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## Tick-borne encephalitis in the Åland Islands, Finland: incidence and disease course since the implementation of a general TBE vaccination programme

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### ABSTRACT

Tick-borne encephalitis (TBE) is a potentially life-threatening viral disease with rising incidence in Europe. This retrospective study investigates the incidence, clinical course, and long-term outcome of TBE in Åland, a region endemic for the disease, following the introduction of a TBE vaccination programme in 2006. All patients diagnosed with TBE in Åland between 2006 and 2023, in accordance with the diagnostic criteria established by the European Centre for Disease Prevention and Control (ECDC), were included in the study. A review of medical records was conducted, and epidemiological and laboratory data were systematically collected. Disease severity and clinical outcome were assessed. TBE was diagnosed in 145 patients (66% male; median age 53 years; 10% children <18 years). The median TBE incidence was 29/100,000/year. Primary care was the first point of contact in 48% of cases. Of all patients, 72 (50%) were unvaccinated, 46 (32%) incompletely vaccinated and 20 (14%) completely vaccinated. Fifty-seven (39%) were diagnosed with meningitis and 88 (61%) with meningoencephalitis. Overall, 117/145 (81%) patients were hospitalized and 13/145 (9%) required intensive care. Severity of disease correlated with increasing age. Two fatalities occurred. Unlike neighbouring regions, Åland did not experience an increase in TBE incidence, likely due to the implementation of the vaccination programme. Most disease courses were monophasic and occurred in unvaccinated individuals. Surprisingly, a significant number of breakthrough infections were observed, particularly among those with incomplete vaccination, who more frequently developed severe disease. However, at two-year follow-up, 86% of patients were considered clinically recovered.

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**KEYWORDS** Tick-borne encephalitis; Åland; severity; vaccination status; disease course; Finland; breakthrough infection; sequelae

### Introduction


Tick-borne encephalitis (TBE), caused by the TBE virus (TBEV), is one of the most serious tick-transmitted diseases. It is an emerging zoonotic infection in Europe [1–7], with more than 10,000 cases annually. Three main subtypes of TBEV, the European (TBEV-Eu), Siberian (TBEV-Sib), and Far Eastern (TBEV-Fe), are known to be human pathogens and their transmission to humans mainly occurs via *Ixodes* ticks [8]. Recently two further subtypes, Himalayan and Baikalian, have been identified and isolated in human cases of TBE [9]. Both the TBEV-Eu and TBEV-Sib subtypes have been identified in Finland, in *Ixodes ricinus* and *Ixodes persulcatus* ticks and in human post-mortem brain tissue samples [10,11]. Most individuals infected by TBEV are asymptomatic but develop TBE-specific antibodies [12–16]. If

symptoms arise, the typical disease course is biphasic. A symptomatic infection presents after an incubation period of 2–28 days, with a 2–8-day non-specific, febrile illness (first phase) [17]. In a portion of the patients, a short asymptomatic period is followed by a symptomatic disease progression (second phase), leading to meningitis, meningoencephalitis, or rarely, meningoencephalomyelitis, with mortality rates of 0.5–2.0% in infections caused by TBEV-Eu/Sib [2,8,18,19]. Up to 50% of TBE cases result in mild to disabling long-term sequelae [20].

The diagnostic criteria for TBE, according to the European Centre for Disease Prevention and Control (ECDC) and intended for epidemiological surveillance, are based on clinical symptoms, most often manifested as a two-phased illness, and laboratory confirmation, e.g. the detection of TBEV-specific IgM and IgG

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antibodies in serum and/or TBEV-specific IgM antibodies in the cerebrospinal fluid (CSF) [2,21]. According to the ECDC case definition, lumbar puncture is not mandatory; therefore, the assessment of central nervous system involvement relies on clinical symptoms rather than laboratory confirmation. In line with this, several studies on TBE have also included patients lacking laboratory confirmation based on cerebrospinal fluid analysis [22,23].

TBE is a viral infection lacking specific treatment. However, effective vaccines against the disease have been available for decades in Europe [24,25].

The Åland Islands, with a population of 31,000 and located in the Baltic Sea on the southwest coast of Finland, is an endemic area for tick-borne diseases [21,26]. TBE, locally also known as Kumlinge disease, was first observed in the 1940s on Kumlinge Island, in the Åland archipelago, and the TBE virus was isolated in the same region in 1959 [27]. Until 2004, TBE infections in Åland represented the majority of all Finnish TBE cases. This led to the launch of a general vaccination programme (described in Supplementary S1) in Åland in 2006, offering three free doses to both children and adults residing on the islands. During 2019–2023, a clear change in Finnish TBE transmission sites was noted, when approximately 90% of all TBE infections were observed in mainland Finland [28]. Nevertheless, during the last two decades, the incidence of TBE in Åland has been persistently high, ranging from 7 to 76/100,000 persons/year.

Thus, TBE still poses a health threat, despite the possibility of free immunization. Wahlberg et al. [29] described the epidemiology and clinical course of TBE in Åland during 1959–2005, prior to the introduction of the vaccination programme. A marked increase in incidence was observed after 2000, reaching 70 cases per 100,000 annually during 2000–2005. No follow-up studies have been conducted since. This study aims to describe the incidence, clinical features, disease severity, diagnostic challenges, and outcomes of TBE in Åland from 2006 to 2023, following the implementation of free vaccination.

