

RESEARCH ARTICLE

Surveillance of endemic foci of tick-borne encephalitis in Finland 1995–2013: evidence of emergence of new foci

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The geographical risk areas for tick-borne encephalitis (TBE) in Finland remained the same until the beginning of the 21st century, but a considerable geographical expansion has been observed in the past 10 years. In order to support public health measures, the present study describes the number of laboratory-confirmed TBE cases and laboratory tests conducted and the associated trends by hospital district, with a particular emphasis on the suspected geographical risk areas. An additional investigation was conducted on 1,957 clinical serum samples throughout the country taken from patients with neurological symptoms to screen for undiagnosed TBE cases. This study identified new TBE foci in Finland, reflecting the spread of the disease into new areas. Even in the most endemic municipalities, transmission of TBE to humans occurred in very specific and often small foci. The number of antibody tests for TBE virus more than doubled (an increase by 105%) between 2007 and 2013. Analysis of the number of tests also revealed areas in which the awareness of clinicians may be suboptimal at present. However, it appears that underdiagnosis of neuroinvasive TBE is not common.

Introduction

Tick-borne encephalitis virus (TBEV) is a clinically important flavivirus causing encephalitic disease with thousands of cases annually in Europe [1]. There are three known subtypes of TBEV: European (Eur), Siberian (Sib) and Far-Eastern (FE). The European subtype is mainly carried by *Ixodes ricinus* ticks in central and north-eastern Europe, whereas the other two are mainly found in *I. persulcatus* ticks in an area reaching from north-eastern Europe to the Russian Far East, China and Japan [2].

TBEV is maintained in nature by ticks and their hosts. Ticks serve both as a reservoir and as vector for the virus [3]. Persistence in small mammals may also

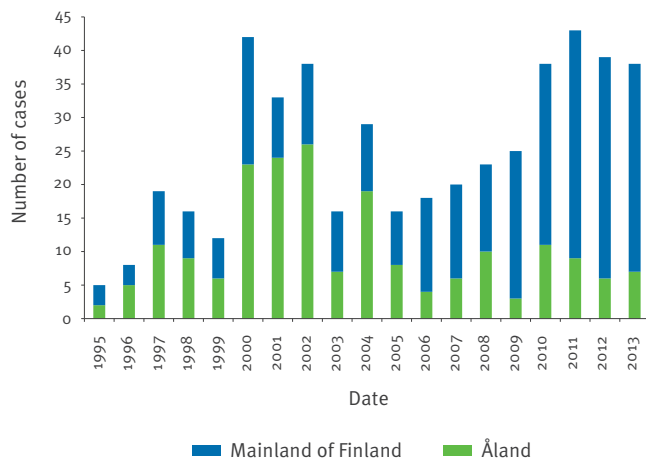
contribute to maintenance [4,5]. *Ixodes* ticks are widely spread generalist ectoparasites [6]. However, circulation of TBEV is dependent on the local vegetation, dynamics of the vertebrate and tick host populations and microclimatic conditions, leading to focal occurrence of TBEV within the distribution area of the host ticks [3].

Humans do not contribute to sustain the circulation of TBEV but can get infected as accidental hosts by a tick bite or through consumption of unpasteurised milk from infected ruminants, particularly goats [7]. Besides genetic host factors, the course and severity of the infection may depend on the virus subtype and strain. Of the three subtypes, TBEV-FE is the one that most frequently induces severe tick-borne encephalitis (TBE), and the reported fatality rate reaches 35% [7]. TBEV-Sib causes a mortality of 2–3% and has been associated with chronic forms of TBE [1]. A biphasic course of infection is considered characteristic for TBEV-Eur: After an average incubation period of eight days, the viraemic phase, lasting one to eight days, manifests with unspecific influenza-like symptoms or remains subclinical [7,8]. After an asymptomatic period, 20–30% of the patients present with a neuroinvasive disease [7]. Although mortality is low for TBEV-Eur, less than 2% [1,9], neuronal degeneration and post-encephalitis syndrome occur in up to one third of the patients and can have sequelae that reduce the quality of life [8,9]. Effective vaccines are available to prevent TBE caused by any of the three subtypes [2,7].

In Europe, the laboratory diagnosis of acute TBE is based on specific IgG and IgM antibody detection from serum and/or cerebrospinal fluid (CSF) [10,11]. Vaccination and natural infection with other flaviviruses produce cross-reactive antibodies, which should be taken into consideration in the interpretation of IgG test results.

FIGURE 1

All tick-borne encephalitis cases reported in the National Infectious Diseases Register, by place of diagnosis, Finland, 1995–2013 (n = 478)



Cases as reported by hospital district of the treating unit [41].

