Tick-borne encephalitis - Update

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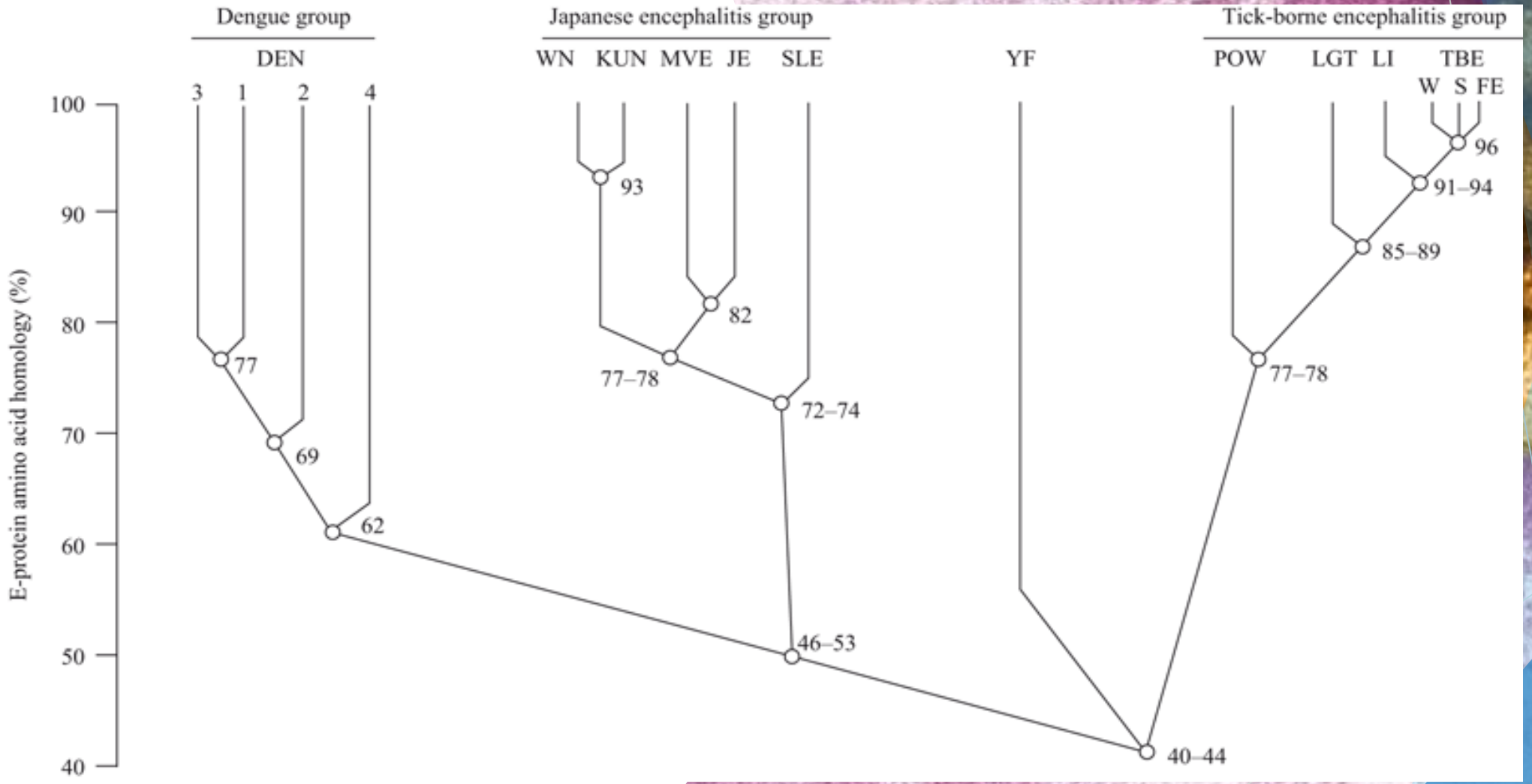
The talk

- The virus
- TBE-Eu in Children
- TBE distribution worldwide
- TBE cases diagnosed in Denmark
- TBE micro-foci
- TBE destribution in Denmark?
- Take home message

TBE-virus



Dobler, G., Gniel, D., Petermann, R., Pfeffer, M., 2012. Epidemiology and distribution of tick-borne encephalitis. Wien. Med. Wochenschr. 1946 162, 230–238. https://doi.org/10.1007/s10354-012-0100-5

