TBE in Denmark

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

History and current situation

Since the 1950s, tick-borne encephalitis (TBE) has been known to be endemic in Denmark, but only on the island of Bornholm. Bornholm is situated east of mainland Denmark, south of Sweden (Fig. 3) and has a different fauna and flora from the rest of Denmark. Bornholm has about 45,000 inhabitants, but about 500,000 tourists visit the island every year.

Freundt carried out a serosurvey during 1958–1962[1] and found TBE antibodies in 1.4% of blood donors and 30% of woodworkers on Bornholm but no antibodies in subjects living in mainland Denmark. In 1963, Freundt found that 8 of 12 patients admitted to the hospital with acute meningoencephalitis of unknown etiology during 1951–1960 had antibodies to tick-borne encephalitis (TBEV).[2] In 2000, TBE was rediscovered on Bornholm, where a retrospective study covering the period 1994–2002 (7 years) identified 14 TBE cases; 2 cases were tourists and 12 were inhabitants of Bornholm, giving an incidence of 3.81 per 100,000 inhabitants.[3] At least 5 patients (37.7%) got permanent sequelae. In addition, 32 forest workers on Bornholm were tested in 2000, and 20% had IgG antibodies but never symptoms. This is similar to the finding of Freundt in 1960. It was concluded that the data did not provide evidence of an increase in incidence of TBE. Ticks (*Ixodes ricinus*) from Bornholm were investigated for TBEV in 2000 and 2% were found to be infected.[4] Since 2001, an average of 2.5 (range 1–8) TBE cases per year have been reported in Bornholm (Fig. 1).

In 2009, we succeeded in identifying a TBEV microfocus in a small forested area, Tokkekøb Hegn on Zealand just north of Copenhagen, which had a severe TBE case reported.[6] A forest worker was infected in his backyard in Tokkekøb. The location is a small, open grass field bordering a lake and with a deer path. The patient had not been traveling. The patient described a similar case of encephalitis in 2008, when another man working in the forest kindergarten just 500m away from the forest worker got tick bites at the same spot. Both subjects had a typical biphasic disease and TBE was diagnosed.[6] Both experienced persistent neurological sequelae, paralysis of one arm (both patients) and neuropsychiatric complications (one patient).

TBEV European (Western) sub-type (TBEV-E) was identified in 2009 in *I. ricinus* tick adults and nymphs from the location identified by both patients (the "smoking gun principle").[6]

In July and September 2011, TBEV-Eu was again identified (endemic) in adults and nymphs at Tokkekøb, and TBEV isolated (isolates T2 and T3). The virus sequence grouped with isolates from Sweden-Norway, whereas one Bornholm TBEV from 2012 grouped into a different subclade from South and Central Bohemia.[7]

A recent (2018) sequenced TBEV isolate from Bornholm (lake Rubinsøen) grouped with TBEV from Switzerland and Finland.[10] Whereas some TBEV microfoci may contain TBEV unchanged for decades (Finland), other foci in Denmark may merely provide permissive conditions for random and repeated TBEV introductions from various geographical locations. TBEV was not identified in 58 tick pools collected 2010–2011 in North Zealand, Fuen, and Jutland by flagging or from roe deer. In addition, 78 patients in North Zealand with "summer flu" after tick bites (July–September 2010) and 96 hospitalized encephalitis patients after tick bites (2007–2009), who were negative for *Borrelia,* all tested negative for TBE antibodies.[7]

This supports a limited TBEV introduction into the new microfocus. Serological testing of roe deer "sentinels"[8] and computer predictions[9] suggest TBEV outside Bornholm. But no other TBE cases have occurred in Denmark outside Bornholm from 2009–2017, and recent flaggings for ticks (September, October 2016 and June, July 2017) from the Tokkekøb microfocus were negative for TBEV.[11] Yearly flaggings will continue, but we believe that the activity of the Tokkekøb microfocus has ended. All this changed by the hot summer in 2018 where 3 cases of TBE occurred, of which two were infected outside Bornholm: in Jutland (north of Esbjerg) and Fuen (near Faaborg), respectively. Moreover, the clinical manifestation of one of these was atypical, showing meningoradiculoneuritis rather than encephalitis.[12]