There is no official definition of a TBEV-endemic area in Finland. However, foci with repeated human cases are considered risk areas. Most of these areas have been visited by our research group for collection of ticks and rodents to confirm the presence of TBEV in ticks and/or host animals and to analyse the TBEV strains and tick species present in the area. Evidence from the past decade suggests a TBEV prevalence of up to 2% in *I. ricinus* and *I. persulcatus* ticks in TBEV foci throughout Finland [12–15].

Finland, together with the Baltic countries and western Russia, lies in the zone where the two main host tick species mix [2]. The overall distribution of tick species in Finland has only been investigated in restricted areas, most of which are endemic TBEV foci. *I. ricinus* is the main tick species found in southern and south-western Finland, while *I. persulcatus* is present in the north-west coast and at the eastern border of the country [12–16]. The TBEV subtypes endemic in Finland are TBEV-Eur and TBEV-Sib [13,15,16]. Interestingly, TBEV-Eur was recently found in *I. persulcatus* ticks in the northernmost known TBE focus, in Simo, Finland [14]. All three subtypes are found in Russia and have been reported in Estonia and Latvia [17–19].

The first cluster of encephalitis cases in Finland occurred in Kumlinge, Åland in the 1940s; TBE, then known locally as Kumlinge disease, was described in 1956 [20] and TBEV was isolated in Kumlinge in 1959 (isolate A52) [8]. The number and geographical distribution of human TBE cases in Finland remained stable for many decades, but in the past 10 years, the disease has become more common and spread to new foci.

In the present study we analysed the development of the geographical distribution and the number of TBE

cases in Finland notified to the National Infectious Diseases Register (NIDR) in the period from 1995 to 2013. In order to further support public health measures, we also describe the number of laboratory-confirmed TBE cases and of conducted laboratory tests as well as the associated trends for each of the 21 Finnish hospital districts, with a particular emphasis on the suspected risk areas. In addition, we used clinical serum samples from patients with neurological infection to investigate to which extent TBE cases and foci may have occurred unnoticed in Finland.

Methods

Tick-borne encephalitis diagnostics, case definition, and reporting

TBE is a notifiable disease in Finland according to the Communicable Disease Act and Decree. Two diagnostic laboratories located in Turku (University of Turku) and Helsinki (HUSLAB, Helsinki University Hospital), perform TBE diagnostics and report acute cases to the Finnish NIDR at the National Institute of Health and Welfare (NIHW). Laboratory-confirmed cases are registered by the hospital district of the treating hospital and dated by the first TBE IgM-positive clinical sample. Cases have been registered since 1995 with information on the place of residence and since 2007, detailed information on place and date of infection, date of first symptoms and clinical features have been collected from medical records and, when possible, in interviews.

The results submitted by the diagnostic laboratories to the Finnish NIDR are reviewed annually by specialists representing NIHW and the reporting laboratories using medical reports of the patients. During the study period (since 2007), this evaluation usually took place during the first months of the following year. Only cases that fulfilled the criteria for acute TBE (described below) are considered as cases and left in the register. In this study, we compared the data in the NIDR before and after the annual evaluation.

In Finland, the case definition of acute TBE is based on disease-specific medical history and clinical findings, absence of previous exposure to other flaviviruses, and detection of TBEV-specific IgG and IgM antibodies in serum and/or CSF. The criteria are consistent with the case definition from the European Centre for Disease Prevention and Control (ECDC) [21], but in addition, also cases with a mild clinical picture, without inflammation in the central nervous system (CNS), are registered. Only the classification ‘confirmed’ is used in Finland.

The TBEV IgM and IgG tests used in Turku are enzyme immunoassays (EIA) (Virion/Serion FSME virus/TBE, Wuerzburg, Germany). In HUSLAB, TBEV IgM is tested by an in-house μ -capture IgM EIA and confirmed by a haemagglutination inhibition (HI) test (described below). In the present study, we used the laboratory-confirmed

data, the re-evaluated data from the NIDR and the data from the interviews conducted by the NIHW.

Screening for antibodies against tick-borne encephalitis virus in sera from patients with central nervous system infection

Clinical serum samples, collected throughout Finland from patients with a CNS infection with suspected viral origin, were screened to identify previously undiagnosed TBE cases (Research permit §32 HUSLAB, 2013). Convenience sampling representing the season of tick activity (i.e. daily mean temperature $\geq 5^{\circ}\text{C}$, in southern Finland this is late April to end of October, in northern areas a shorter period) was conducted in a sampling frame of serum specimens from patients with a suspected neurological infection, retrieved in 1997, 2005–07 and 2011–12 and representing different geographical areas in Finland.

The samples had at the time of collection been sent to HUSLAB for screening of IgG and IgM antibodies against a panel of agents potentially causing CNS infection, including human herpesvirus 6, herpes simplex virus 1 and 2, varicella zoster virus and *Mycoplasma pneumoniae*, but not TBEV. We excluded samples without diagnostic finding for the agents listed above as well as samples from patients who already had a diagnosis of TBE following an independent request to study anti-TBEV antibodies. Altogether 1,957 specimens were selected for this investigation.

