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Tick-borne encephalitis: Acute clinical manifestations and severity in 581 cases from Germany, 2018–2020

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SUMMARY

Objectives: Tick-borne encephalitis (TBE) is a growing public health problem with an average of 361 cases notified annually to Germany's passive surveillance system since 2001. We aimed to assess clinical manifestations and identify covariates associated with severity.

Methods: We included cases notified 2018–2020 in a prospective cohort study and collected data with telephone interviews, questionnaires to general practitioners, and hospital discharge summaries. Covariates' causal associations with severity were evaluated with multivariable logistic regression, adjusted for variables identified via directed acyclic graphs.

Results: Of 1220 eligible cases, 581 (48%) participated. Of these, 97.1% were not (fully) vaccinated. TBE was severe in 20.3% of cases (children: 9.1%, ≥70-year-olds: 48.6%). Routine surveillance data underreported the proportion of cases with central nervous system involvement (56% vs. 84%). Ninety percent required hospitalization, 13.8% intensive care, and 33.4% rehabilitation. Severity was most notably associated with age (odds ratio (OR): 1.04, 95% confidence interval (CI): 1.02–1.05), hypertension (OR: 2.27, 95%CI: 1.37–3.75), and monophasic disease course (OR: 1.67, 95%CI: 1.08–2.58).

Conclusions: We observed substantial TBE burden and health service utilization, suggesting that awareness of TBE severity and vaccine preventability should be increased. Knowledge of severity-associated factors may help inform patients' decision to get vaccinated.

Introduction

Tick-borne encephalitis (TBE) is a vaccine-preventable, tick-borne viral infection. Only the European virus subtype is endemic in Germany. The typical disease course is biphasic, consisting of a first phase with general symptoms such as headache and fever, a symptom-free interval, and a second phase with neurological manifestations.[1]

In Germany, laboratory diagnosis of acute TBE became statutorily notifiable in 2001. District health authorities retrospectively ascertain clinical manifestations. From 2001–2020, a mean of 361 cases was notified annually, with 85% of cases originating from the federal states Bavaria and Baden-Wuerttemberg in the south of Germany.[2]

Both the German and European Union case definitions[3] include only laboratory-confirmed cases. Notably, however, the latter is restricted to cases with central nervous system (CNS) involvement, while the former additionally includes clinical cases without CNS involvement. Only about half the cases are reported to have CNS symptoms in German routine surveillance data.[4] It remains unknown if the other half only experience mild, febrile forms of TBE without CNS involvement, or if CNS involvement is underreported. The present study addressed this knowledge gap by comprehensively assessing CNS involvement. Severity ranges from mild symptoms to meningitis to severe meningoencephalitis or -myelitis.[4] Overall, 70–95% of TBE infections remain sub-clinical[5,6] and < 1% of symptomatic cases die.[4] Children generally experience milder TBE than adults[7,8] and disproportionately often elude diagnosis.[2,9] There

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is a common belief that TBE is always benign in children,[8] potentially causing low vaccine uptake.[4] Only few studies have characterized outcomes such as cognitive function following TBE in children, which was a particular focus of the present study.

Age, monophasic course, CNS comorbidities, and general comorbidities were found to be independently associated with severe TBE in multivariable analysis.[10–12] Results were, however, inconsistent regarding diabetes,[10,12] male sex,[10–12] laboratory parameters,[12] and computed tomography (CT) findings.[12] Further possible predictors of severity include blood type,[13] ticks' blood meal duration (proxy: large tick at removal),[14] immunosuppression, autoimmune diseases, and chronic inflammatory comorbidities.

We conducted intensified TBE surveillance on cases notified 2018–2020. Primary objectives were to assess clinical manifestations and health care utilization, as well as to identify factors associated with TBE severity.

Methods

Study population and data collection

All TBE cases notified from 01 January 2018–31 December 2020 in Bavaria or Baden-Wuerttemberg meeting the national case definition[15] were eligible (Fig. 1) to be included in this cohort study. This article reports data from the first data collection point, occurring as soon as possible after disease onset. A follow-up on TBE sequelae will be reported separately. The national case definition requires clinical manifestations (≥1 of: meningitis, encephalitis, myelitis, or non-specific symptoms [≥2 of: chills, severe malaise, headache, muscle/limb/back pain]) plus laboratory confirmation (simultaneously elevated TBE-specific immunoglobulin (Ig)M and IgG antibodies in serum or cerebrospinal fluid, an increase in IgG antibodies in serum, intrathecal antibody synthesis, or detection of TBE viral nucleic acid in blood or cerebrospinal fluid[4,15]). Study invitations relied on 114 district health authorities. Eligibility further required the contactability via the district health authority and fluency in German. Following written informed consent, cases answered 30-minute standardized telephone interviews conducted by USUMA GmbH, Berlin, Germany. In addition, cases' general practitioners (GPs) completed questionnaires and provided hospital discharge summaries.