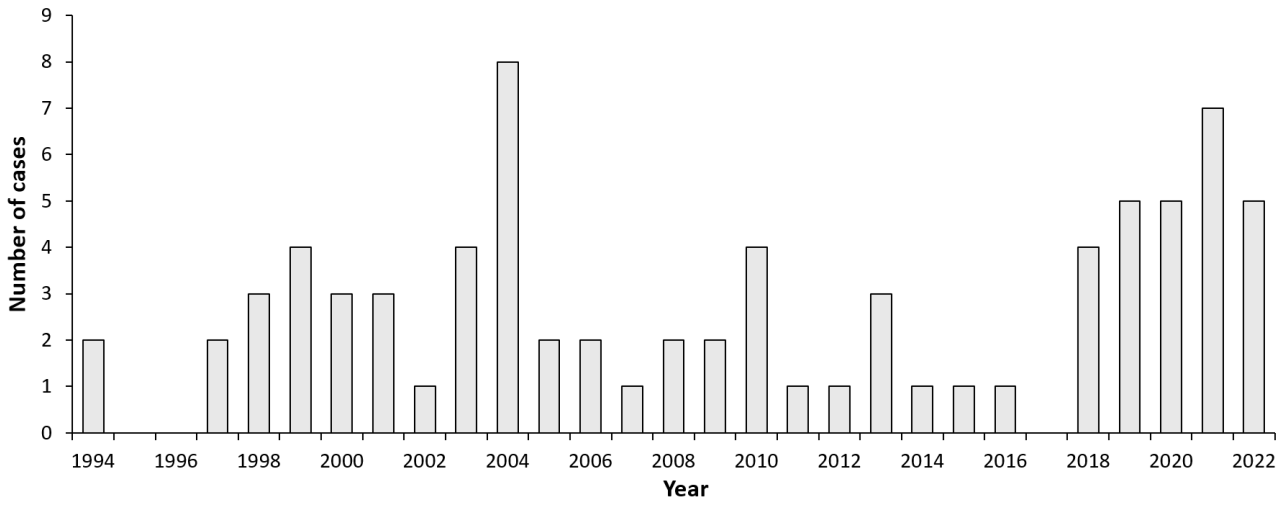
In June–July 2019 four cases (one case appeared during the publication of the three) were hospitalized, infected in the same wood area Tisvilde Hegn in Northern Zealand, bordering a playground. A new micro-focus was identified with a very high prevalence of 8% and only in nymphs. Whole genome sequencing showed clustering with a TBEV from Norway.[13]

In 2022, Denmark had 5 hospitalized cases of typical TBE diagnosed at Statens Serum Institut, 3 males and 2 females ranging between 31–73 years of age. Only one of the five cases was from Bornholm island and the rest were infected in North Zealand.

Overview of TBE in Denmark

Table 1: Virus, vector, transmission of TBE in Denmark	
Viral subtypes, distribution	TBEV European (Western) subtype[7]
Reservoir animals	Roe deer[8]
Infected tick species (%)	2%[4]
Dairy product transmission	Not documented

Figure 1: Burden of TBE in Denmark over time[3,5,6]