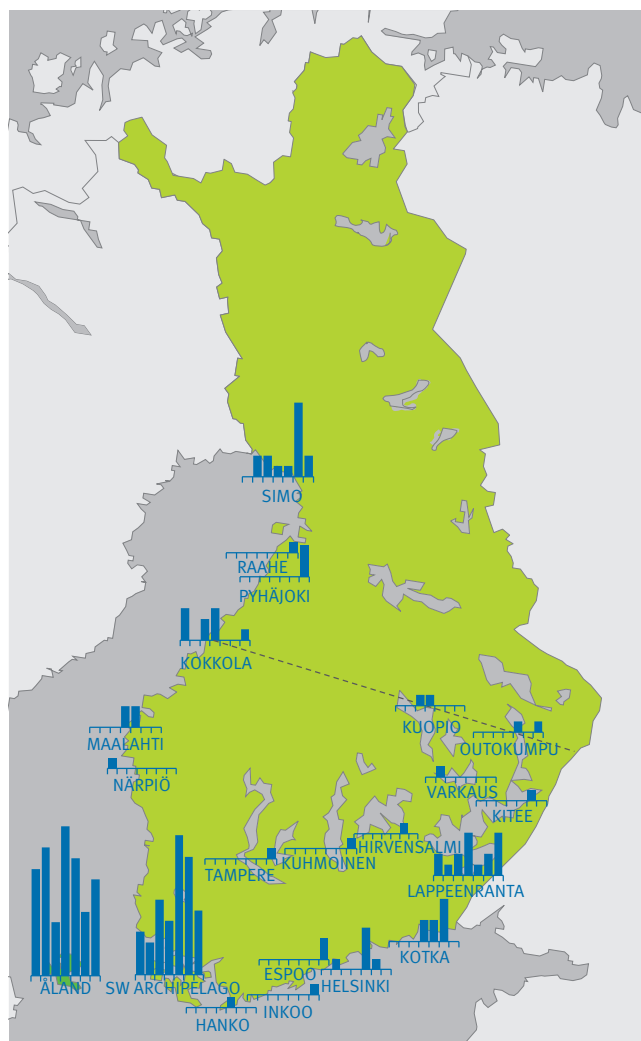
The samples from 2005 to 2007 and 2011 to 2012 were screened with a modified μ -capture IgM EIA described earlier [22], except than an anti-FSME monoclonal antibody (Mab) [23] and a peroxidase-conjugated donkey anti-mouse IgG antibody (Jackson immunoresearch, West Grove, United States) were used in place of a peroxidase-conjugated anti-TBEV-Mab. The specificity of positive IgM reactions was further confirmed with an in-house HI test [24]. These methods are in routine use in the diagnostic laboratory at present. Samples from 1997 were screened with an IgM-EIA (Progen Biotechnik GmbH, Heidelberg, Germany) and with an in-house HI test [24], the methods in routine use in the diagnostic laboratory at that time.

Data from diagnostic laboratories conducting tick-borne encephalitis virus serology in Finland 2007 to 2013

We surveyed the databases of the two diagnostic laboratories conducting TBEV serology in Finland, the University of Turku and HUSLAB, including the referral information and TBE diagnostic test results (ethical permit THL/402/5.05.00/2014). Each patient was included only once in the data analysis. The patients were grouped by hospital district. Information on sex and age was only available for patients tested in HUSLAB, which represented 57% of all diagnostic data. Each municipality or private healthcare provider in a hospital district can choose the laboratory to which they send the specimens for TBEV antibody testing.

FIGURE 2

Cases of tick-borne encephalitis, by geographical place of infection, Finland, 2007–13 (n = 192)



All 192 cases with adequate information of the place of infection in Finland are included in the figure. Data of some geographically continuous areas were combined as follows: Simo: Simo and Kemi; Helsinki: Helsinki and Sipoo archipelago; Lappeenranta: Lappeenranta, Imatra, Lemi and Joutseno; Kotka: Kotka and Hamina archipelagos; Kokkola: Kokkola and Kannus. The south-western (SW) archipelago extends to Kemiö in the south-east, includes the archipelago of Uusikaupunki in the north and excludes Åland in the west. The x axis of the graphs represents the date in years from 2007 to 2013. The y axis represents the cases (min=1 case, e.g. Tamper, Kuusmoinen and Inkoö 2013; max=14 cases, e.g. Åland 2010)

The northern limit of distribution of *Ixodes ricinus* in the 1960s is marked with a dashed line.

The proportion of specimens sent to HUSLAB or to the University of Turku by each hospital district varied (the proportion sent to HUSLAB varied between 2.4% and 100%).