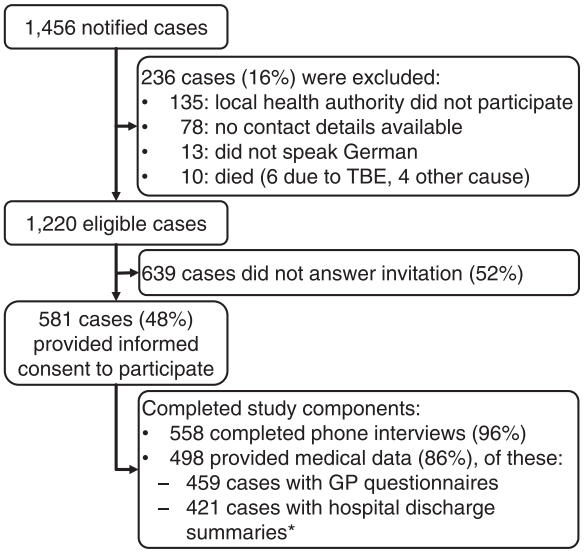


Fig. 1. Study eligibility, participation and completeness of study components of TBE cases notified in Bavaria or Baden-Wuerttemberg in 2018–2020 and meeting the case definition. GP, general practitioner. *A single summary was provided for 305 cases (72%), up to 6 summaries for 116 cases (28%).

Data management and analysis

Medical students extracted data from hospital discharge summaries. Questionnaires were double-entered and validated using MS Access. A single practicing neurologist rated EEG, CT, and magnetic resonance imaging (MRI) results as normal/pathological. Every mention in any source was counted for symptoms. We defined a variable-specific evidence hierarchy to reconcile disagreements between data sources: hospital discharge summaries were considered most reliable for medical parameters (comorbidities, ICU admission, etc.), followed by GP questionnaires. Comorbidities reported in medical sources were supplemented by plausible patient-reported comorbidities. Hypertension and diabetes were relatively common and thus retained as individual comorbidities, while other comorbidities were grouped as chronic-inflammatory comorbidities, comorbidities of the CNS, and other comorbidities by a physician. Case interviews were considered most reliable for factors that may not have been ascertained during hospitalization, such as biphasic course and vaccination history.

Severity was initially categorized as "mild" or "moderate" based on absence or presence of neurological symptoms. Next, the duration of hospital stay was considered, so that e. g. patients with neurological symptoms but ≤3 days in hospital were moved from "moderate" to "mild." The definition of "severe" required either > 20 days in hospital, ICU admission, or reporting of the specific severe diagnoses of myelitis or radiculitis in hospital discharge summaries (see Appendix 1 for details).

Self-reported recovery from TBE was assessed during telephone interviews with the modified RANKIN scale,[16] which measures the functional outcome of disease. The Glasgow coma scale (GCS) assesses patients' impairment of consciousness and scores were extracted from hospital discharge summaries.

Data were analyzed in Stata 17®. Descriptive statistics were reported as means, medians, and percentages. Differences were tested with Mann Whitney U, Chi-squared and Kruskal Wallis tests and trends with the Cochran-Armitage test, as appropriate. P values of < 0.05 were considered statistically significant. Where stated, p values of 0.001 were applied to account for multiple comparisons. Proportions were reported among non-missing observations when < 10% of data were missing.

The outcome was dichotomized (mild + moderate vs. severe TBE). To assess factors associated with severity, we first explored the underlying causal structure with a directed acyclic graph (DAG) in Dagitty[17] to identify the minimal adjustment set to estimate the total causal effect on TBE severity for each exposure of interest (Appendix 2, Appendix 3). We report adjusted odds ratios (OR) with 95% confidence intervals (CI). For univariable estimators, see Appendix 4.

Ethics

The study was approved by the Ethics Committee of Charité–Universitätsmedizin Berlin, No. EA2/059/18.

