Chapter 12b

TBE in Sweden

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E-CDC risk status: endemic (data as of end 2022)

History and current situation

Tick-borne encephalitis virus (TBEV) was isolated in Sweden for the first time in 1958 from ticks and from 1 tick-borne encephalitis [TBE] patient.[1] In 2003, Haglund and colleagues reported the isolation, the antigenic and genetic characterization of 14 TBEV strains from Swedish patients based on samples collected 1991–1994.[2] The first serum sample, from which the TBEV was isolated, was obtained 2–10 days after onset of disease and found to be negative for anti-TBEV immunoglobulin M (IgM) by enzyme-linked immunosorbent assay (ELISA), whereas TBEV-specific IgM (and TBEV-specific immuno-globulin G/cerebrospinal fluid [IgG/CSF] activity) was demonstrated in later serum samples taken during the second phase of the disease.

Of 20 patient serum samples inoculated into the brain of suckling mice, 14 induced obvious signs of illness (death or clear physical signs in all cases, 5–7 days after inoculation), and TBEV was isolated from all animals. Three earlier Swedish TBEV patient isolates from 1958,[1] 1959, and 1966, respectively, were included in the same study. Phylogenetic analyses of the partial sequence (domain III) of the E gene revealed that all Swedish TBEV strains grouped together with the previously characterized strains (Neudoerfl, Kumlinge-A52, Hypr, and TBE 263) of the Western or European subtype of TBEV (TBEV-EU).

In 2007, a partial TBEV sequence (approximately one-third of the viral genome) from a small pool of ticks collected in the Stockholm archipelago on the island of Torö was reported.[3]

The sequence was characterized and compared with those of other tick-borne flaviviruses, which again led to classification of the virus as TBEV-EU. The same group reported in 2011 on the first complete genome of a Swedish TBEV strain by completing the earlier partial sequencing (see above).[4] The total RNA was sufficient for the sequencing of a complete TBEV genome (Torö-2003), without conventional enrichment procedures such as cell culture or amplification in suckling mice. Sequence analyses also revealed that Torö-2003 belongs to the TBEV-EU subtype, being most similar to TBE 263 with 97.4% and 98.8% homologies at the nucleotide and amino acid levels, respectively.

In 2014, Veje and co-workers reported 2 cases of TBE in which TBEV RNA could be detected in urine by real-time polymerase chain reaction (PCR) during the encephalitic phase.[5] The TBEV RNA quantities from 1 patient allowed sequencing of 10,432 nucleotides (nt), which confirmed the PCR finding in urine, and phylogenetic analysis showed that the virus belonged to the TBEV-EU clade.

In 2016, Henningsson and associates reported isolation and a complete TBEV sequence from a biting tick.[6] By performing nt sequencing of the virus strain (Tick/SWE/Habo/2011/1) via 2 different strategies (deep sequencing of the A549 isolate and direct sequencing of PCR amplicons of RNA extracted from the tick, respectively), the authors showed that the 2 sequences were identical over 3,382 nt, thereby suggesting that the virus isolation procedure did not introduce a selection bias with regard to the compared nt sequences.

As in other areas of Europe, the number of reported TBE cases has increased during the last 25 years. The mortality of TBE in Sweden is significant (1.4%)[7] and the associated morbidity and long-term sequelae make it a disease of great importance in the endemic regions.[8–10] TBE has been reported in Sweden from diagnostic laboratories on a voluntary basis since the 1970s and notification has been mandatory since 2004. During the years 2007–2019, between 181 and 391 (year 2017) cases of TBE were reported annually in Sweden despite the fact that vaccination has increased in the exposed population. There are 2 TBE vaccines available in Sweden: FSME-Immun (Pfizer) introduced in 1988 and Encepur (Bavarian Nordic) introduced in 2003.