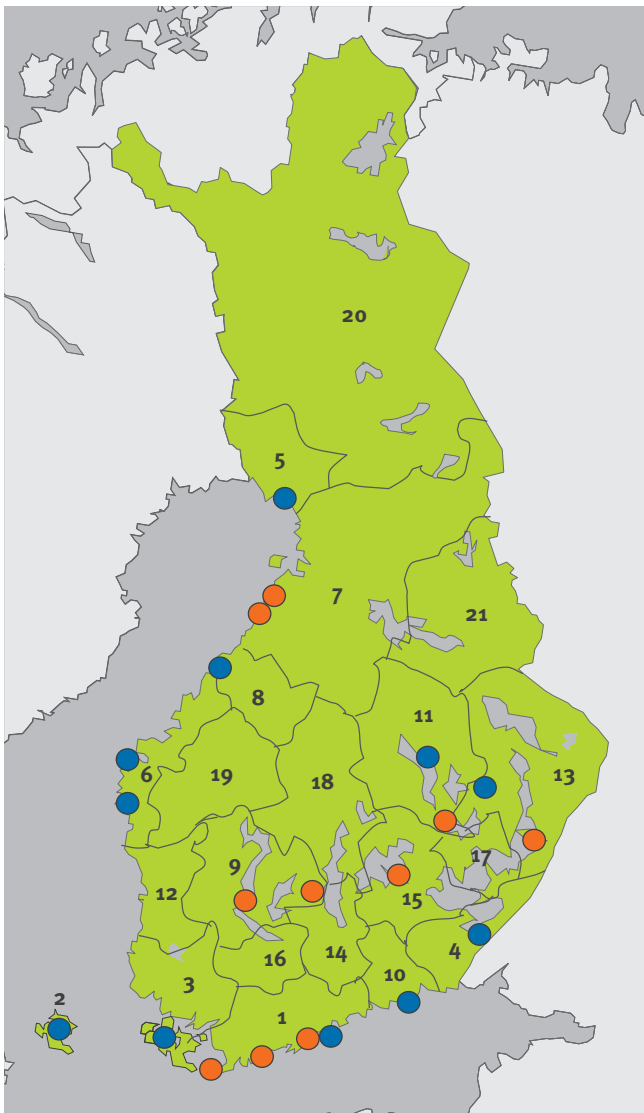
Results

Descriptive analysis of notified tick-borne encephalitis cases in Finland in 1995 to 2013

Altogether 478 acute TBE cases were reported to the NIDR in the period from 1995 to 2013 (annual average: 25 cases; range: 5–43) (Figure 1). Of these, 196 were

FIGURE 3

Hospital districts with continuous or sporadic occurrence of tick-borne encephalitis, Finland, 2007–13 (n = 192)



Blue circles: districts with continuous occurrence of human cases; red circles: places with sporadic cases. Sporadic was defined as only one case registered in a single year or as occurrence of the case/cases during the last year of the study. Cases are shown by geographical site of infection.

Numbers represent hospital districts as listed in Table 1.

reported from the Åland islands, a highly endemic area in south-western Finland. After 2006, when the national immunisation programme started providing vaccination for the population of Åland (n = 28,666 in 2013 [25]), the majority of infections occurred on the Finnish mainland (i.e. areas other than Åland) (Figure 1), however, the incidence still remained highest on Åland.

Geographical distribution

Adequate data on the place of infection was available for 208 (92%) of the 226 cases reported between 2007 and 2013 (Figure 2). Of the total 226 cases, 74 (33%) were female; the median age was 48 years for men (range: 1–85) and 50 years for women (range: 4–81).

In comparison, the median age for men in 2013 in the whole population was 39 years and for women 43 years according to Statistics Finland (personal communication Niina Haataja, June 2014). The median age of 3,190 patients tested for suspected acute TBEV infection was 43 years (range: 0–91), of whom 50% were female.

Of the 208 TBEV cases for whom detailed information was available, the infection site of 192 cases was in Finland (Figure 2).

Figure 2 shows recent, earlier unreported areas with human TBE cases in Finland, namely Raahe, Pyhäjoki, Maalahti, Kuopio, Outokumpu, Varkaus, Kitee, Hirvensalmi, Kuhmoinen, Kotka, Tampere and Espoo. In many of these areas, infections have remained sporadic (Figure 3), however, some of these areas emerged only in the last year of the study and the development cannot be assessed yet.

Of the cases with the infection site in Finland, 129 (67%) acquired the infection in their place of residence or in a neighbouring municipality. In the highly endemic areas of Åland and the south-western archipelago, respectively two thirds (46/67) and half of the cases (25/49) were local residents. In the Simo-Kemi region, 13 of 16 infections were acquired by local residents, whereas the proportion was four of eight in Kotka, archipelago seven of nine in Kokkola and 15 of 16 in Lappeenranta. Infections among local residents predominated also in the rest of the endemic areas. Altogether 16 cases were acquired abroad, mainly in countries neighbouring Finland: 10 persons acquired their infection in Estonia, three in Sweden, and one each in Russia, Austria and Switzerland.