Results

Participant characteristics and acute severity

Of 1220 eligible cases, 581 (48%) participated (Fig. 1). Non-participants did not differ from participants in key parameters (Appendix 5). Notifications occurred at a median of 20 days (interquartile range (IQR) = 13–27) and interviews at 93 days after symptom onset (IQR = 66–146). Completeness across study components was high (Fig. 1).

The mean age of the study participants was 48.6 years (SD = 19.9 years, range 2–89) and 63.3% were male. Among 66 cases in children

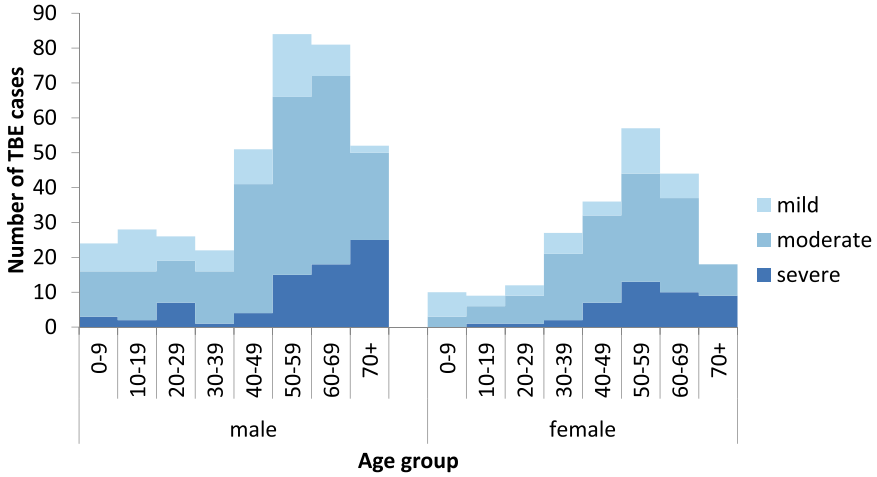


Fig. 2. TBE cases notified in Bavaria or Baden-Wuerttemberg in 2018–2020 and participating in the study by age, sex, and acute disease severity, n = 581.

(11.4%), 50 (76%) were boys (Fig. 2). Of the 97.1% cases resident in TBE risk areas, 40.5% were unaware of this before contracting TBE. TBE vaccination was reported in 78 cases (13.4%); 17 were fully vaccinated (2.9%), i.e., reporting ≥3 vaccine doses (plus recommended booster doses where applicable) with the last dose < 3 or < 5 years ago as per manufacturer's instructions. Comorbidities were present in 247 cases (42.5%, including: hypertension (21% overall) and diabetes (4% overall)), chronic inflammatory comorbidities (16.0%), and CNS comorbidities (30.4%).

Mild TBE occurred in 19.8% of cases (n = 115), moderate TBE in 59.9% (n = 348) and severe TBE in 20.3% (n = 118), (Fig. 2). Sixty mild cases were not hospitalized. Severity did not differ by sex (p = 0.98), but increased with age group (p < 0.001), with 48.6% classified as severe among ≥70-year-olds. The median delay between onset and interview was 3–4 weeks longer in severe cases. Thirty-one children (47.0%) experienced moderate and 6 (9.1%) severe TBE. All but two of 66 children had biphasic courses; four required intensive care. A teenager was the most severely affected, requiring protracted inpatient care including intubation and remaining unable to sit up in bed without help after nine months (modified RANKIN scale[16] score = 5).

The clinical diagnoses categories ascertained in routine surveillance data (non-specific symptoms/meningitis/encephalitis/myelitis) were available in 398 of 581 cases (68.5%). Of these 398 cases, 361 (90.7%) were hospitalized, compared to 160 of the 183 remaining cases without study data on clinical diagnoses (87.4%, p_{Chi2}=0.229). CNS involvement was reported in only 56.3% of these 398 cases according to routine data, but was documented in 83.9% of these cases according to our study. There was little over-reporting of severity in routine data (21 cases (5.3%) without CNS involvement according to our study had CNS diagnoses in routine data). In contrast, we observed considerable underreporting in routine data (131 cases (32.9% of all cases; 75.3% of cases reported without CNS involvement) without CNS involvement in routine data, of whom 52 in fact had meningitis and 79 encephalitis/myelitis according to study data).