## Materials and methods

### Identification of cases

Patients were initially identified through microbiological laboratory findings, followed by a detailed review of their medical records by clinicians experienced in tick-borne infections. Patients in Åland with findings of TBEV-specific IgM antibodies (serum and/or CSF) between years 2006 and 2023 ( $N = 173$ ) were assessed according to ECDC criteria: clinical symptoms of central nervous system (CNS) involvement (for example, meningitis, meningoencephalitis, encephalomyelitis, encephaloradiculitis) and either

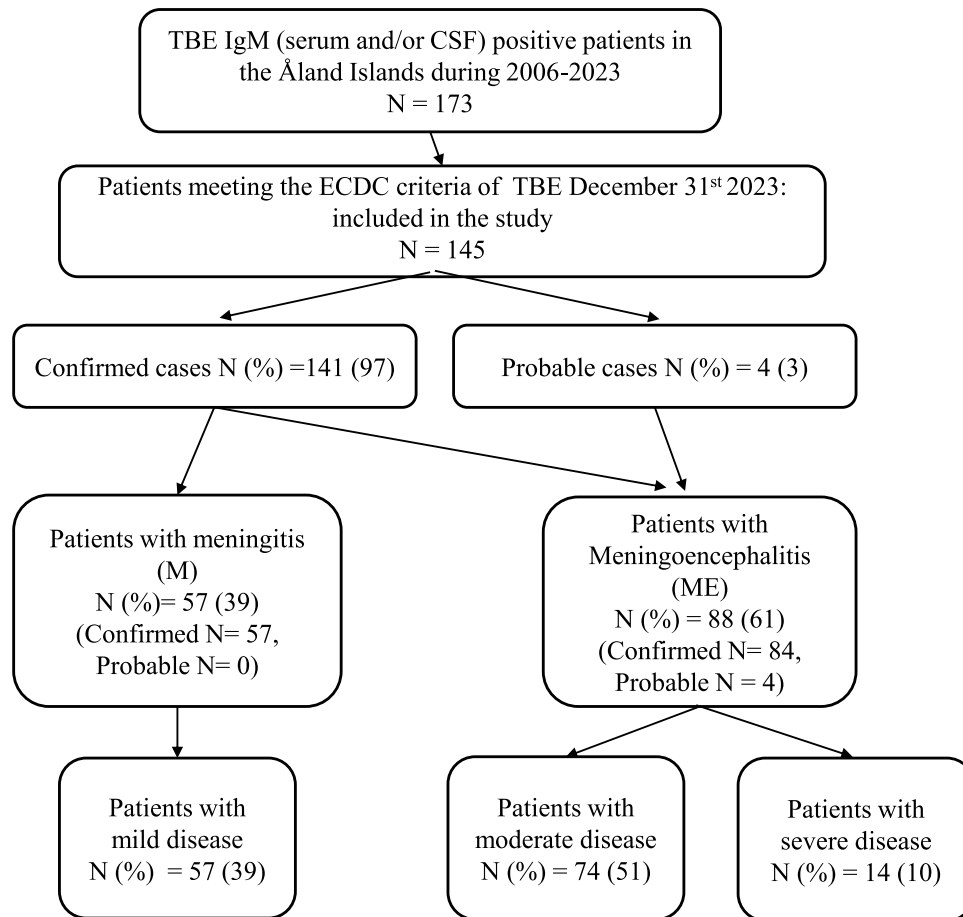
TBEV-specific IgM and IgG antibodies in serum, or IgM antibodies in CSF [2,21,30]. Details on laboratory methodology are provided in Supplementary, S2. Pleocytosis was supportive of a TBE diagnosis but did not constitute an inclusion criterion. Assays based on the detection of TBEV RNA were not in clinical use in Åland at the time of inclusion; therefore, all microbiological diagnostics were based on serology. Clinical and laboratory criteria were met by 145 patients who were included in the study (Figure 1). Symptoms associated with meningitis or meningoencephalitis are listed in Supplementary, S1. In this study cohort, a confirmed case was defined by the presence of TBEV-specific IgM and IgG antibodies in serum, IgM antibodies in CSF, and/or seroconversion in paired serum samples. A probable case was defined by the presence of TBEV-specific IgM antibodies in serum alone. The course of acute disease was further classified as mild, moderate, or severe. All meningitis patients were classified as mild, in line with earlier studies [23]. Patients with encephalitic symptoms were classified as moderate or severe depending on the level of care. Patients in need of intensive care were classified as severe, as well as patients with mortal outcome, regardless of the care level. This classification was applied due to the retrospective study design, in which the required level of care was considered the most reliable surrogate marker for symptoms classified as severe, e.g. multifocal symptoms and/or altered consciousness [23].