Seasonality

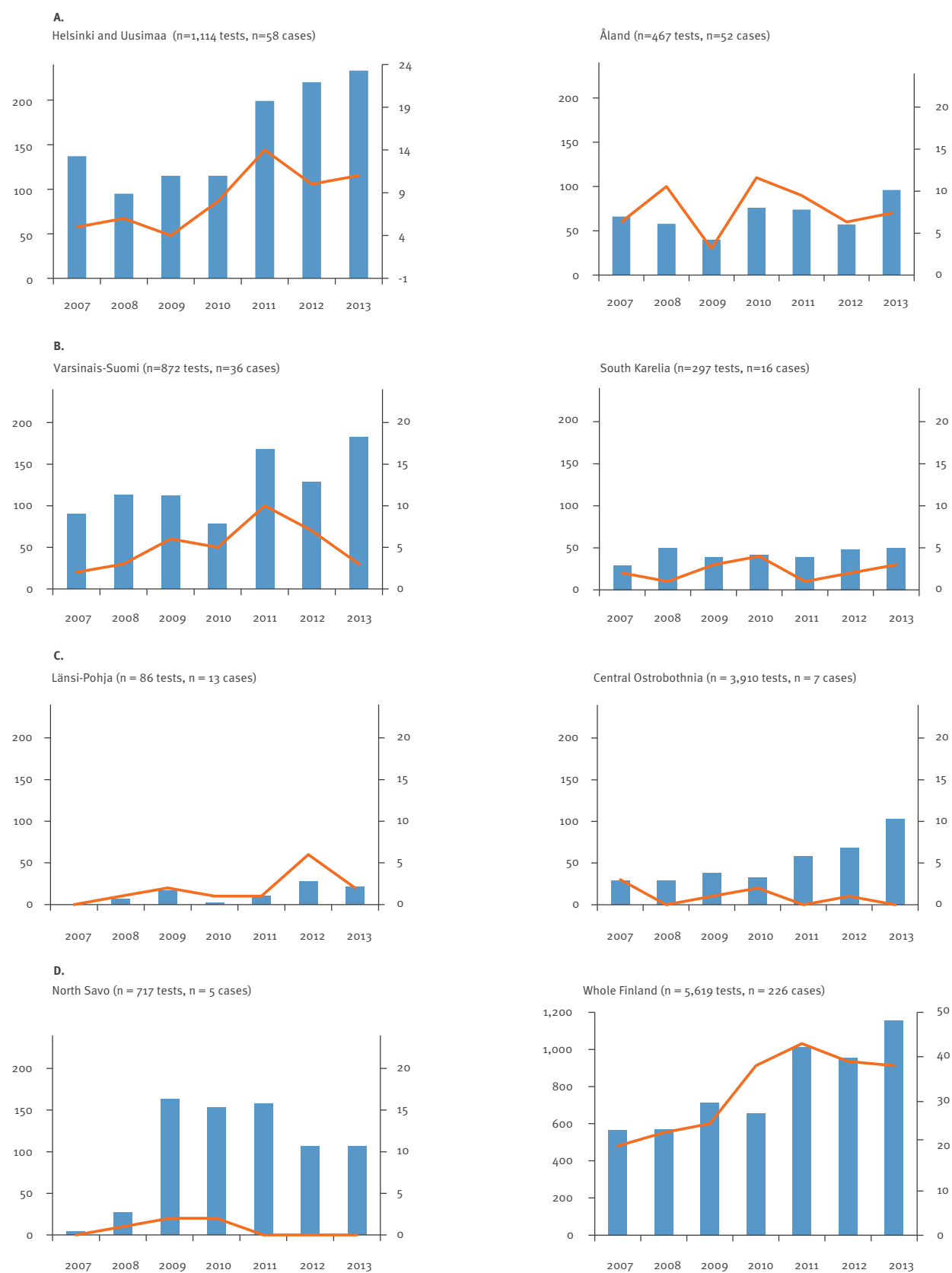
Acute TBE cases were reported from 20 April through 19 November. At both the start and the ends of this period, cases were detected in the south-western region. In Åland, 37 of 65 cases were reported evenly distributed from June to August, while 17 of the 65 cases were observed in September. In the south-western archipelago, there was a small peak in the number of cases in July and August, corresponding to the holiday season. Note that cases among residents of Åland were registered by the date of the first TBEV-positive sample, while the cases from other parts of Finland were reported by the first date of symptoms. In Åland and the south-western archipelago, infections in late autumn were particularly common in 2010, 2011 and 2013. In the south-eastern endemic area of Lappeenranta, 16 cases were reported from May to October, nine of them in August and September, while in the northern parts of the country, most cases were reported in June, with only one case in August and none later.