Clinical characteristics

A biphasic course was reported by 58% overall with a 7-day interval between phases (median; range = 1–33). Children more often experienced biphasic courses, with longer intervals (Table 1). As severity increased, biphasic courses were less common (72%/60%/42%, p_{trend} < 0.001).

The first, prodromal phase was characterized by fatigue (89.5%), fever (76.5%), headache (71.1%), myalgia (67.3%), and gastrointestinal symptoms (48.6%). Fever was more common in children (90.2% vs. 73.9%, p = 0.04), and myalgia in adults (71.6% vs. 45.1%, p < 0.001). In the second phase—or the only reported phase in monophasic courses—general, meningeal and neurological symptoms were frequently reported (Table 1). Sleep ratings worsened as severity increased (33.0%/45.5%/56.6% poor sleep, p_{trend} < 0.001).

Approximately 3 months after onset, 51% of cases reported persisting symptoms (RANKIN scores 1–5). The symptom-free proportion (RANKIN=0) decreased with severity (78.9%/46.9%/26.6%, p_{trend} < 0.001).

Health care utilization

Health care utilization was high overall with 90% requiring hospitalization (Fig. 3). The median interval between onset and hospital admission was 14 days (IQR = 5–20 days). In 2020, the first year of the COVID-19 pandemic, this interval was the same as in 2018–2019. Most cases were treated on neurological (58.4%), internal medicine (22.3%), or pediatric wards (10.0%). Duration of hospital stay increased with severity: (4.7/10.3/25.3 days, p < 0.001). Health care utilization increased markedly with age (Fig. 3). Neuroimaging and laboratory results are available in Appendix 6.

At the time of interview, 194 of 581 cases (33.4%) had already received rehabilitation; in 13.4% it was ongoing and 28.1% planned additional rehabilitation. Among those who had not received rehabilitation before the interview, this was planned for 33 cases (9%). Besides in-/outpatient rehabilitation, 28.3% of cases required additional physiotherapy, 12.7% occupational therapy and 2.9% speech therapy. Almost all employed cases (91%) required sick leave, on average 34 days beyond hospitalization. Of these, 34.4% were still on leave at interview. Of all cases, 33% received informal care by family members. Most parents (67.7%) missed work days to care for their child; the median duration was 7 days (range: 2–95 days).

Diagnosis and treatment

Half the cases (50.5%) reported receiving a diagnosis other than TBE initially. This occurred 10% more frequently in low-incidence than high-incidence districts (57.5% vs. 47.6%, p = 0.04). Children tended to be misdiagnosed more often than adults (62.9% vs. 49.0%, p = 0.13). Frequent initial diagnoses were influenza (35.0%), Lyme borreliosis (11.3%), gastrointestinal infection (8.5%), another viral infection (8.5%), and stroke (7.1%). In cases from 2020, 9% reported initial COVID-19 misdiagnoses.

Antibiotic prescription (in 63.4% of 571 cases with data) and antiviral treatment (aciclovir given in 53.5% of 381 cases with data)

Table 1
. Acute TBE manifestations in cases notified 2018–2020 in Bavaria and Baden-Wuerttemberg (n = 581). When the disease course was biphasic, only symptoms in the second phase are shown; for prodromal symptoms, see text.