Clinical course of TBE-Eu in children

- Incubation from tick bite to symptom debut 7-14 days.
- Similar to the clinical picture seen in adulthood but generally less severe
  - Biphasic course in ≥ 70 % of children
    - **Phase 1: The ”viremic” fase**
      - **Unspecific transient febrile illness lasting typically 2-4 days (1-14 days)**
        - **Headache (≈ 40%), vomiting (≈ 20%), adynamia (≈ 15%)**
      - **Followed by a short asymptomatic period**

Fever in young children and/or meningial signs: Not always

    - **Phase 2: Acute TBE**
      - **Fever (≈ 100%), headache and meningial signs (≈ 90-100%), vomiting (≈ 65-90%) and vertigo (≈ 10%).**
      - **Varying degree of meningitis (≈ 63-80%), meningoencephalitis (20-40 %) and meningoencephalomyelitis (very rare).**

Fritsch, P. et. al. 2008. Tick-borne encephalitis in Styrian children from 1981 to 2005: a retrospective study and a review of the literature. Acta Paediatr. 97, 535–538.
Sundin, M., 2017. TBE in children, in: Dobler, G., Erber, W., Schmitt, H.-J. (Eds.), TBE – The Book. Global Health Press, Singapore, pp. 85–90
Fowler, A., Forsman, L., Eriksson, M., Wickstrom, R., 2013. Tick-borne encephalitis carries a high risk of incomplete recovery in children. J. Pediatr. 163, 555–560.

Table I. Demographic details, symptoms, laboratory findings, results of examinations, and hospitalization details in 66 children with TBE

	All children with TBE (n = 66)	Mild TBE (n = 30)	Moderate TBE (n = 11)	Severe TBE (n = 25)
Age in years (range)	10.8 (3-17)	9.7 (3-17)	11.9 (6-17)	10.7 (4-17)
Male, n (%)	40 (61)	17 (57)	7 (64)	16 (64)
Biphasic course, n (%)	48 (73)	22 (73)	11 (100)	15 (60)
Symptom-free interval in days, n (range)	7.8 (2-24)	10.3 (2-24)	6.2 (3-11)	7 (2-14)
Known tick bite, n (%)	35 (53)	18 (60)	5 (45)	12 (48)
Symptoms in the acute phase				
Headache	64	29	11	24
Fever	65	30	11	24
Stiffness of neck	19	6	3	10
Sensitivity to light and/or sound	24	4	5	15
Nausea	56	23	11	22
Abdominal pain	18	6	3	9
Focal neurologic abnormality	26	0	6	20
Altered consciousness	20	0	0	20
Seizures	6	0	0	6
Examination of CSF	65/66	30/30	11/11	24/25
Pleocytosis (WBC $\geq$6 cells/mm^3)	65/65	30/30	11/11	24/24
Number of WBC/mm^3 (mononuclear cells)	80.5 (58.9)	75 (53.0)	80.3 (63.4)	86.1 (60.3)
Abnormal EEG	27/33	0/5	5/5	22/23
Abnormal neuroimaging	1/9	-	0/1	1/8
CT	0/6	-	0/1	0/5
MRI	1/3	-	-	1/3
Hospitalization: children, n (%)	46 (70)	13 (43)	10 (91)	23 (92)
Duration of hospital stay, days (range)	7.3 (2-25)	6.0 (2-16)	5.5 (2-10)	10.5 (2-25)

CT, computed tomography; *MRI*, magnetic resonance imaging.

TBEV infection was classified as mild TBE (meningeal symptoms); moderate TBE (meningeal symptoms and one of the following: seizures, focal neurologic abnormality, or pathologic EEG); or severe TBE (altered consciousness, focal neurologic findings, or seizures in combination with pathologic EEG or neuroimaging).

Fowler, A., Forsman, L., Eriksson, M., Wickstrom, R., 2013. Tick-borne encephalitis carries a high risk of incomplete recovery in children. J. Pediatr. 163, 555-560.

Laboratory work-up

- Diagnosis
  - Anti-TBEV antibodies in serum.
  - Convalescent serum (1-2 weeks after initial sample) with titre increase will support the diagnosis.
  - CSF antibody detection and/or TBEV specific PCR can be performed.

- Limitations
  - Cross-reactivity to other flavivirus (YF, JE & DEN) or vaccination.