Source Data: Appendix—Figure 1

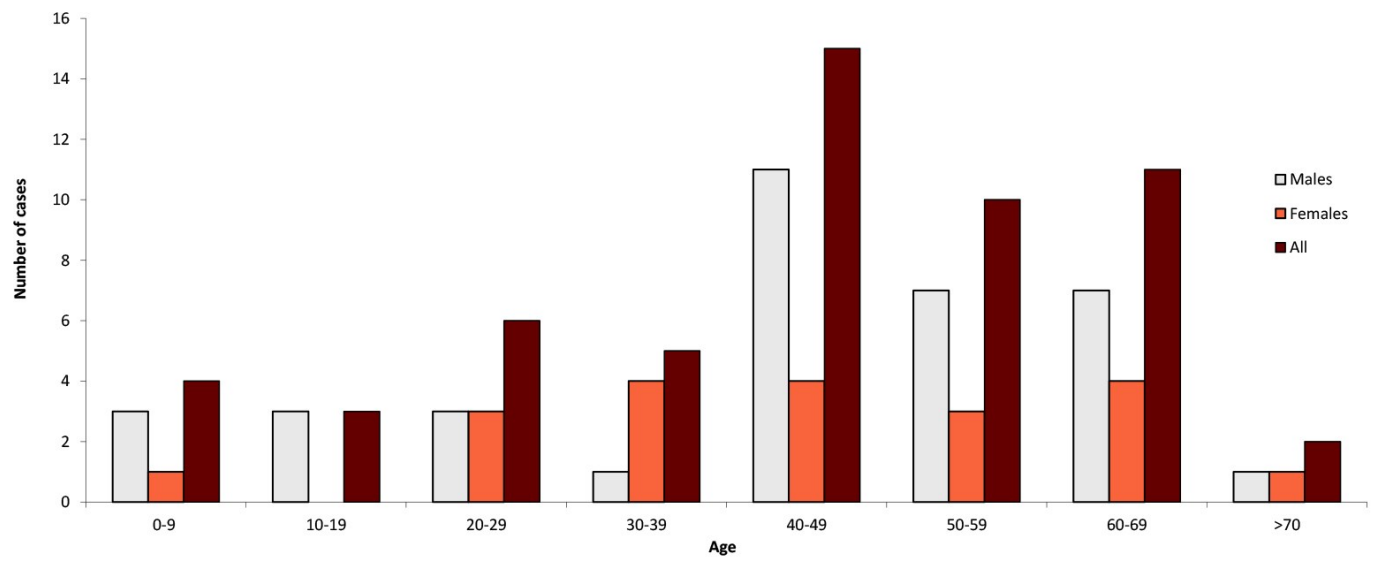
One of the TBE cases in 2008 and one in 2009 were infected in Tokkekøb microfocus;[6]
all others were infected on Bornholm Island, Denmark.

According to the Danish legislation, TBE is not a notifiable disease. However, since the SSI in Copenhagen performs centralized diagnostic testing, a line-item list is compiled for laboratory confirmed cases (since 2001).

Table 2: TBE reporting and vaccine prevention in Denmark	
Mandatory TBE reporting	TBE is not a notifiable disease in Denmark (DK) and there is no mandatory reporting
Other TBE surveillance	Statens Serum Institut (SSI) does the centralized TBE diagnostic in DK and compiles line-lists of confirmed cases
Special clinical features	Biphasic disease. Risk groups are people that regularly spend time in woods outside paths in areas where TBE is endemic (Bornholm)
	37.7% with permanent complications. No TBE deaths are registered in Denmark[3]
Available vaccines	Ticovac (Pfizer)
Vaccination recommendations and reimbursement	In 2001, the Danish Health Authorities recommended TBE vaccination for a defined at-risk population in Bornholm In 2009, the recommendations allowed reimbursement to regular visitors in endemic areas in DK[3,5]
Vaccine uptake by age group/risk group/general population	Unknown*
Name, address/website of TBE National Reference Center	Dept. Virology & Microbiology Diagnostic, Statens Serum Institut, 5 Artillerivej, DK-2300 Copenhagen S, Denmark (www.ssi.dk)