Clinical characteristics and symptoms	0–17 years		18–64 years		65–90 years		p for difference
	n = 66		n = 394		n = 121		(bold if < 0.001)
Biphasic course	n	%	n	%	n	%	
Biphasic course*	54	82%	238	60%	45	37%	**< 0.001**
Interval between phases (days)*		9.7 (SD=4.8)		7.6 (SD=5.0)		8.6 (SD=6.1)	
General symptoms							
Fatigue	63	95%	384	97%	115	95%	0.450
Fever	65	98%	380	96%	110	91%	0.005
Myalgia[a]	53	80%	352	89%	99	82%	0.084
Gastrointestinal symptoms	58	88%	315	80%	95	79%	0.263
Bad sleep quality*	18	29%	184	48%	51	44%	0.040
Meningeal signs							
Headache	65	98%	383	97%	103	85%	**< 0.001**
Nuchal stiffness	45	68%	246	62%	44	36%	0.002
Light sensitivity	49	74%	216	55%	52	43%	0.002
Neurological symptoms							
Impaired balance	37	56%	328	83%	106	88%	**< 0.001**
Concentration deficit	34	52%	315	80%	93	77%	**< 0.001**
Memory deficit	16	24%	239	61%	87	72%	**< 0.001**
Impaired coordination (ataxia)	25	38%	215	55%	88	73%	**< 0.001**
Dysphasia (speaking)	11	17%	193	49%	74	61%	**< 0.001**
Impaired consciousness	28	42%	183	46%	81	67%	**< 0.001**
Tremor[b]	19	29%	183	46%	55	45%	0.099
Sensory impairment	12	18%	149	38%	37	31%	0.020
Pareses[c]	7	11%	87	22%	36	30%	0.049
Hearing impairment[d]	7	11%	78	20%	32	26%	0.073
Dysphagia (swallowing)	8	12%	35	9%	29	24%	**< 0.001**
Seizures	6	9%	39	10%	13	11%	0.586
Respiratory difficulty/paralysis	5	8%	4	1%	8	7%	0.003
Severity							
Mild	29	44%	81	21%	5	4%	**< 0.001**
Moderate	31	47%	251	64%	66	55%	
Severe	6	9%	62	16%	50	41%	
RANKIN score at interview*							
0: no symptoms	48	77%	180	46%	45	39%	**< 0.001**
1: no significant disability	12	19%	118	30%	40	35%	
≥2: slight disability, or worse	2	3%	82	21%	30	26%	

* n for sleep quality and RANKIN score = 62 cases aged 0–17, 381 cases aged 18–64, 115 cases aged 65–90.
[a] affected body parts: 63% legs, 50% arms, 46% back, 21% neck/shoulders, 10% entire body.
[b] affected body parts: 72% hands, 41% arms, 28% legs, 11% head/neck, 10% upper body, 4% voice.
[c] affected body parts: 66% arms, 54% legs, 38% facial muscles, 36% neck, 35% shoulders, 30% eye muscles, 9% respiratory paralysis.
[d] 63% sensitivity to sound, 55% hearing loss, 48% tinnitus.

were common. Cases with a GCS < 15 upon admission (16 (4.2%) of 381 cases with data) were more likely to receive the following medication than cases with a GCS of 15 (365 cases, 95.8%): antibiotics 94.1% vs. 66.4%, p = 0.02; antivirals (aciclovir) 75.0% vs. 52.6%, p = 0.08; neuroleptics (mainly pregabalin and levetiracetam) 25.0% vs. 8.5%, p = 0.03; glucocorticoids 27.3% vs. 5.1%, p = 0.002. This pattern was reversed for antipyretic and pain medication (mainly paracetamol, ibuprofen, and metamizole): 38.5% vs. 53.6%, p = 0.28). Six percent overall received various glucocorticoids, mostly prednisolone. Overall, almost two-thirds (63.4%) received antibiotics (adults: 65.4%, children: 48.5%, p = 0.007). Ceftriaxone was given most commonly (86.0%), followed by ampicillin (19.2%), and doxycycline (9.2%). According to patients, antibiotics were prescribed before TBE diagnosis in 73.7% and afterwards in 26.3%.