- Confirmatory test
  - TBE antibody neutralisation test (NT) may serve to confirm TBE specificity.
    - TBEV and LIV can not be distinguished from each other by NT.

Supportive laboratory results and examinations

- Nonspecific inflammatory signs
  - Leukocytosis
  - Elevated C-reactive protein (CRP)
  - Elevated erythrocyte sedimentation rate (ESR)
  - Thrombocytopenia in some
  - Elevated transaminases in some
- Lumbar puncture
  - Pleocytosis with a mononuclear preponderance has been described.
  - Elevated cerebrospinal fluid protein/albumin levels in some.
- EEG and MRI can in some cases support the diagnosis

Treatment

- NONE

- Vaccination
- **Children 1-15 years of age**
- **Primary vaccination - TicoVac Junior**
  - **1. dose -** 0,25 ml i.m.
  - **2. dose -** 0,25 ml i.m. 1-3 months after 1. dose (14 days interval if need for quick immunisation)
  - **3. dose** 0,25 ml i.m. 5-12 months after 2. dose.

- **Booster vaccination**
  - **1. dose -** 0,25 ml i.m. 3 years after 3. dose of the primary vaccination.
  - **Hereafter -** 0,25 ml i.m. every 5 years.

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Short-term morbidity and long-term sequelea

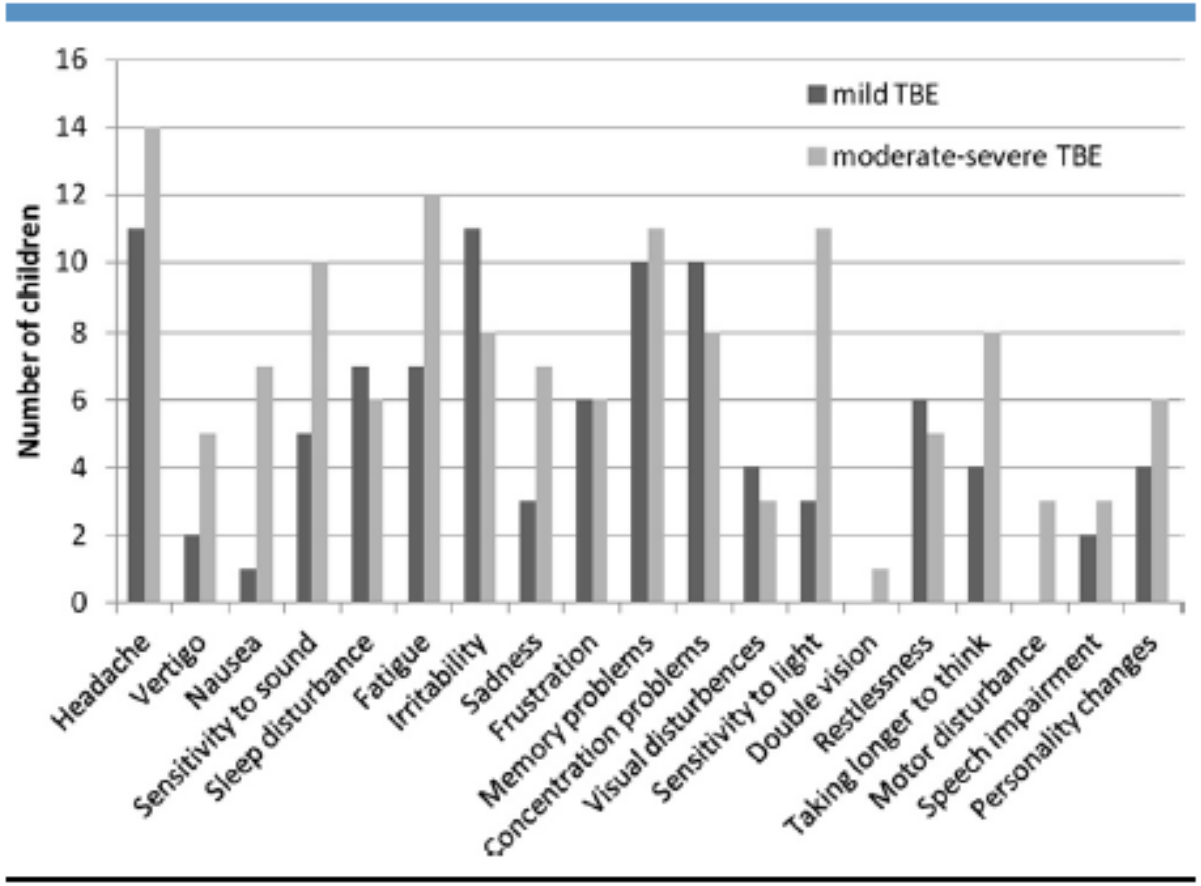

Figure 1. Persisting symptoms at follow-up 2-7 years post-TBE in 20 children with mild and 22 children with moderate-to-severe TBE.