Patients who had not received any vaccine against TBE were classified as unvaccinated. Patients with incomplete vaccination had either received less than three doses or not received the recommended booster doses, according to the national guidelines by the Finnish Institute for Health and Welfare (THL), Supplementary, S1. Patients with complete vaccination had received a full initial three-dose vaccination series and when needed, recommended boosters, in line with the current TBE vaccination programme. The occurrence of TBE in patients with either complete or incomplete vaccination was referred to as a breakthrough infection.

### Follow-up and assessment of outcome

Åland-resident patients were included in the follow-up cohort. Medical records from the hospital and primary care were examined. The follow-up time was set to 2 years from acute disease. Follow-up varied between patients and during the study period, due to revised medical protocols. The total follow-up period was divided into shorter follow-up intervals of one–three, three–six, six–twelve and twelve–24 months, respectively.

Sequelae were determined based on the patient's subjective symptoms and the physician's medical



**Figure 1.** Flow chart, study inclusion and distribution of patients by disease severity.

assessment (appointment or phone interview) during each follow-up interval. The main sequelae were divided into five groups: (1) fatigue; (2) headache; (3) cognitive dysfunction; (4) vertigo and balance difficulties; and (5) ataxia, tremor and/or neurological dysfunction (Supplementary, S2).

### Statistical analysis

The statistical calculations were performed with the IBM SPSS ver. 29.0.2.0 for Windows software. Differences between patient groups were analysed with the Mann-Whitney *U*-test for continuous variables and with Fisher's exact test or Pearson's chi-square test for categorical variables. Kruskal-Wallis and Fisher's exact test were used when differences between three or more groups were analysed. Differences with  $p < 0.05$  were deemed statistically significant.

## Results

### Epidemiological and demographic data, including vaccination status

Between 2006 and 2023, 145 patients were diagnosed with TBE in Åland. The median number of yearly cases was eight, ranging from two to 23 cases per year (Figure 2). This number is equivalent to 29/

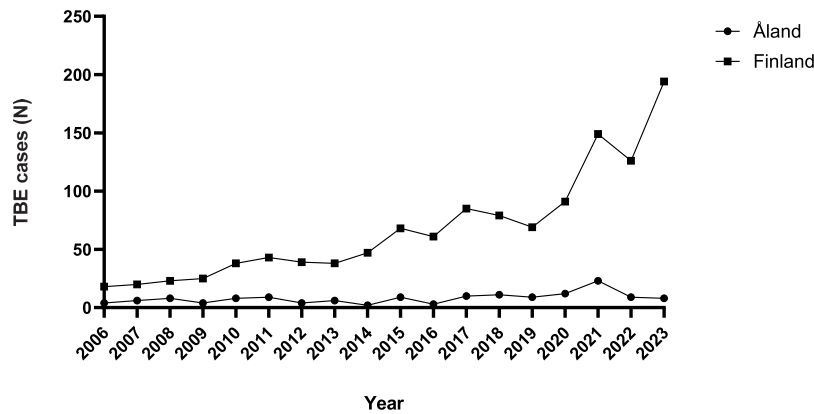
100,000 persons/year for the entire period. The highest incidence was seen in the summer and autumn, with a peak in September (Figure 3).

Of the included patients, 14/145 (9.7%) were under the age of 18 years. The median age did not differ significantly between genders. A history of a recent tick bite was reported by 91/145 (62.8%).

Seventy-two (49.7%) patients were unvaccinated, 46 (31.7%) had received an incomplete vaccination, and 20 (13.8%) were completely vaccinated. For seven patients, the vaccination status could not be retrieved. At the time of infection, 13/145 (9%) patients were immunosuppressed by a previously diagnosed condition and/or immunosuppressive treatment (Table 1 and Supplementary, S3). Of the immunosuppressed patients, 6/13 (46%) were unvaccinated, 4/13 (31%) incompletely vaccinated and 1/13 (8%) had received a complete vaccination series. The vaccination status did not differ significantly from that observed in the overall study cohort.

### Clinical course in the acute phase

Symptoms in the acute phase were defined as symptoms occurring from symptom onset up to one month, including monophasic and biphasic disease courses (Supplementary, S2).



**Figure 2.** Annual number of TBE cases reported in Åland ( $N = 145$ ) and in Finland overall ( $N = 1213$ ) during 2006–2023.  $N$ ; number.

Of the 145 patients, 57 (39.3%) presented with meningitis and 88 (60.7%) with meningoencephalitis. No cases of myelitis or radiculitis were observed. Fifty-seven (39.3%) patients were classified as having mild disease, 74 (51.0%) as moderate, and 14 (9.7%) as severe. A biphasic disease course was observed in 54 patients (37.2%), while a monophasic course was reported in 91 patients (62.8%).