Factors associated with severe TBE

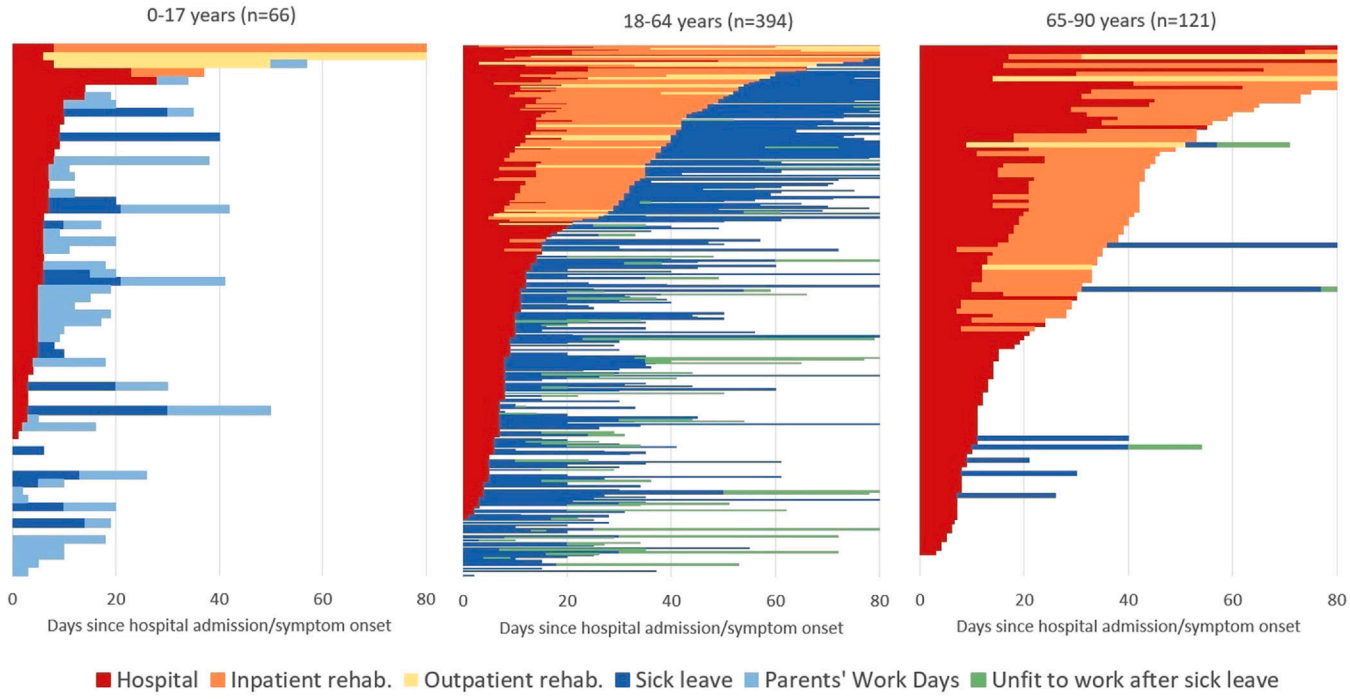
Severe acute TBE was associated with age, hypertension, and monophasic disease. CNS comorbidities and chronic-inflammatory comorbidities were weakly associated with severity (Fig. 4).

Discussion

This study contributes novel insights into clinical manifestations, factors associated with TBE severity, and health care utilization in 581 cases aged 2–89 years. Routine surveillance data poorly captured TBE severity and underreported the proportion of cases with CNS involvement. Study data documented meningitis, encephalitis, or myelitis for 84% of cases, far exceeding the ~50% reported with CNS involvement in routine data. Given that 80% of notified German TBE cases reported "without CNS involvement" are hospitalized,[4] it seems plausible that notification of CNS involvement is incomplete. Findings suggest that in fact > 80% of German cases experience CNS involvement and would thus also meet the European Union reference definition,[3,18] and only a small proportion < 20% experience mild, non-CNS febrile forms of TBE.

Of all cases, 20% were severe (children: 9%, ≥70 years old: 49%). In other studies, this proportion ranged from 15% to 68%,[10–12] placing our definition of severity on the restrictive end of the spectrum. Others usually defined severity based on diagnoses such as encephalitis,[11,12,19] while our definition considers health care utilization in addition to symptoms, thus more directly reflecting patient experience. Notably, we did not observe more severe disease among males with our method, contrasting our previous findings[4] based on surveillance data alone.

Every one-year age increase was associated with 4% higher odds of severe TBE, similar to previous reports.[10–12] Hypertension was associated with over twice the odds of severe TBE, which to our knowledge has not been described previously. Radzišauskienė et al.[12] identified comorbidities as a factor associated with severity, but did



	0-17 years	18-64 years	65-90 years	Total
n	66	394	121	581
Hospitalization	74.2%	89.8%	97.5%	89.7%
Days (SD)	7.0 (4.7)	11.2 (7.9)	17.6 (15.0)	12.3 (10.3)
ICU	8.2%	10.7%	25.4%	13.8%
Days (range)	9.0 (3-26)	5.9 (1-62)	5.6 (1-28)	6.0 (1-62)
Any rehabilitation	6.1%	32.5%	51.2%	33.4%
Weeks (range)	13 (2-33)	4.7 (1-24)	4.4 (2-20)	4.7 (1-33)
Sick leave	42.4%	74.6%	9.9%	57.5%
Days (range)	17.2 (3-87)	34.1 (1-207)	31.5 (6-68)	33.1 (1-207)
Unfit to work after sick leave	-	22.1%	-	-
Days (range)	-	24.3 (2-168)	-	-