- Median of 5-18 days of care in paediatric hospital wards
- 5% to 22% of TBE children is admitted to the ICU
- Death is very rare.

Fowler, A., Forsman, L., Eriksson, M., Wickstrom, R., 2013. Tick-borne encephalitis carries a high risk of incomplete recovery in children. J. Pediatr. 163, 555–560. https://doi.org/10.1016/j.jpeds.2013.01.037

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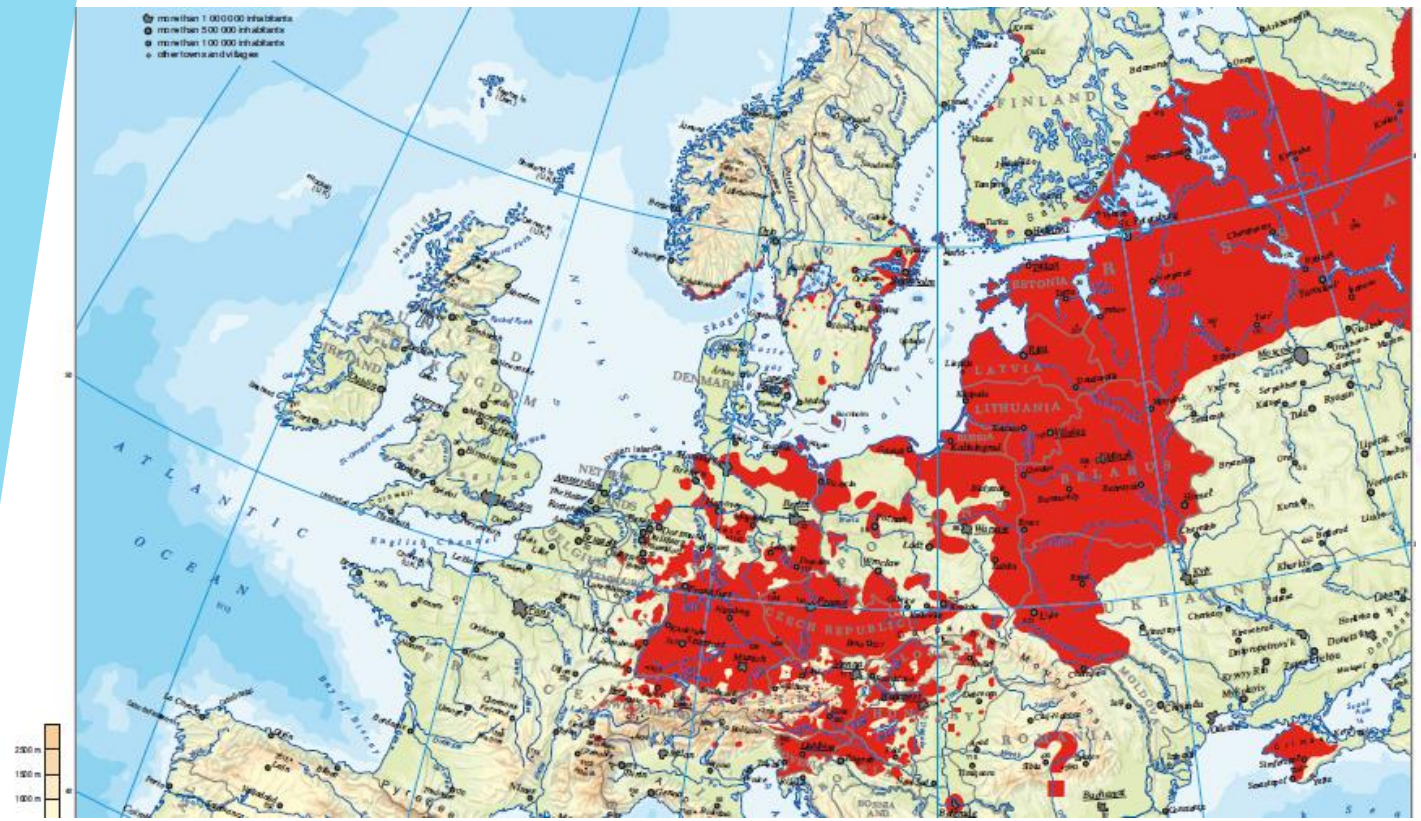