Diagnosis

The average time from first symptoms to test-positive laboratory specimen was 13.4 days (range: 0–68,

FIGURE 4

Diagnostic laboratory tests for the detection of acute tick-borne encephalitis (n = 5,619) vs diagnosed cases (n = 226), Finland 2007–13



Columns: number of tests performed are presented in columns (scale on left). Line graphs: cases reported in the National Infectious Diseases Register by the hospital district of the treating unit (scale on right).

The areas in Finland with highest case numbers are shown. North-Savo is included as the area with the largest ratio of tests conducted vs cases detected.

TABLE 1

Diagnostic tests for the detection of acute tick-borne encephalitis, by hospital districts, Finland, 2007–13 (n = 5,619)

Hospital district		Patients tested	Tests/100,000 inhabitants ^a	Cases ^b	Positive tests %	Cases by site of infection ^c	Incidence/100,000 average 1995–2014
1	Helsinki and Uusimaa	1,114	70	58	5.2	10	0.55
2	Åland	467	1,629	52	11.1	67	39.47
3	Varsinais-Suomi	872	184	36	4.1	49	0.85
4	South Karelia	297	225	16	5.4	16	1.46
5	Länsi-Pohja	86	134	13	15.1	15	1.24
6	Vaasa	471	279	10	2.1	5	0.38
7	Northern Ostrobothnia	139	34	10	7.2	4	0.17
8	Central Ostrobothnia	357	456	7	2.0	9	1.22
9	Pirkanmaa	175	34	4	2.3	2	0.14
10	Kymenlaakso	72	41	4	5.6	8	0.20
11	North Savo	721	290	4	0.6	3	0.23
12	Satakunta	167	74	2	1.2	0	0.18
13	North Karelia	84	50	3	3.6	3	0.12
14	Päijät-Häme	96	45	1	1.0	0	0.03
15	South Savo	36	34	1	2.8	1	0.15
16	Kanta-Häme	42	24	1	2.4	0	0.09
17	East Savo	37	83	1	2.7	0	0.17
18	Central Finland	42	17	1	2.4	0	0.04
19	Southern Ostrobothnia	17	9	1	5.9	0	0.03
20	Lapland	59	45	0	0.0	0	0.04
21	Kainuu	4	5	0	0.0	0	0
Private laboratories ^d		264	NA	NA	NA	NA	NA
All		5,619	102	255	4.5	192	0.53

NA: not applicable; NIDR: National Infectious Diseases Register; NIHW: National Institute of Health and Welfare; TBE: tick-borne encephalitis. Incidence data and the cases were provided by the NIHW in the NIDR [41]. Hospital districts are listed by case numbers reported in the NIDR in descending order. For a map of the hospital districts see Figure 3.

^a Number of inhabitants in the hospital district in 2013.

^b TBE cases reported by the NIHW in the NIDR in 2007 to 2013, by hospital district of the treating unit.

^c TBE infections in 2007 to 2013 that occurred in the geographical area of the hospital district.

^d The sending unit is not known for the private laboratories, however, the positive cases are included in the register of NIHW by area of the laboratory. In our analysis, we only analysed the frequency of the positive samples in this set of samples.

median: 13). From 2007 to 2013, 106 TBE patients (68%) had noticed a tick bite before developing clinical TBE (75% of the 208 interviewed patients provided this information). The number of laboratory tests conducted in each hospital district varied between five and 1,629 tests conducted per 100,000 inhabitants in total in the period from 2007 to 2013 (Figure 4, Table 1). Åland had the largest number of cases (n = 67, Åland as geographical site of infection) and the largest number of tests conducted per 100,000 inhabitants (1,629/100,000). Of the five hospital districts with most cases (Åland, Varsinais-Suomi, South Karelia, Länsi-Pohja, and Helsinki and Uusimaa), the smallest ratio of tests conducted vs cases diagnosed 2007 to 2013 was seen in Varsinais-Suomi and Länsi-Pohja (Figure 4, Table 1). Of the areas with sporadic cases (between one and 10 cases altogether in the study period), the

largest ratio of tests conducted vs cases detected was seen in North Savo, Vaasa, and Central Ostrobothnia (Table 1).

During the study period, three patients died with acute TBE (1.3% of all reported cases): a person in their 60s with a neuroinvasive TBE, a person in their 70s with TBEV encephalitis and a person in their 80s with confirmed TBEV encephalitis. The latter patient had received only one dose of TBE vaccine three weeks before the infection.