Vaccination against TBE is voluntary in Sweden. The vaccination schedule recommended in Sweden follows the recommendations of the manufacturers, with one exception being that after dose 4 and onwards, a 5-year interval is recommended, irrespective of age (the manufacturers recommend 3-year booster intervals after the age of 50). The change to a 5-year interval after dose 4 and onwards was based on a large study of the serological response in 535 persons in Sweden after TBE vaccination.[11] However, if TBE vaccination is initiated over age 60, the recommended schedule is 1 extra dose 2 months after the second dose, i.e. the initial vaccination includes 4 doses at 0, 1, 3, and 5–12 months.

The number of vaccine doses sold in Sweden has averaged from 500,000 to 600,000 annually since 2006, but increased to 1.2 million doses per year in 2018. Because TBE

vaccination is not included in any official vaccination registry, the actual number of immunized individuals is unknown.

To estimate the TBE vaccination coverage in the greater Stockholm region, a questionnaire was sent to a randomized sample of 8,000 individuals in 2013.[12] Three percent of all respondents reported being vaccinated against TBE at least once. Based on these findings, the estimated TBE incidence in the unvaccinated regional population was 8.5–12/100,000, which is comparable to highly endemic areas in the Baltics and Central Europe.

The protection rate of the vaccine has been estimated to be 96% to 98% according to field studies in Austria. In a study from 2010, data from 27 Swedish patients with clinical symptoms and signs of TBE, together with serological evidence of TBEV infection despite active vaccination, was presented.[13] Vaccination failures were characterized by a slow and initially non-detectable development of TBEV-specific IgM, seen together with a rapid rise of IgG and neutralizing antibodies in serum. The majority (70%) of the 27 patients were above age 50, which indicated the need for a modified immunization strategy in the elderly (as noted above).

Recently, a new tool (TBE suspension multiplex immune-assay, TBEV SMIA) for improved diagnostics of TBEV infections was reported.[17] The TBEV SMIA can accurately differentiate TBEV infections from TBE vaccination and further studies have now been initiated to evaluate the efficiency of the assay for diagnosis of potential vaccine failures.

Recently, the TBEV SMIA was evaluated using samples from 14 previously confirmed Swedish TBEV vaccine failure patients.[18] The conclusion was that detection of antibodies directed to TBEV NS1 antigen is a useful tool to considerably simplify and improve the quality in investigations regarding suspected TBEV infection in vaccinated patients.

In northern Europe, including Sweden, TBEV-EU is usually transmitted to humans by the common tick, *Ixodes ricinus.* Pettersson and colleagues investigated the prevalence in host-seeking *I. ricinus* southern and central Sweden and reviewed all relevant published records on the prevalence of TBEV in ticks in northern Europe.[14] Estimated mean minimum infection rate (MIR) of TBEV in nymphal and adult *I. ricinus* for northern Europe (i.e. Denmark, Norway, Sweden, and Finland) was 0.28% and 0.23% for southern Sweden. Also, the infection prevalence of TBEV was significantly lower for nymphs (0.10%) than for adult ticks (0.55%). In a well-known TBEV-endemic region, Torö island, southeast of Stockholm, the TBEV prevalence was 0.51% in nymphs and 4.48% in adult ticks.

In a review of the ecology and epidemiology of TBE in Sweden, Jaenson and colleagues analyzed the possible reasons behind the gradually increasing incidence of human TBE during the last 20 years.[15] The authors made the following conclusions:

i. Due to a large roe deer population during the 1980s and 1990s, the Swedish tick population gradually increased. At the turn of the century, the tick population in Sweden was probably larger than ever.

ii. The roe deer population gradually declined after its peak in the late 1980s and early 1990s.

iii. During the decline of the roe deer population, a gradually larger proportion of the tick larvae and nymphs probably fed on small mammals, which are reservoir-competent hosts for TBEV. Consequently, since the mid-1990s, a larger proportion of the tick population became infected with TBEV.