TBE-complex distribution

Maps from Pfizer

TBE cases diagnosed in Denmark

Figure 2. Total number of TBE cases and presumed place of infection, 2001-12

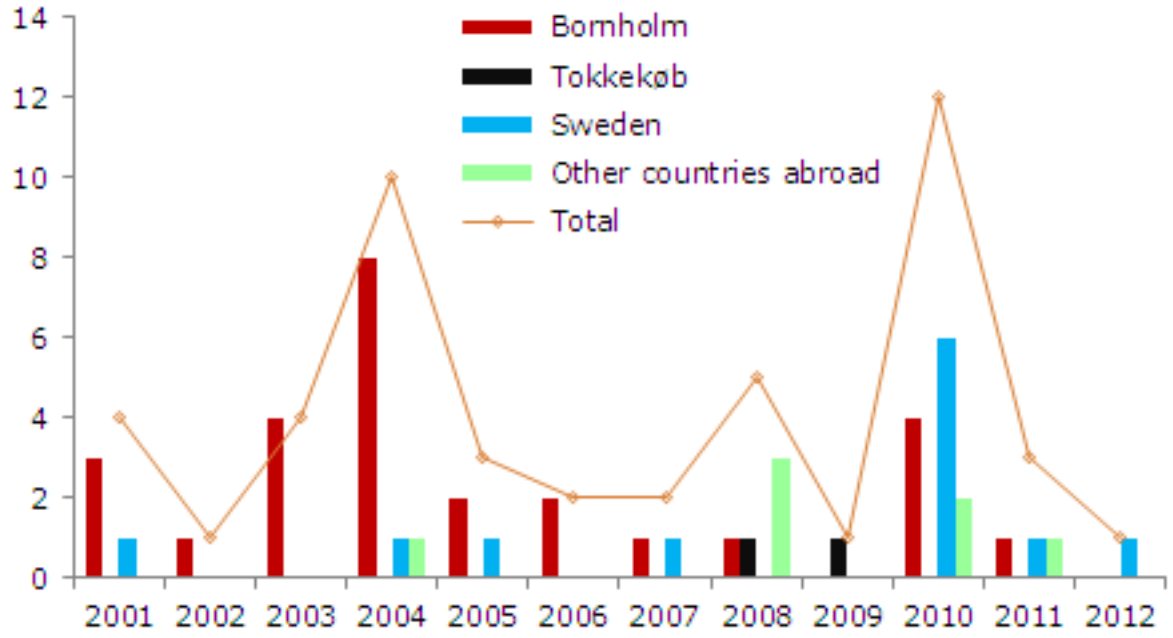
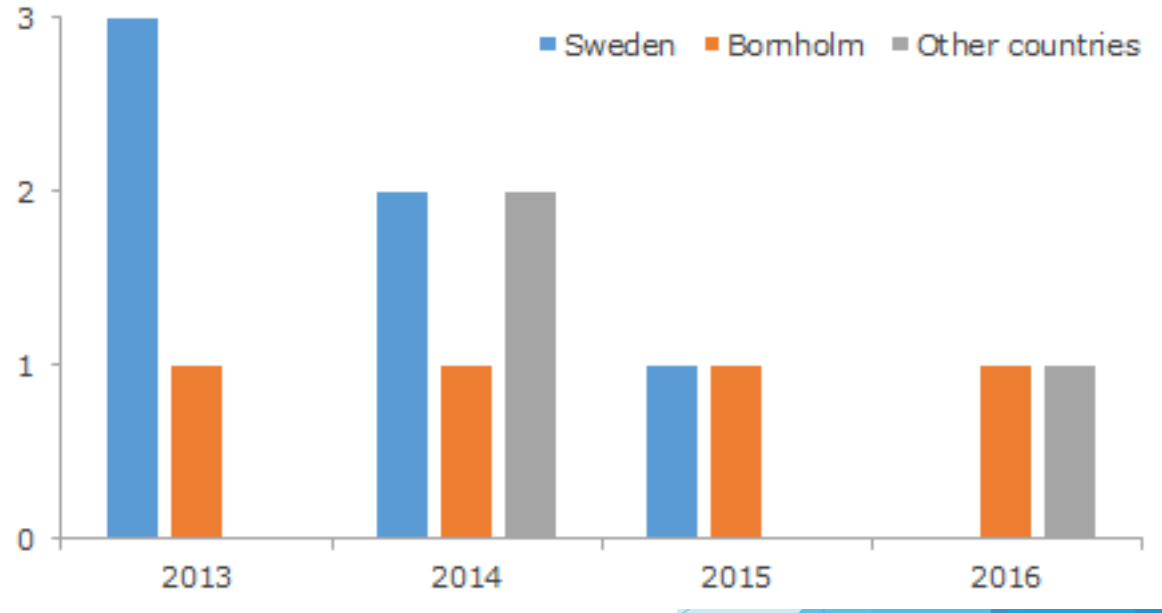


