n = 639	p-value
Demographics	n (%)	n (%)	
Mean age (in years, SD)	48.6 (20)	49.3 (21)	0.43
Median age (in years, IQR)	53 (36-63)	53 (35-65)	
Male	368 (63%)	411 (64%)	0.72
From Bavaria	255 (44%)	322 (50%)	0.08
From Baden-Wuerttemberg	326 (56%)	317 (50%)	
Symptoms			
No CNS symptoms	260 (45%)	291 (46%)	
Meningitis	208 (36%)	223 (35%)	0.95
Encephalitis/Myelitis	113 (20%)	125 (20%)	
Hospitalisation			
Hospitalised	488 (84%)	542 (85%)	0.70
TBE-vaccinated (≥1 dose)			
Not vaccinated	509 (88%)	567 (89%)	
Vaccinated	57 (10%)	45 (7%)	0.14
Missing	15 (3%)	27 (4%)	
Year of notification			
2018	190 (44%)	241 (56%)	
2019	156 (51%)	150 (49%)	0.15
2020	235 (49%)	248 (51%)	

SD = standard deviation; IQR = interquartile range; CNS = central nervous system

Appendix 6 (Table). Neuroimaging and laboratory results in hospitalised TBE patients, as extracted from hospital discharge summaries (n=421) and GP questionnaires (provided data only for EEG, CR and MRI results, n=459).

Parameter	n with data	n performed	% performed	result available for n:	n elevated/ pathologic al	% elevated/ pathologic al
EEG	482	203	42.1%	193	127	65.8%*
CT	446	278	62.3%	258	20	7.8%
MRI	486	303	62.4%	289	67	23.2%
C-reactive protein	331			331	212	64.0%
Leukocytes	330			330	181	54.8%
Lumbar puncture performed	411	356	86.6%			
CSF pleocytosis				341	336	98.5%
CSF protein				331	286	86.4%
CSF lactate				317	46	14.5%
CSF glucose				317	21	6.6%

CSF = cerebrospinal fluid; EEG = electroencephalography; CT = computed tomography, MRI = magnetic resonance imaging

*Pathological EEG was more frequent in children than adults (86.4% vs. 63.2%, p=0.03).

References

1.   Textor J, van der Zander B, Gilthorpe MS, Liskiewicz M, Ellison GT. Robust causal inference using directed acyclic graphs: the R package 'dagitty'. Int J Epidemiol. 2016 Dec 1;45(6):1887-94. PubMed PMID: 28089956. Epub 2017/01/17. eng.