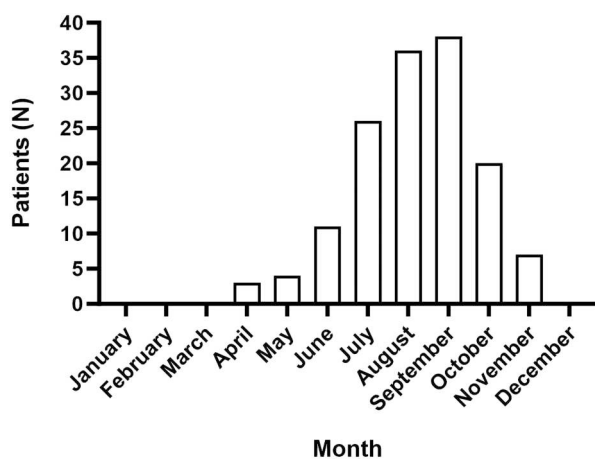
The initial healthcare contact for 70 (48.3%) patients occurred at a primary care facility. In contrast, 72 patients (49.7%) first sought care at an emergency department. Despite this, 117 (80.7%) patients were eventually hospitalized. The length of hospitalization varied, with a median of eight days, and a maximum of 131 days. Thirteen (9%) patients needed intensive care, two of whom needed mechanical ventilation. Brain imaging and EEG were performed in 63 (43.4%) and 16 (11%) patients, respectively. Two fatal cases occurred.

### Characteristics of mild, moderate, and severe disease

Increasing age was significantly associated with severity of disease ( $p = 0.005$ ). The median age for mild disease was 47 years; for moderate disease, 54 years; and

for severe disease, 66 years. No patient under the age of 18 years had a severe disease course. Gender did not affect disease severity.

Among patients with severe disease, 8/14 (57%) had incomplete vaccination, 1/14 (7%) had completed vaccination, and 4/14 (29%) were unvaccinated; vaccination status was unknown for one patient. A significant association between incomplete vaccination and severe disease was observed ( $p = 0.03$ ). Overall, 13/145 (9%) patients were immunosuppressed due to disease and/or medication, of whom three had mild disease, five had moderate disease, and five had severe disease. Of all patients with mild, moderate and severe disease, 5.3%, 6.8% and 36%, respectively, were immunosuppressed. Immunosuppression was significantly associated with severe disease ( $p = 0.007$ ). A biphasic disease course was significantly more common in patients with mild disease (51%,  $p = 0.02$ ) compared to those with moderate (30%) or severe disease (21%). During the study period, two fatal outcomes were observed, resulting in a fatality rate of 1.4%. However, TBE was registered as the primary cause of death in only one patient. Both deceased individuals were male and over 60 years of age. Neither patient was immunosuppressed by medication; however, one had a history of malignancy, and both had pre-existing comorbidities. One was unvaccinated, and the other had incomplete vaccination. Following enrolment, the disease trajectories of the two patients diverged markedly. One patient was hospitalized less than one week prior to death, while the other required prolonged hospitalization, including intensive care and mechanical ventilation.



**Figure 3.** Month of the year in which TBE diagnoses were established ( $N = 145$ ).  $N$ ; number.

### Blood and CSF findings

Routine serum and CSF sampling in the acute phase of disease varied, due to individual assessments and level of care. Plasma C-reactive protein (CRP) was analysed in 142/145 (98%) patients with a median level of 3.8 mg/L (IQR, 1–13 mg/L). Patients with meningoencephalitis had significantly ( $p = 0.002$ ) higher CRP

**Table 1.** Demographic characteristics, vaccination status, and clinical features of the acute disease course among patients in the study cohort ( $N = 145$ ).

	All patients $N = 145^{\wedge}$	Meningitis $N = 57$	Meningoencephalitis $N = 88$	$p$ -value
Age years, median (IQR)	53 (35–66)	44 (29–60)	53 (40–87)	<b>0.011</b>
Female $N = 50$ , median (IQR)	49 (33–66)	48 (27–60)	54 (36–68)	0.447
Male $N = 95$ , median (IQR)	54 (32–66)	44 (30–59)	58 (45–67)	<b>0.009</b>
Children <18, $N$ (%)	14 (10)	7 (12 <sup>#</sup> )	7 (8 <sup>#</sup> )	
Gender Male, $N$ (%)	95 (66 <sup>#</sup> )	38 (67 <sup>#</sup> )	57 (65 <sup>#</sup> )	0.859
Female, $N$ (%)	50 (35 <sup>#</sup> )	19 (33 <sup>#</sup> )	31 (35 <sup>#</sup> )	
Vaccination status :	72 (50 <sup>#</sup> )	37 (65 <sup>#</sup> )	35 (40 <sup>#</sup> )	<b>0.021</b>
Unvaccinated, $N$ (%)	46 (32 <sup>#</sup> )	11 (19 <sup>#</sup> )	35 (40 <sup>#</sup> )	
Incomplete vaccination, $N$ (%)	20 (14 <sup>#</sup> )	6 (11 <sup>#</sup> )	14 (16 <sup>#</sup> )	
Complete vaccination, $N$ (%)	7 (5 <sup>#</sup> )	3 (5 <sup>#</sup> )	4 (5 <sup>#</sup> )	
Unknown vaccination, $N$ (%)				
Immunosuppression*	13	3 (23)	10 (77)	0.249
$N$ (% within immunosuppressed patients)				
First care facility:	72 (50 <sup>#</sup> )	22 (39 <sup>#</sup> )	50 (57 <sup>#</sup> )	0.16
Emergency department, $N$ (%)	70 (48 <sup>#</sup> )	35 (61 <sup>#</sup> )	35 (40 <sup>#</sup> )	
Primary care, $N$ (%)	3 (2 <sup>#</sup> )	0 (0 <sup>#</sup> )	3 (3 <sup>#</sup> )	
Other, $N$ (%)				
Inpatient care, $N$ (%)	117 (81 <sup>#</sup> )	42 (74 <sup>#</sup> )	75 (85 <sup>#</sup> )	0.131
Intensive care, $N$ (%)	13 (11 <sup>#</sup> )	0 (0 <sup>#</sup> )	13 (18 <sup>#</sup> )	<b>0.002</b>
Duration of hospitalization in days, median (IQR)	$N = 112$ 8 (6–15)	7 (4–9)	10 (7–19)	<b>&lt;0.001</b>
Biphasic disease course, $N$ (%)	54 (37 <sup>#</sup> )	29 (51 <sup>#</sup> )	25 (28 <sup>#</sup> )	<b>0.008</b>
Lumbar puncture performed, $N$ (%)	114 (79 <sup>#</sup> )	35 (61 <sup>#</sup> )	79 (90 <sup>#</sup> )	<b>&lt;0.001</b>
Head CT/MRI performed, $N$ (%)	63 (44 <sup>#</sup> )	15 (26 <sup>#</sup> )	48 (55 <sup>#</sup> )	<b>&lt;0.001</b>
EEG performed, $N$ (%)	16 (11 <sup>#</sup> )	0 (0 <sup>#</sup> )	16 (18 <sup>#</sup> )	<b>&lt;0.001</b>