Figure 1. Number of cases with presumed TBEV infection, 2013-2016

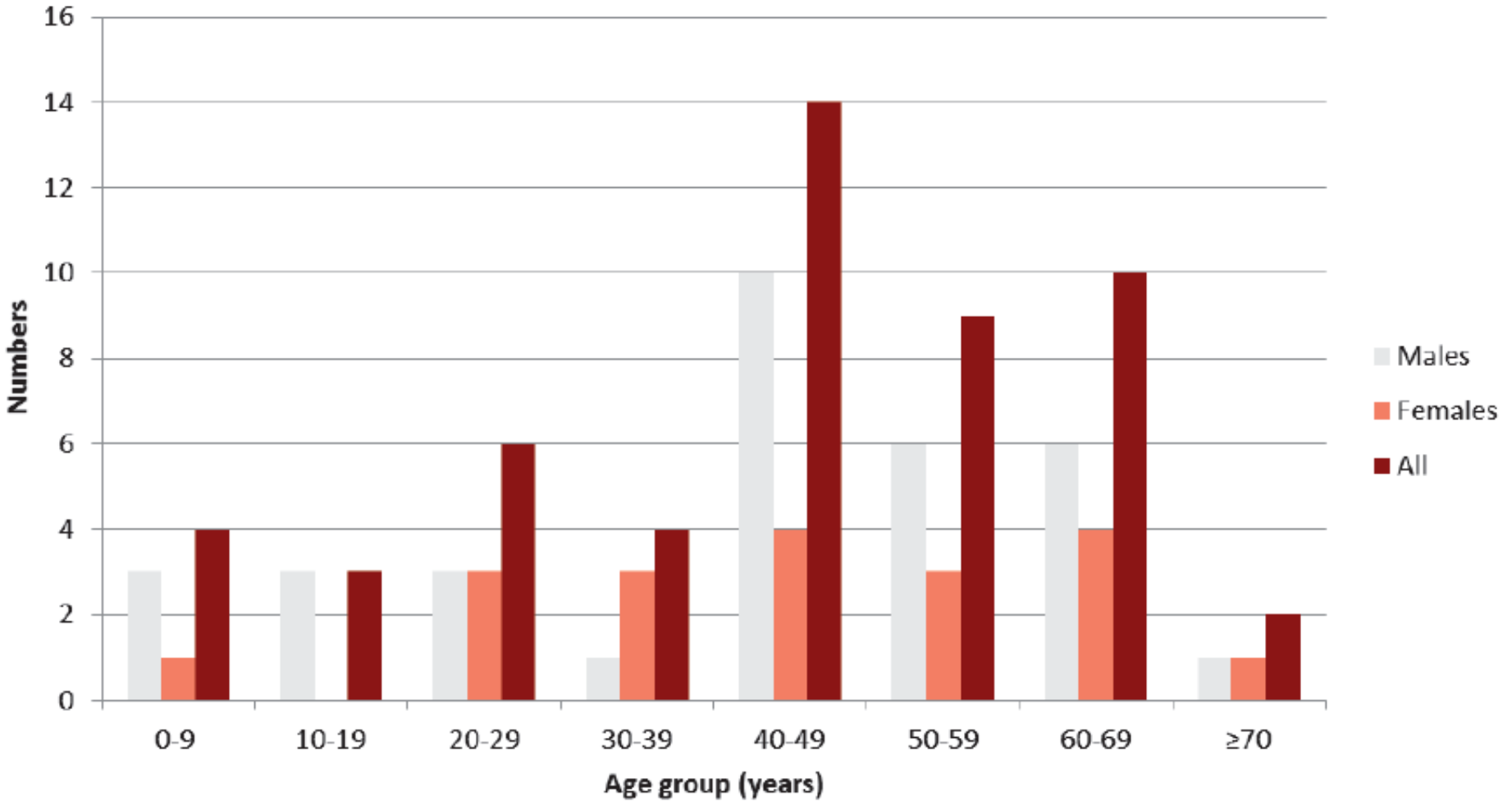


Andersen, P.H., Mølbak, K., Fomsgaard, A., 2013. EPI-NYT - 2013 - uge 25 - Statens Serum Institut [WWW Document]. URL http://www.ssi.dk/Aktuelt/Nyhedsbreve/EPI-NYT/2013/Uge%2025%20-%202013.aspx (accessed 06.11.18).

Ocias, L., Frans, Krogfelt, K.A., Worsøe Rosenstierne, M., Fomsgaard, A., Bødker, R., 2017. Infektion med TBE-virus i Danmark 2013-2016 (No. Uge 40), EPI-NYT. Statens Serum Institut, Copenhagen. https://www.ssi.dk/English/News/EPI-NEWS/2017/No%2040%20%202017.aspx (accessed 06.11.18)

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

Denmark 1994-2000 (14 cases) + 2001-2015 (38 cases)



Source Data: Appendix—Figure 2

Fomsgaard, A., 2017. TBE in Denmark, in: Dobler, G., Erber, W., Schmitt, H.-J. (Eds.), TBE – The Book. Global Health Press, Singapore.

TBE outside of Bornholm?