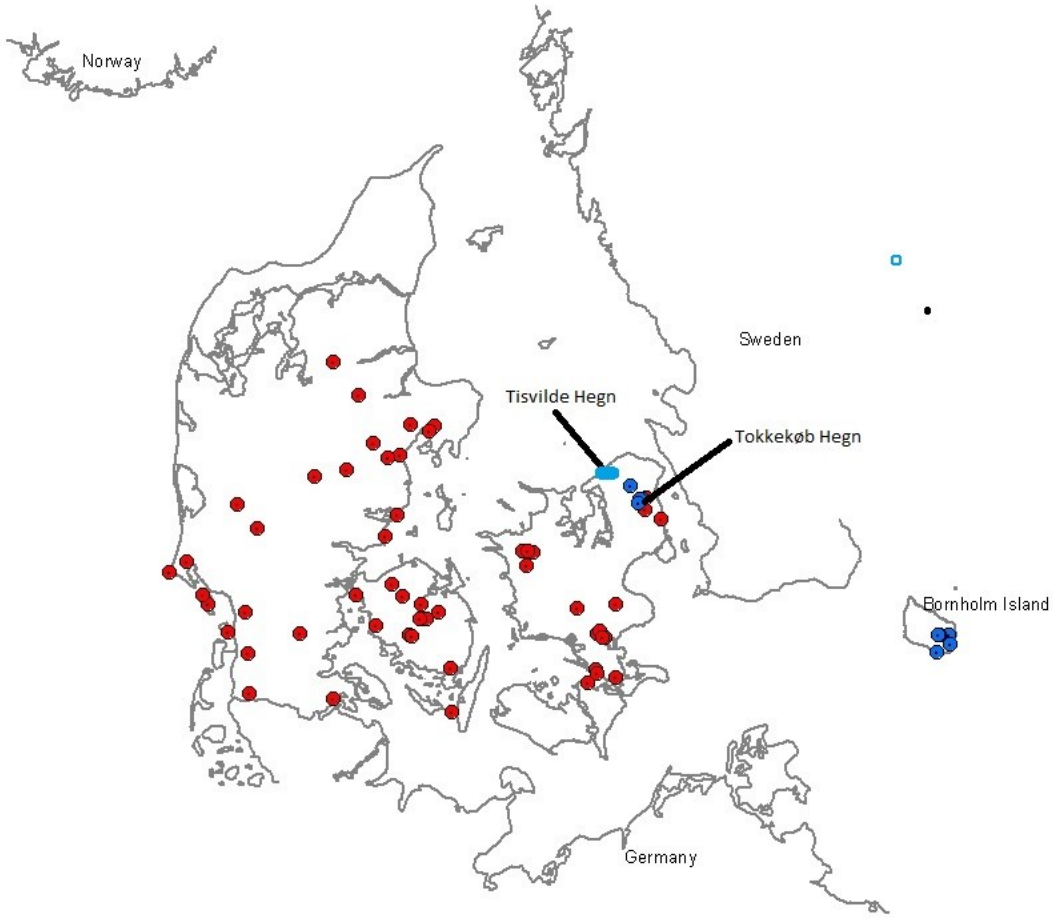
**In 2001, the Danish Health Authorities recommended TBE vaccination for a defined at-risk population in Bornholm. The vaccine coverage is not known, but starting in 2015 a prospective registration of all vaccines is mandatory in Denmark, which will clarify these issues.*

Figure 2: Age and gender distribution of TBE in Denmark[3,5,6]



Source Data: Appendix—Figure 2

Figure 3: TBEV-isolation and TBE cases in Denmark[7]



Isolate TBEV European (Western) subtype, T2; Tokkekøb Hegn, North Zealand[7]

Figure of Denmark showing endemic Bornholm and the TBEV microfocus Tokkekøb Hegn, North Zealand (TBEV isolate T2, 2011) and Tisvilde Hegn (2019); red dots indicate tick sampling from animals, blue dots indicate flagging.[7]

Appendix

Source data: Figure 1

Year	Number of cases	Incidence / 10^5
1951-1960	8	
		…
1994	2	
1995	?	
1996	?	
1997	2	
1998	3	
1999	4	
2000	3	3.81
2001	3	
2002	1	
2003	4	
2004	8	
2005	2	
2006	2	
2007	1	
2008	2	
2009	2	
2010	4	
2011	1	
2012	1	
2013	3	
2014	1	
2015	1	
2016	1	
2017	0	
2018	4	
2019	5	
2020	5	
2021	7	
2022	5	

Source data: Figure 2

Age group (years)	Males	Females	All
0-9	3	1	4
10-19	3	0	3
20-29	3	3	6
30-39	1	4	5
40-49	11	4	15
50-59	7	3	10
60-69	7	4	11
>70	1	1	2

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Citation:
Fomsgaard A. TBE in Denmark. Chapter 12b. In: Dobler G, Erber W, Bröker M, Schmitt HJ, eds. *The TBE Book*. 6th ed. Singapore: Global Health Press; 2023.
doi:10.33442/26613980_12b9-6

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