Note: CT; Computed tomography. MRI, magnetic resonance imaging. EEG, electroencephalogram. The bold  $p$ -values indicate significant differences between meningitis and meningoencephalitis patients. IQR; interquartile range.

\*Through disease or immunosuppressive therapy.

<sup>#</sup>% within column (all patients, patients with meningitis or meningoencephalitis).

<sup>^</sup>Total  $N$  if not otherwise stated.

<sup>^</sup>Unvaccinated (no TBE vaccine doses received); incomplete vaccination (fewer than three doses or booster doses overdue according to Finnish Institute for Health and Welfare [THL] recommendations); complete vaccination (three doses and when required recommended boosters administered in accordance with THL guidelines).

levels (median, 6.6 mg/L; IQR, 2–20) than patients with meningitis (median, 2.2 mg/L; IQR, 1–6).

The plasma sodium levels were analysed in 138/145 (95%) patients, with a median of 136 mmol/L (IQR, 134–139), without significant differences between patients with meningitis or meningoencephalitis. Hyponatremia (sodium <137 mmol/L) was seen in 71/138 (51%) patients.

Lumbar puncture was performed on 114/145 (78.6%) patients. In patients aged <18 years, lumbar puncture was performed in only 57% of the cases. Pleocytosis (CSF leucocyte count  $\geq 5 \times 10^6/L$ ) was seen in 104/114 (91%) patients. The median CSF leucocyte count was  $48 \times 10^6/L$  (IQR, 17–93), mononuclear cells predominated in 91/104 (88%) cases. CXCL13 levels were analysed in 75 CSF samples (72%), with a median of 22.0 pg/mL (IQR 0–67).

### Characteristics of patients with vaccination breakthrough infections

Vaccination status was known for 138/145 (95%) patients. Median age was highest among completely vaccinated, followed by those with incomplete vaccination. The incompletely vaccinated were significantly ( $p = 0.002$ ) more likely to have a severe disease course in the acute phase compared to the unvaccinated

group. Among patients with a history of complete vaccination, no correlation with severe disease was observed (Table 2).

The CSF cell count and CRP levels did not differ significantly between the vaccination groups.

In the initial serum sample, IgM antibodies were undetectable or indeterminate in twelve patients (18%) who had received complete or incomplete vaccination, compared to five patients (7%) in the unvaccinated group. Although IgM antibodies were detectable in most patients during follow-up sampling, one fully vaccinated patient remained IgM-negative twelve days after the initial sample. In this case, the diagnosis was ultimately confirmed by a significant IgG antibody elevation (Supplementary Table, S4).

### Long-term outcome

Sequelae were defined as symptoms persisting from one month post-onset of the disease through the end of the two-year follow-up period and categorized into five groups: fatigue; headache; cognitive dysfunction; vertigo and/or balance difficulties and ataxia; tremor and/or neurological dysfunction. Six/145 (4%) patients were non-residents and therefore lost to follow-up. For 20/145 (14%) local patients, no follow-