Fig. 3. Health care utilization and sick leave in TBE cases by age group, n = 581. Each horizontal line represents one case. The first 80 days since hospital admission or, in non-hospitalized cases, since symptom onset, are shown. Data are sorted by the sum of hospital plus rehabilitation days. "Sick leave" = work days for adults, school days for children; both minus the days in hospital. "Unfit to work after sick leave" = unfit for usual work after sick leave ended. "Parents' Work Days" = days parents missed work to care for sick child. Rehabilitation in the table includes both inpatient and outpatient rehabilitation. The denominator for percentages is the column total, except intensive care (denominator: number hospitalized) and Unfit to work after sick leave (denominator: number on sick leave).

not analyze hypertension alone. CNS comorbidities were linked to severity, as in[12]. Lenhard et al.[10] reported male sex and diabetes as relevant in a smaller cohort, but this was not seen in our study or other, larger studies.[11,12]

Monophasic courses were observed more frequently (43%) than previously reported (23–28%),[1,19–21] and were associated with 50–70% higher odds of severe TBE both in our study and elsewhere.[10–12] This might be related to underlying, partly age-related immune responses or viral variants.[22]

Blood type plays a role in dengue fever severity,[13] but was not associated with TBE severity in our study. We did not observe higher severity in cases reporting removing large, fully engorged ticks, who had likely been attached longer and potentially transmitted a larger viral load.[14]

Children experienced considerable morbidity; 56% had moderate or severe TBE. Neurological symptoms were common, 78% were hospitalized and half the moderate/severe cases reported incomplete recovery. However, as severely ill children are more likely to be diagnosed and hence reported, the true proportion of mild TBE may be higher. It remains uncertain if biphasic courses are indeed predominant in children, as observed here and elsewhere,[9,21] or if "typical" biphasic courses are simply diagnosed more readily, see also.[23] The frequency of severe symptoms observed here exceeded that in other studies.[8,9] This could be due to under-recognition of mild cases in Germany or to inclusion of self-reported symptoms. The findings suggest that, first, clinicians should more readily consider TBE in children even without biphasic courses. Second, the common assumption among physicians and parents that TBE is always benign in children may be questioned. Given the low vaccination rates at school entry of around 35% in risk areas,[2,24] there is potential for prevention.

The observed high rate of initial misdiagnosis, more pronounced in children and low-incidence regions, suggests that diagnosing TBE is challenging and that awareness of current guidance[25] should be