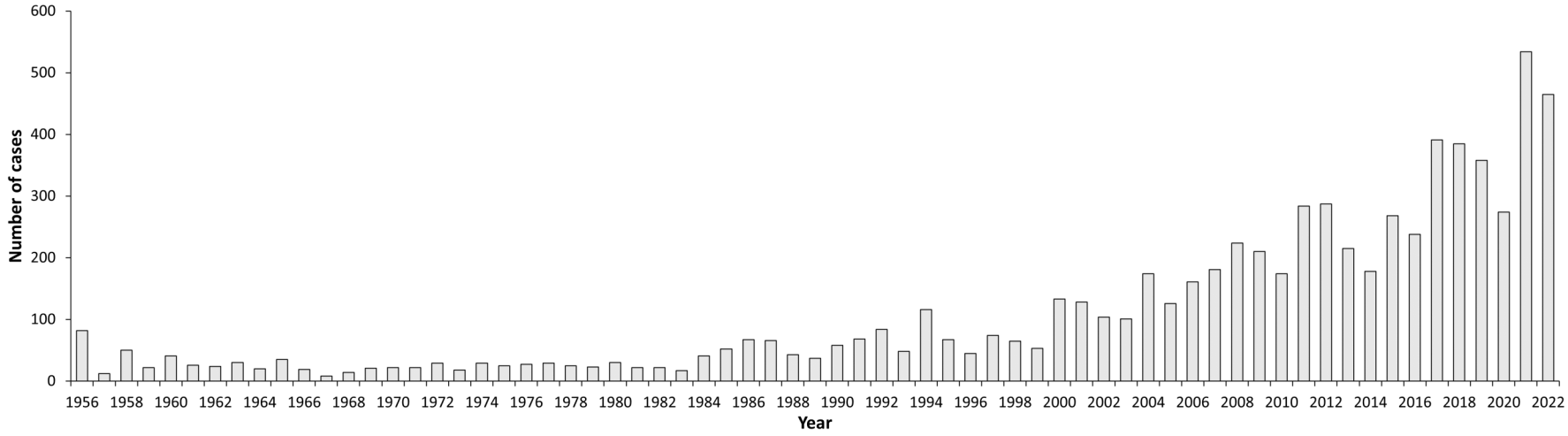
iv. Climate change and weather events associated with higher temperatures further influenced the infection prevalence in the tick population and therefore also the annual incidence in humans.

Overview of TBE in Sweden

Table 1: Virus, vector, transmission of TBE in Sweden	
Viral subtypes, distribution	Only western/European TBEV (TBEV-EU), southern part of the country[1-6]
Reservoir animals	Not documented
Infected tick species (%)	*I. ricinus*, 0.23% to 4.48%[14]
Dairy product transmission	Not documented