**Table 2.** Patient characteristics with regard to vaccination status<sup>a</sup> (N = 145).

	All patients N = 145	Complete vaccination N = 20	Incomplete vaccination N = 46	Unvaccinated N = 72	Unknown N = 7	p-value
Gender:						0.192
Male, N (%)	95 (66)	12 (60 <sup>^</sup> )	32 (70 <sup>^</sup> )	49 (68 <sup>^</sup> )	2 (29 <sup>^</sup> )	
Female, N (%)	50 (35)	8 (40 <sup>^</sup> )	14 (30 <sup>^</sup> )	23 (32 <sup>^</sup> )	5 (71 <sup>^</sup> )	
Age, median (IQR)	53 (35–66)	59 (10–82)	58 (5–86)	43 (4–84)	64 (24–76)	<0.001
Immunosuppression, N (%)	13 (9)	1 (5 <sup>^</sup> )	4 (9 <sup>^</sup> )	6 (8 <sup>^</sup> )	2 (29 <sup>^</sup> )	0.290
Disease severity, N (%):						<b>0.012</b>
Mild	57 (39)	6 (30 <sup>^</sup> )	11 (24 <sup>^</sup> )	37 (51 <sup>^</sup> )	3 (43 <sup>^</sup> )	
Moderate	74 (51)	13 (65 <sup>^</sup> )	27 (59 <sup>^</sup> )	31 (43 <sup>^</sup> )	3 (43 <sup>^</sup> )	
Severe	14 (10)	1 (5 <sup>^</sup> )	8 (17 <sup>^</sup> )	4 (6 <sup>^</sup> )	1 (7 <sup>^</sup> )	
Fatal outcome, N %	2	0	1	1	0	
Inpatient care, N (%)	117 (81)	17 (85 <sup>^</sup> )	39 (85 <sup>^</sup> )	54 (75 <sup>^</sup> )	7 (100 <sup>^</sup> )	0.358
Intensive care, N (%)	13 (11)	1 (6 <sup>^</sup> )	7 (18 <sup>^</sup> )	4 (7 <sup>^</sup> )	1 (14 <sup>^</sup> )	0.337
Duration of hospitalization in days, median (IQR)	8 (6–15)	11 (5–17)	12 (7–23)	7 (5–10)	9 (4–10)	<b>0.027</b>
Symptoms, N (%):						
Fever	129 (89)	15 (75 <sup>^</sup> )	41 (89 <sup>^</sup> )	66 (92 <sup>^</sup> )	7 (100 <sup>^</sup> )	0.193
Headache	107 (74)	14 (70 <sup>^</sup> )	35 (76 <sup>^</sup> )	54 (75 <sup>^</sup> )	4 (57 <sup>^</sup> )	0.687
Gastrointestinal dysfunction*	85 (59)	11 (55 <sup>^</sup> )	24 (52 <sup>^</sup> )	45 (63 <sup>^</sup> )	5 (71 <sup>^</sup> )	0.648
Balance and coordination difficulties	39 (27)	9 (45 <sup>^</sup> )	16 (35 <sup>^</sup> )	27 (38 <sup>^</sup> )	3 (43 <sup>^</sup> )	0.859
Cognitive impairment	15 (10)	3 (15 <sup>^</sup> )	21 (46 <sup>^</sup> )	13 (18 <sup>^</sup> )	2 (29 <sup>^</sup> )	<b>0.006</b>
Nerve dysfunction <sup>#</sup>		5 (25 <sup>^</sup> )	6 (13 <sup>^</sup> )	3 (4 <sup>^</sup> )	1 (14 <sup>^</sup> )	<b>0.023</b>

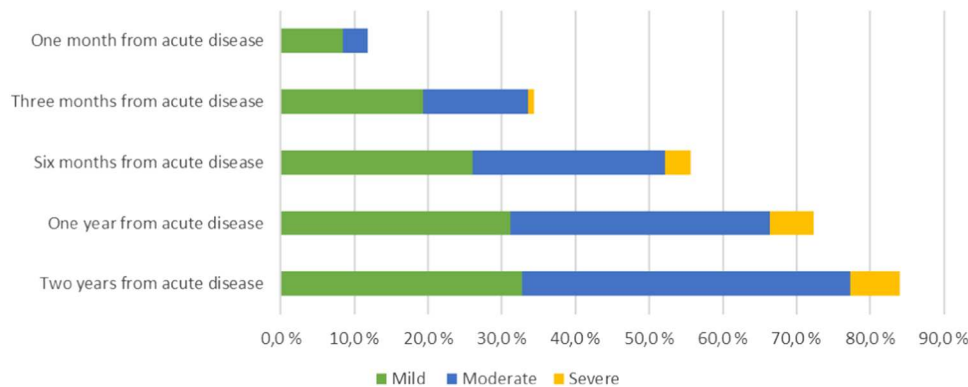
Note: IQR; interquartile range.

<sup>a</sup>Unvaccinated (no TBE vaccine doses received); incomplete vaccination (fewer than three doses or booster doses overdue according to Finnish Institute for Health and Welfare [THL] recommendations); complete vaccination (three doses and when required recommended boosters administered in accordance with THL guidelines).

\*Nausea, vomiting, and/or loss of appetite.

<sup>#</sup>Weakness in the extremities, cranial nerve paresis, ataxia.

<sup>^</sup>% within vaccination status group.