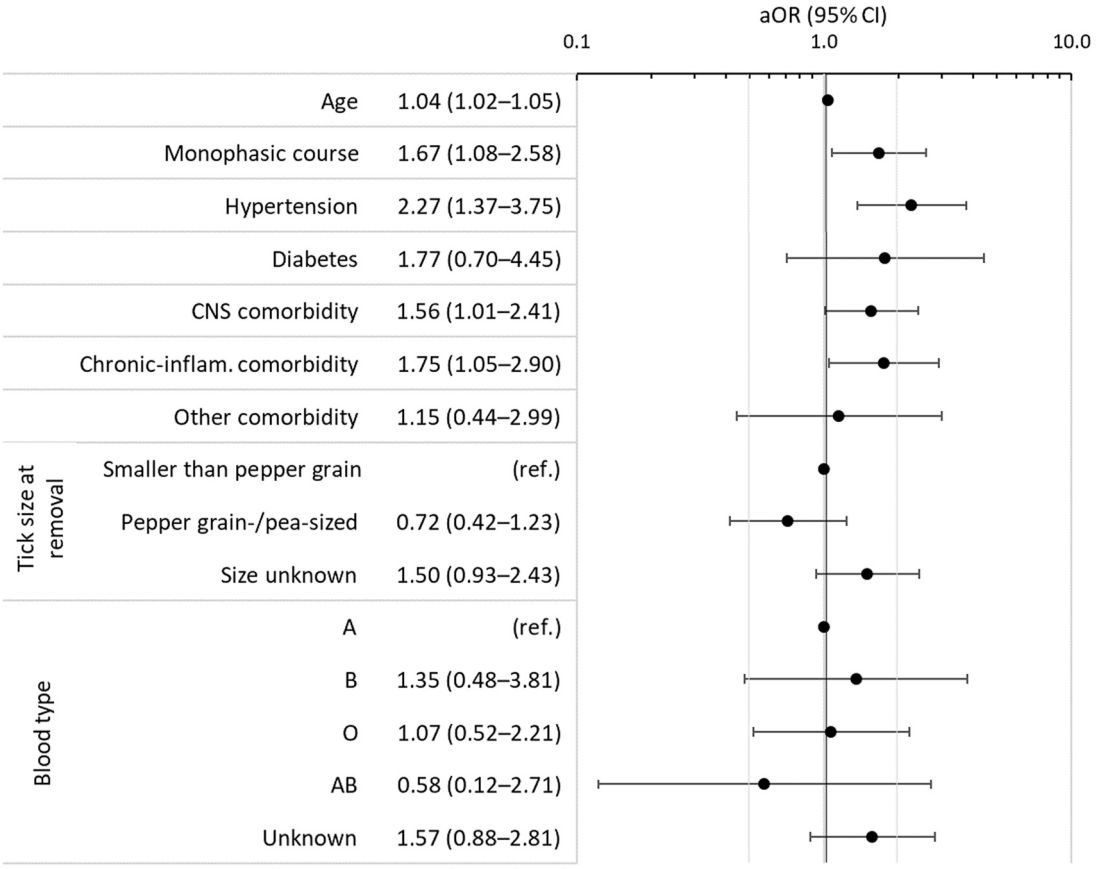


Fig. 4. Factors associated with severe acute TBE: results of logistic regression analyses. For unadjusted univariable estimators, see Appendix 4. aOR = adjusted odds ratio; CI = confidence interval; CNS comorbidity = comorbidities of the central and peripheral nervous system; (ref.) = reference group.

increased. Some diagnostic uncertainty related to TBE vaccinations or serological cross-reactivity with other flaviviruses[1] remained in > 11% of cases. Thus, increased diagnostic validation within routine surveillance is needed.

Antiviral use was in line with recommendations,[25] but 6% of cases received glucocorticoids, which are not recommended,[25] suggesting a need for higher awareness among clinicians. Confounding by indication seems to be present, as severity upon admission (GCS) was strongly associated with pharmacologic therapy. Thus, treatment effects cannot be rigorously studied in observational designs such as ours. Antibiotics were commonly prescribed, in contrast to Slovenian and Czech findings.[9,21] Antibiotics are often given early when diagnostic uncertainty is high and timely treatment is key until diagnoses such as bacterial meningitis are ruled out.[1,20] Cases however reported that 26% of antibiotics were prescribed *after* TBE diagnosis, although we could not verify this. Future research should elucidate if antibiotic overuse is present, as reported for other viral infections,[26] which would suggest a need for improved antimicrobial stewardship.

Approximately three months after onset 79% of mild, 47% of moderate and 27% of severe cases reported symptom resolution. A correlation of acute TBE severity with unfavorable outcomes was also observed in other studies.[19,20,27]

Limitations of our study firstly include delays in data collection. As severe cases provided data particularly late, differences between mild and severe cases regarding symptom resolution may be underestimated. Secondly, possible selection bias could only be assessed against routinely reported demographic and clinical data. No indications of selection bias were discernible, but we were unable to compare participants and non-participants regarding other characteristics, such as education and underlying health status. Thirdly, data were partly self-reported. This may explain the higher frequency of certain symptoms compared to previous reports.[20,28] However, possible inaccuracy, e.g., due to recall bias, was minimized by cross-validation with medical data.

Strengths firstly include the large sample size representative of TBE cases and clinical practices in Southern Germany, facilitated by case-centered rather than clinic-centered recruitment, and the high level of completeness across study components. Even with only 48% response, high external validity can be assumed, as key parameters were similar among participants and non-participants. Secondly, the inclusion of 10% non-hospitalized cases broadened the severity spectrum to more accurately identify factors associated with severity. Thirdly, we considered productivity losses in addition to symptoms to better capture the true—substantial—TBE burden.

Conclusion

Our study revealed potential deficits in current practices, including under-ascertainment of CNS symptoms in routine surveillance and diagnostic and therapeutic challenges. The observed high proportion of moderately or severely ill children (56%) is informative for physicians and parents remaining skeptical of TBE vaccinations in children. While we described factors associated with severity such as age and specific comorbidities like hypertension, it remains largely uncertain why some cases barely develop symptoms and others become severely ill. Therefore, the public health goal must be to improve prevention in endemic areas through increased TBE vaccine uptake.

Declaration of Competing Interest

None.

Acknowledgments

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Disclaimers

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.jinf.2023.02.018.

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