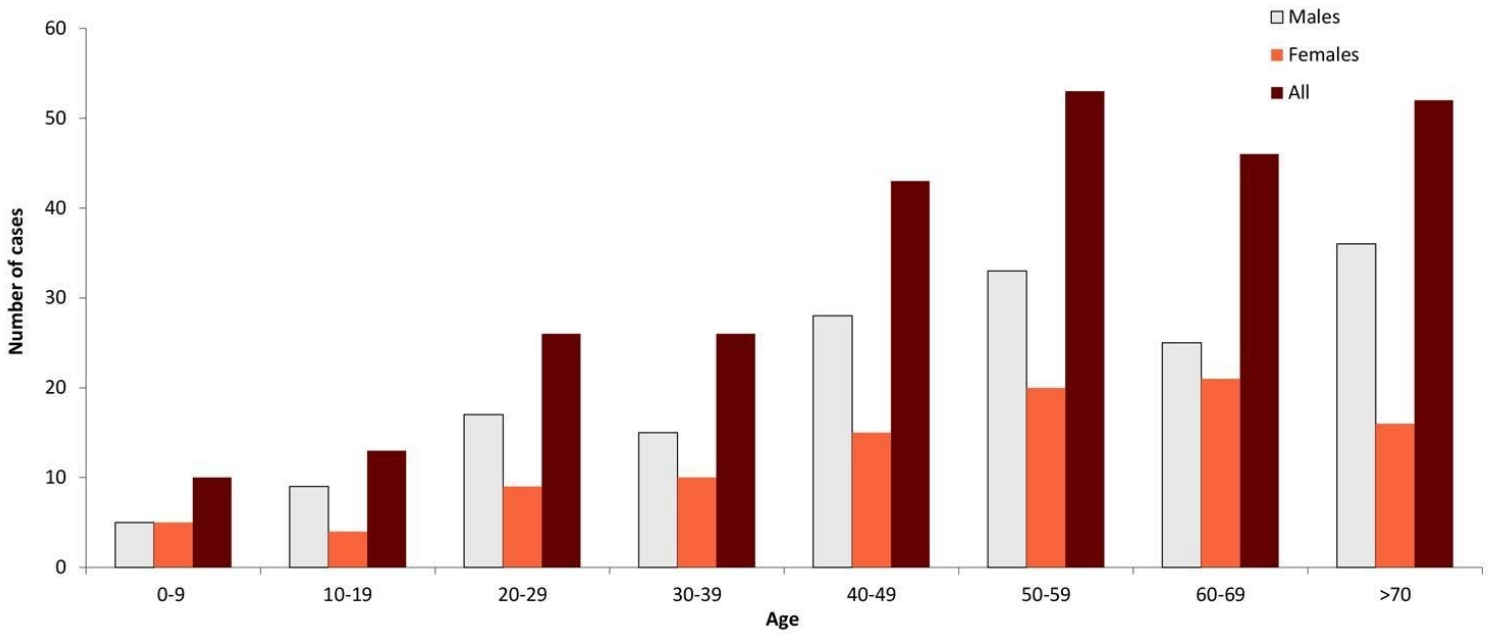
Table 2: TBE reporting and vaccine prevention in Sweden	
Mandatory TBE reporting	Each diagnostic laboratory plus the responsible physician report to the Public Health Agency of Sweden **Case definition**: **TBEV-infection (viral TBE)** **Suspected case:** - Epidemiological link - Clinical symptoms consistent with TBE - Pleocytosis (CSF) and/or neurological symptoms of encephalitis - Detection of TBEV-specific serum IgM **Confirmed case:** **At least one of the following:** - Detection of TBE-specific IgM and IgG in serum - Detection of TBE-specific IgM in CSF - Seroconversion or significant titer rise in paired serum samples - Detection of TBEV RNA in CSF (or post-mortem in brain tissue) - Detection of TBEV RNA in serum **Note**: Previous TBE vaccination and/or immunosuppression influence the patients' antibody responses and thus repeated sampling may be necessary for an accurate diagnosis. Also earlier infections, or vaccinations, against other flaviviruses may complicate the diagnostics due to cross-reactive antibodies. *Source: The Public Health Agency of Sweden (see below)*
Other TBE surveillance	No
Clinical characteristics	36%–40% with sequelae (after 1 year); mortality: 1.4%[7-8]
Available vaccines	FSME-Immun (Pfizer) introduced in 1988 and Encepur (Bavarian Nordic) introduced in 2003. 500,000–600,000 doses/year;[13,16] 1,200,000 doses/year in 2018 (unpublished data)
Vaccination recommendations and reimbursement	Revised each year No reimbursement
Vaccine uptake by age group/risk group/ general population	No data available
Name, address/ website of TBE NRC	The Public Health Agency of Sweden SE-171 82 Solna , Sweden www.folkhalsomyndigheten.se