**Figure 4.** Recovery rate at five time points during the 2-year follow-up period (total N = 119). The different colours indicate patients' disease severity during the acute phase. N; number.

up after acute disease was carried out, most likely due to mild disease. Two patients had a fatal outcome related to TBE. Follow-up for 117/119 resident patients with known outcomes was conducted by physicians either at the department of internal medicine or within primary health care through telephone consultations or scheduled appointments (Figure 4). At the two-year follow-up, sequelae were identified in twelve patients in addition to the two with fatal outcomes. An additional five patients reported ongoing symptoms; however, these were deemed likely to be attributable to pre-existing comorbid conditions. Of the 119 follow-up patients, 19 (16%) had some remaining symptoms at the conclusion of the two-year follow-up period (Figure 4). When the 20

residents without follow-up were also considered recovered, 86% of patients were classified as recovered two years after the acute disease. Eighty-seven/145 (60%) patients were of working age, 76/87 (87%) of whom were known to require medical leave due to the TBE infection. Information regarding the need for medical leave was missing for four patients, and the duration was missing for an additional two. Among working-aged patients with known durations of medical leave, twelve patients/74 (16.2%) required a leave shorter than one month. The duration of medical leave for subsequent patients was one to three months for 34/74 (45.9%), three to six months for 13/74 (17.6%), six to twelve months for nine/74

(12.2%), and more than one year for 6/74 (8.1%) patients.

## Discussion

This is the first study to describe the epidemiology and clinical course of TBE in Åland since the implementation of a TBE vaccination programme in 2006. As of the beginning of the twenty-first century, a considerable increase in the number of TBE cases has been noted in Finland and Europe. However, a corresponding increase in TBE incidence has not been observed in Åland. The anticipated decline in TBE incidence, previously observed in other European regions following the implementation of vaccination programmes, is notably absent in this context [31,32]. Increased awareness of TBE in Åland, driven by vaccination programme-related information campaigns, education of healthcare workers, and public media outreach, may explain why no notable decline in reported cases has been observed. Moreover, during the study period, TBE serology, which had previously been performed in Helsinki, was transferred to Åland, and rapid TBE IgM diagnostics became available. In addition, the development of TBEV PCR and NS1 serology for clinical use was also initiated in Finland. Nevertheless, based on the increased incidence in neighbouring areas, we believe that general vaccination has had a positive impact on preventing TBE also in Åland. Unfortunately, the available data on vaccination coverage within the Åland population are limited. However, it is known that by the end of 2005, approximately 20% of Åland residents had received at least one dose of the vaccine [29], compared to approximately 70% in 2013 [33]. In addition, the general vaccination programme resulted in a TBEV IgG seroprevalence of 88% among adults in Åland in 2018 (Nyman, D., unpublished work). Also, in blood donors in Åland, studied between 1995 and 2018, the proportion of TBE-vaccinated donors increased from 2.7% to 81% [34]. Nevertheless, a reliable analysis of vaccine efficacy is not feasible with the data currently available.

The epidemiology, symptoms, and clinical signs of TBE in Åland have not significantly changed over time [29]. The disease is still more prevalent in older age groups and among men, and most cases are diagnosed between June and October, with fever and headache being the most prevalent symptoms. In Finland, the geographic spread of the TBEV-Sib has been documented over recent decades. Still, the consistent patterns in both acute and long-term outcomes of TBE observed in Åland suggest that TBEV-Sib has not yet become a significant concern in this region. Overall, the findings of this study align with previous research regarding the clinical outcome of TBE. A more severe disease was seen in older patients and those with a

monophasic disease course [18,35–37]. Severe cases were also more likely to have higher plasma CRP levels [18,37]. In contrast to many previous studies, all cases were classified as either meningitis or meningoencephalitis. Patients with myelitis, which often constitutes up to 10% of all cases, were not observed in this cohort [30,39,40]. Yet studies on TBE are often difficult to compare, owing to a lack of consensus regarding case definitions, inclusion criteria, and definitions of disease severity. Many studies have included only patients with pleocytosis, which requires a lumbar puncture. Such a proceeding may result in a selection bias, overlooking milder, quickly resolving cases and infections in children.

Studies on TBE have most likely underestimated the number of infections and overestimated the severity, as testing has been more commonly performed in patients with severe disease. Conversely, in this study, the diagnoses for 41 patients were based solely on serum serology in combination with the clinical presentation, as no lumbar puncture was performed. Consequently, microbiological confirmation of CNS involvement was not achievable. Although lumbar puncture remains the gold standard for diagnosing CNS infections, it is not always performed in clinical practice in Åland when no clear medical indication is perceived – even when CNS symptoms and the suspicion of TBE are present.

The present study aimed explicitly to present the complete and verified picture of TBE in Åland, an isolated archipelago, where medical professionals, as well as the public, are highly aware of the disease. In this context, a suspicion of TBE is frequently raised in primary care, where serum TBEV IgM antibody testing may be conducted— even in mild cases. Lumbar puncture is essential first and foremost in patients presenting with encephalitic symptoms, both for diagnostic confirmation and to exclude differential diagnoses. In the present study, lumbar puncture was not performed in 21% of cases due to a milder clinical presentation, diagnosis established in primary care settings, and owing to medical contraindications.