Screening of clinical samples for antibodies to tick-borne encephalitis virus

Of the 1,957 clinical serum samples from patients who had an infection with CNS symptoms in summer or autumn of the studied years, but had not previously

TABLE 2

Patients with central nervous system infections with unknown aetiology, Finland, 1997–2012 (n = 1,957)

Year	Period of samples collection	Number of samples	New cases ^a	Hospital district ^b	Proportion %	All cases registered in that year (NIHW)
1997	1 August–31 October	383	1	Helsinki and Uusimaa	0.26	19
2005	15 May–31 August	409	0	No cases	0.00	16
2006	16 May–31 August	250	1	Åland	0.40	18
2007	20 June–23 August	221	0	No cases	0.00	20
2011	1 June–31 October	374	3	Helsinki and Uusimaa (2 cases), Kymenlaakso (1 case)	0.80	43
2012	1 June–31 October	320	0	No cases	0.00	39

NIHW: National Institute of Health and Welfare; TBEV: tick-borne encephalitis virus.

^a Patients with no previous TBEV diagnosis.^b Hospital districts as presented in Figure 3.

been tested positive for anti-TBEV antibodies, five (0.3%) were positive in both serological tests and fulfilled the diagnostic criteria of acute TBE (Table 2). Of these five cases, three were from the hospital district of Helsinki and Uusimaa, one from Åland and one from Kymenlaakso.

Tick-borne encephalitis surveillance system in Finland

Positive TBE test results, mainly positive TBEV IgM EIA results, are reported automatically to the NIDR as diagnostic TBE findings by the clinical laboratories. For the period 2007 to 2013, the case re-evaluation procedure at the NIHW resulted in a 12.4% decrease (range: 0–30.7 per year) in the annual number of TBE cases (data not shown). In most cases, this was because no IgG or HI seroconversion could be shown and the positive IgM test result was most probably unspecific.

Discussion

This study demonstrates that in the past eight years, human TBE cases have emerged in new areas in Finland. An increasing number of TBE cases have been reported particularly along the north-western coast and in the south-western archipelago. Case numbers in Finland peaked in the early 2000s, mainly because of a significant increase in TBE cases reported in Åland. The TBE incidence on Åland reached a peak in 2002 with 100 per 100,000 population. Awareness of the disease led to an increase in TBE immunisations and since 2006, the national vaccination programme has provided the vaccine for residents of Åland, where the vaccination coverage in 2012 was estimated at 70.7% [26,27]. While the number of TBE cases on Åland has been steadily decreasing, the overall incidence between 2007 and 2013 was still higher than in other parts of Finland. Furthermore, there have been indications of vaccine failure infections in Finland during the recent years (data not shown), as also reported in Sweden [28]. Vaccine failures have so far been studied systematically only on Åland. Age and number of vaccination doses have been reported as the most important

factors influencing the immunological response to vaccination [29].

Case numbers have decreased considerably also in some of the smaller TBE foci in Finland that have been known for decades. These include Kokkola and the island of Isoaari in Helsinki, where our research group detected the Siberian and European TBEV subtypes, respectively, in rodents in 2008 and 2009, indicating that TBEV is still endemic, even if human cases are rare or absent [4]. We can assume that the observed decrease in case numbers was mainly due to increased awareness and subsequent immunisation. However, fluctuation of TBEV prevalence in ticks, annual fluctuations in host rodent and tick populations, virulence of the circulating virus strains [30], and the probability for tick co-feeding may also regulate the risk of acquiring TBEV infection.

TBEV is, at least currently, found in very local foci in Finland. Even if a municipality is recognised as an endemic area, the true risk for a TBEV infection is restricted to areas smaller than the municipality. Studied foci and the patient cases reported are concentrated, in addition to Åland, along the coastline of the Baltic Sea and of Lake Saimaa, the largest inland waterway in Finland. Typically the foci are surrounded by water and appear on islands or headlands. This may be due to the favourable microclimatic conditions, vegetation and a suitable structure of host mammal populations for TBEV and ticks. Also human exposure to ticks by the water is emphasised. Åland, the south-western archipelago and the Kotka archipelago are common holiday destinations and summerhouses, characteristic of the Finnish people, are usually located by water. In 2013, there were 498,700 summerhouses in Finland (population 5,451,270) [31]. In the south-western parts of the country, the highest density of summer houses overlaps with the areas where the TBE incidence peaks. The majority of the cases in Finland were recorded in the municipality of residence or in the neighbouring municipality. Still, even in those cases, the infections were often acquired at a summerhouse

located by the sea or a lake and only rarely at the permanent residence. The focal nature and the infection risk at the summerhouse should be considered when the immunisation policies are planned and the budget for the provided immunisations are allocated.

During the last two decades, TBE case numbers have been increasing in many European countries, especially in northern Europe and northern parts of Russia [1-3,33,34]. Climate change is one, not completely understood, factor in this development [2,35]. In Finland and the neighbouring countries Sweden and Russia, host tick species and TBEV endemic foci have moved to more northern latitudes. In addition, *I. ricinus* has become more abundant in Sweden [14,34,36], and *I. ricinus* is found at higher altitudes in the central European mountain area [37]. At the same time, it has been predicted that TBEV may become rare or that the seasonality of cases may change in the traditionally highly endemic areas in central Europe [3,38]. Besides climate, human behavioural factors such as land use, socioeconomic changes, increased awareness of the disease and changes in the healthcare system have an influence on reported TBE case numbers [3,39].