Figure 1: Burden of TBE in Sweden over time



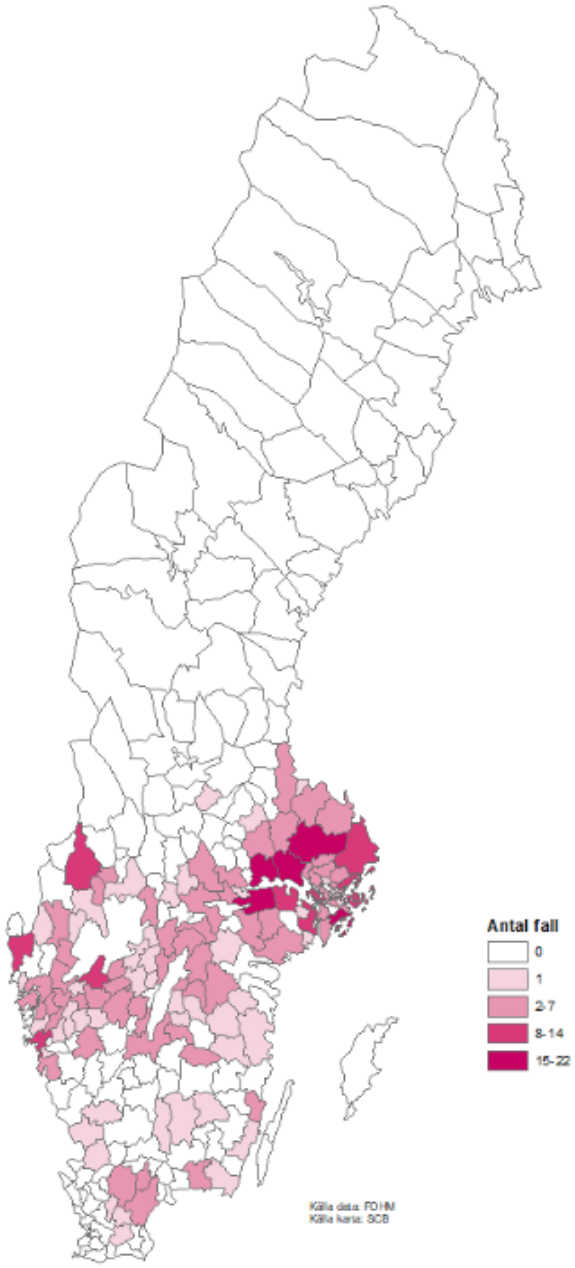
Source Data: Appendix—Figure 1

Figure 2: Age and gender distribution of TBE cases in Sweden (2018)



Source Data: Appendix Figure 2

Figure 3: TBE cases per municipality in 2021



Source Data: PHA Sweden. Available online here: https://www.folkhalsomyndigheten.se/nyheter-och-press/nyhetsarkiv/2022/april/sasongen-for-tbe-narmar-sig/)

Appendix

Source data : Figure 1

Year	Number of cases	Incidence / 10^5
1956	82	1.1
1957	12	0.16
1958	50	0.67
1959	22	0.29
1960	41	0.55
1961	26	0.34
1962	24	0.32
1963	30	0.39
1964	20	0.26
1965	35	0.45
1966	19	0.24
1967	8	0.1
1968	14	0.18
1969	21	0.26
1970	22	0.27
1971	22	0.27
1972	29	0.036
1973	18	0.22
1974	29	0.036
1975	25	0.3
1976	27	0.33
1977	29	0.35
1978	25	0.3
1979	23	0.28
1980	30	0.36
1981	22	0.26
1982	22	0.26
1983	17	0.2
1984	41	0.49
1985	52	0.62
1986	67	0.8
1987	66	0.78
1988	43	0.51
1989	37	0.43
1990	58	0.68
1991	68	0.79
1992	84	0.97
1993	48	0.55
1994	116	1.3
1995	67	0.76
1996	45	0.51
1997	74	0.84
1998	65	0.73
1999	53	0.6
2000	133	1.5
2001	128	1.4
2002	104	1.2
2003	101	1.1
2004	174	1.9
2005	126	1.4
2006	161	1.8
2007	181	2
2008	224	2.4
2009	210	2.2
2010	174	1.8
2011	284	3
2012	287	3
2013	209	2.17
2014	178	1.83
2015	268	2.72
2016	238	2.38
2017	391	3.86
2018	385	3.76
2019	358	3.47
2020	274	2.64
2021	534	5.11
2022	465	4.42

Source data: Figure 2

Age group (years)	Males	Females	All
0-9	5	5	10
10-19	9	4	13
20-29	17	9	26
30-39	15	10	26
40-49	28	15	43
50-59	33	20	53
60-69	25	21	46
>70	36	16	52

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