What distinguishes TBE cases in Åland from the typical TBEV-Eur disease presentation is the low number of patients with a biphasic disease course. In fact, <50% of the cases had a biphasic course of disease. Many previous studies have reported a biphasic disease course for 60% to 87% of all TBE cases [18,19,41]. Nevertheless, a recent Norwegian study [22] also reported biphasic disease, albeit at a lower rate of 53.3% of all cases. A substantial proportion of monophasic disease presentations was observed in Åland even prior to the implementation of the general vaccination programme, with 51.2% of TBE patients on Åland between 1959 and 2005 presenting with a biphasic course of illness [29]. The retrospective design of this study may have influenced the findings due to potential recall bias and limitations in the

completeness of patient histories. Due to the retrospective design, vaccination data also relied mostly on anamnestic data, and the exact time from the last vaccine dose was not available.

A more unexpected finding was the high number of breakthrough infections. More than 45% of all the patients had been either completely or incompletely vaccinated against TBE. One explanation is that good vaccine coverage alone decreases the total number of cases, such that the relative incidence of vaccine breakthroughs increases. However, many studies have described vaccine breakthrough infections as rare events [42,43]. The cohort in this study is not large enough to draw far-reaching conclusions about breakthrough cases, although an association was observed between severe disease and vaccination [35,43,44]. Earlier studies have made suggestions, later disputed [45], that breakthrough infections are more likely to be severe. A recent Austrian study reported a higher proportion of severe TBE among vaccinated individuals, attributing this not to low field effectiveness but to the insufficient protection against severe disease [46]. In this study, such an association was not seen for patients with complete vaccination, i.e. true breakthrough infections. However, in many previous studies, complete and incomplete vaccinations are not always clearly distinguished, or only complete vaccination is considered. If incomplete vaccination is identified as a risk factor for severe TBE, efforts should focus on improving adherence to the vaccination programme. In Finland, in areas in which general vaccination is implemented, the government offers three cost-free vaccination doses, and the subsequent doses are self-funded. The risk with this approach is that the citizens interpret three vaccine doses as sufficient for life-long protection against TBE.

The high number of breakthrough infections also represents a general challenge for TBE diagnostics. We know that the seroreactivity of previously TBE vaccinated patients differs from that of non-vaccinated, mainly with respect to the absence of IgM antibody production early in the disease course [13,47,48]. This pattern was also observed in this study. However, five non-vaccinated patients were also initially IgM negative. Interestingly, previous observations have shown that disease caused by TBE-Sib may initially present without detectable IgM antibodies [10]. However, virus strain typing was unfortunately not feasible at the time of patient inclusion, and this interpretation therefore remains speculative in the context of the present study. Therefore, clinicians relying on traditional whole virus IgM and IgG antibody detection face new challenges in interpreting the serological results in a vaccinated population. The use of NS1 serology, a recent addition to the TBE diagnostics assay panel, may also offer diagnostic support in previously vaccinated patients by only being reactive in true infection

and not following vaccination [49–52]. However, for patients in this study, the assay was not yet available in clinical routine.

TBE is often presented as a disease with long-lasting morbidity [53–56]. In the present study, sequelae differed dramatically among patients. Some required no follow-up, whereas others needed long-term rehabilitation. However, at the end of the 2-year follow-up period, 86% of resident patients had fully recovered.

Strengths of this study include the comprehensive inclusion of all confirmed TBE cases in Åland during the study period, the clinical evaluation of patients and the systematic review of medical records by a small group of experienced physicians. However, the study also has certain limitations, including the retrospective study design, with the risk of missing data and recall bias, the small cohort size, and the different follow-up regimens. Another limitation is that CSF was not obtained from all patients with suspected CNS infection as part of routine clinical practice, which contributes to uncertainty regarding CNS involvement in a substantial proportion of the cohort. In the context of sequelae, a particular challenge lies in distinguishing symptoms attributable to TBE from those arising due to underlying comorbidities, especially in elderly patients.

## Conclusions

Following the implementation of a general vaccination programme, the incidence of TBE in Åland has not significantly declined, although the increasing trend observed in neighbouring regions is absent. Most infections occur in unvaccinated individuals; however, a notable proportion affects vaccinated persons, particularly those with incomplete vaccination, who appear to be at greater risk of severe disease. Compared to other European countries, monophasic disease presentations remain more prevalent in Åland. Despite the high morbidity associated with TBE, 86% of patients are considered recovered two years after the acute phase.

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## Author contributions

Conceptualization; JS, MN; Data curation; JT, CJ, GH, MN; Formal analysis; JT, JS, MN; Funding acquisition; JT, JS, MN; Investigation; JT, GH, CJ, MP; JS, MN; Methodology; JT, CJ, JS, MN; Project administration; JS, MN; Resources; JS, DN, CJ, MN; Software; JT, JS; Supervision; DN, JS,

MN; Validation; JT, JS, MN; Visualization; JT, JS; Roles/ Writing – original draft; JT, CJ, JS, MN; Writing – review & editing; JT, GH, CJ, DN, MP, JS, MN.

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No potential conflict of interest was reported by the author(s).

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## Ethical approval

This study was approved by the Ethics Committee of ÅHS (1/2021). The confidentiality of the study data is guaranteed. The ethics committee required that all parties involved be informed about participation in the study, but no written consent was required.

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