No recent systematic countrywide survey on the distribution of TBEV and the host *Ixodes* ticks is available in Finland, although areas with known human infections have been investigated. The geographical distribution of TBEV in Finland was last surveyed in the 1960s by screening of anti-TBEV antibodies in cattle sera collected throughout the country [40]. The northern limit of *I. ricinus* ticks was found at the latitude of Kokkola-Joensuu [40] (indicated in Figure 2). In a survey of 106 TBE patients between 1959 and 1987 the identified geographical sites of infection were Åland, the south-western region of Finland, Kokkola, the Helsinki region and north-eastern Finland [8]. In the present study, TBE cases were detected beyond these regions, particularly more to the north at the west coast (i.e. in the Raahe, Pyhäjoki and Simo-Kemi regions, 64°5' to 65°7' N). However, according to earlier unpublished results (personal communication: Markus Brummer-Korvenkontio, March 2015), anti-TBEV antibodies were already detected (by HI test and neutralisation) twice, two years apart, in a single cow in the 1960s in Tervola, a municipality next to Simo, suggesting that TBEV may have been endemic in the area already 50 years ago, even if no human cases were noted. The foci of Raahe and Pyhäjoki, as well as those in the inland lake region described here have not been reported previously.

I. persulcatus ticks are found on the north-west coast, overlapping, at least in Simo and in North Karelia, with emerging foci; at least in the Simo-Kemi region the ticks are carrying TBEV [13-16]. In south-western endemic areas, where *I. ricinus* is carrying TBEV, human cases were reported in the period between 20 April and 19 November. The course of TBEV infection suggests that tick exposure occurred a few days to three weeks earlier. In the northern regions, where *I. persulcatus* ticks

are present, no autumnal cases were recorded. This may be due to different behaviour of the tick species or because the vegetation period is shorter in the northern parts of the country.

The number of samples sent to diagnostic laboratories for TBE testing in Finland increased by 105% during the study period. However, the number of samples sent for TBE diagnostic tests did not in all hospital districts correlate with the TBE incidence. Awareness of TBE in northern parts of the country has increased since the first cases reported in Simo in 2008, but the number of tests conducted is still moderate. The district of Helsinki and Uusimaa stood out with a high number of tested samples, even if only a few infections were acquired in this area. TBE cases connected to travel in Finland or abroad or to a summerhouse in Finland were characteristic for the capital region. The observed increase in the number of infections with Parainen (south-western archipelago) as the geographical place of infection is reflected in the number of cases registered in Helsinki and Uusimaa. The third highest number of diagnostic samples was from North Savo, although only three sporadic human cases are known from this region (in Kuopio and Varkaus). Comparing the number of tests conducted with the number of cases diagnosed, the ratio was particularly low for Varsinais-Suomi and Länsi-Pohja, suggesting potential lack of awareness among clinicians for TBE in these known endemic areas.

We screened 1,957 patients for anti-TBEV antibodies. Patients had CNS infection of suspected viral origin but no previous TBEV suspicion or diagnosis. Five of them (0.25%) were found positive. We conclude that undiagnosed TBE forms only a minor fraction of this particular patient group. In addition, it is evident that the TBEV surveillance system in Finland, i.e. reporting the cases by laboratory results even if the clinical case definition is not fulfilled, is not sufficiently specific to avoid false positive reporting. As the Finnish NIDR is publicly available online, registering TBE cases without full laboratory support (i.e. unspecific results) may raise unnecessary public concern in certain areas.

Conclusion

The overall TBE incidence in Finland is increasing and the virus is emerging in new geographical locations. Based on the present study, we have the following recommendations on TBE surveillance and prevention: (i) surveillance should be based on cases that fulfil the case definition at the time when the data are deposited and the data should be evaluated frequently; (ii) irrespective of the funding arrangements, vaccination programmes should be targeted to all people staying in TBE-endemic regions for several weeks between May and October, not only permanent residents; (iii) in certain areas with a higher risk of transmission, awareness among clinicians should be increased; (iv) geographical information of TBE foci should be more precise and up-to-date, and used to estimate the population at risk.

A comprehensive study of TBEV prevalence (TBEV RNA in ticks and antibodies in host mammals in Finland) and a survey of the distribution of the two tick species should be conducted.

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Conflict of interest

None declared.

Authors' contributions

ET, OV and TM designed and initiated the study. ET and TM collected the serum samples and performed and analysed the laboratory work. ET, SK, ST, and MK collected and analysed the data on laboratory confirmed TBE cases and ET, SK and TV the data on laboratory tests conducted. ET, SK, ST, TV, MK and OV wrote the manuscript.

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