TBE predicted in Danmark

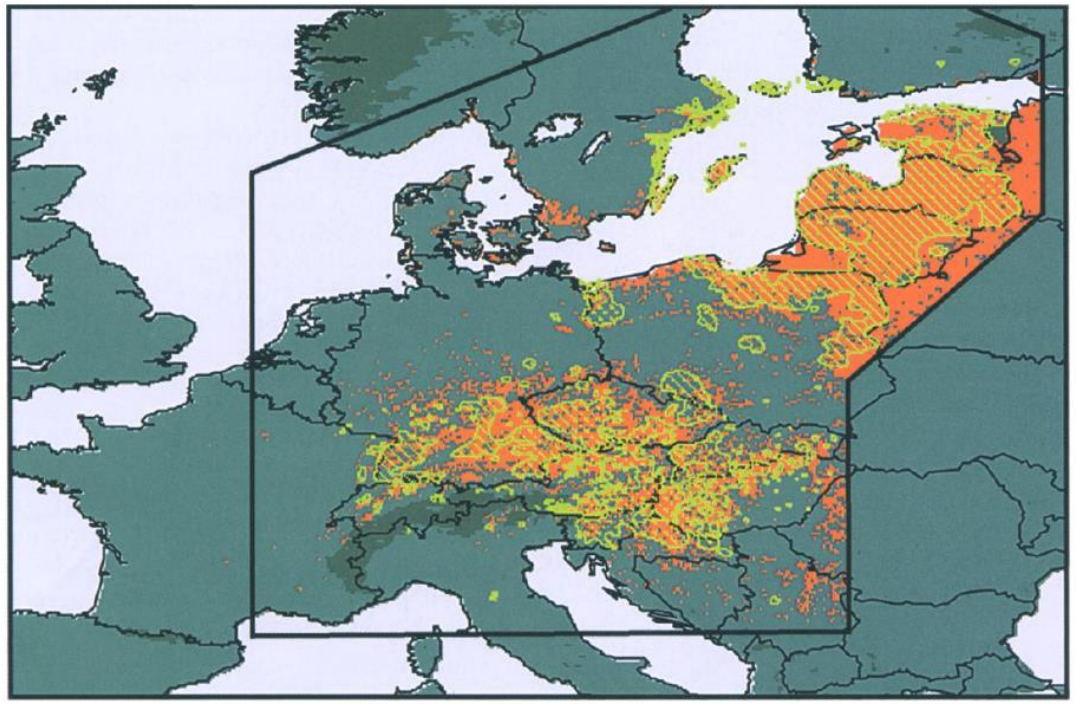
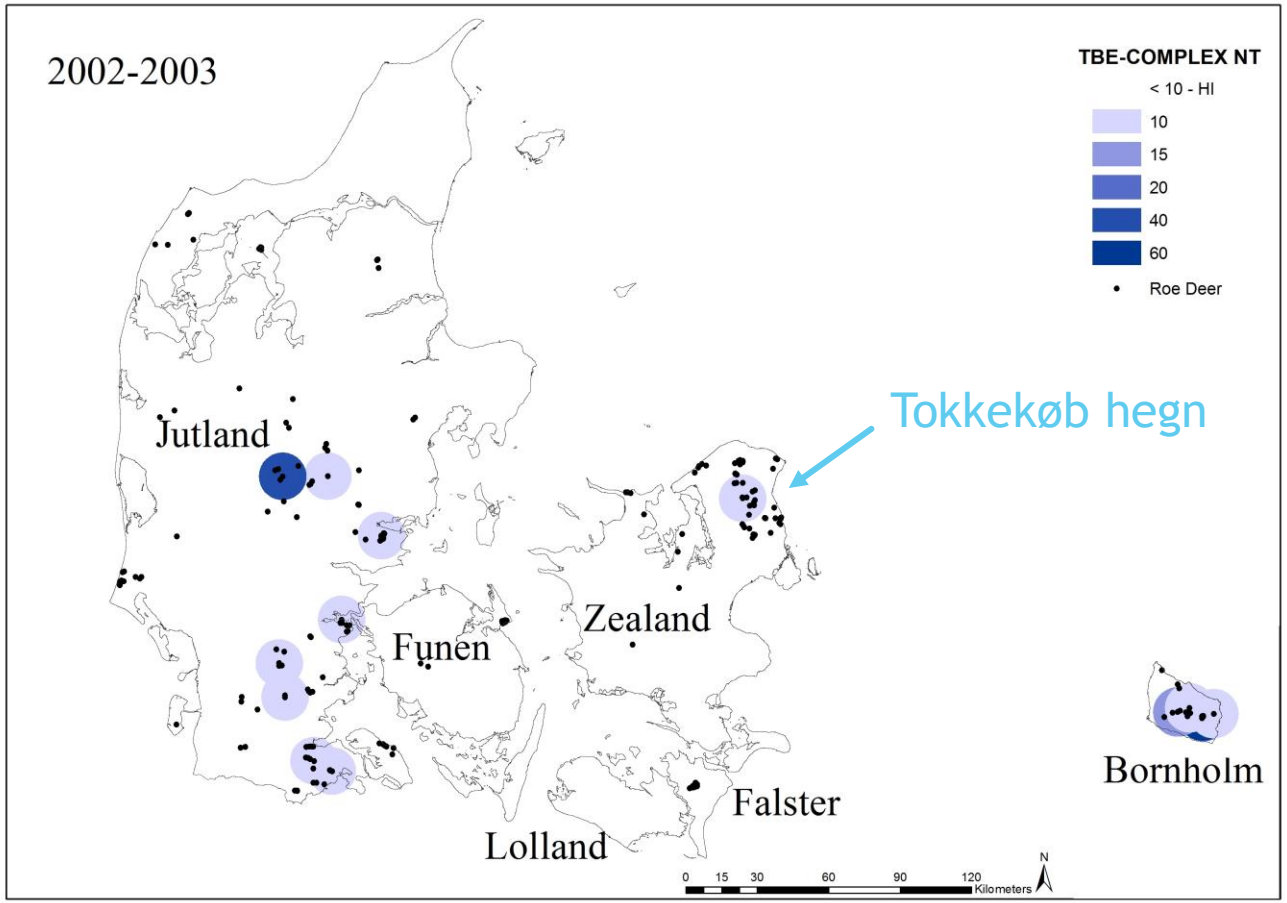


Figure 3. Predicted (red) and observed (yellow hatched) European distribution of tick-borne encephalitis virus (TBEV), based on analysis of remotely sensed environmental variables and elevation within the outlined area. TBEV occurs extensively to the east of this area, in Russia, Belarus, Ukraine and Romania (Immuno 1997), but is not yet mapped in any detail. High mountain areas (darker green), where satellite data are less reliable due to more frequent cloud contamination, were excluded from the analysis. (From Randolph 2000, with permission from Academic Press.)



Randolph, S.E., 2001. The shifting landscape of tick-borne zoonoses: tick-borne encephalitis and Lyme borreliosis in Europe. Philos. Trans. R. Soc. Lond. B. Biol. Sci. 356, 1045–1056. https://doi.org/10.1098/rstb.2001.0893

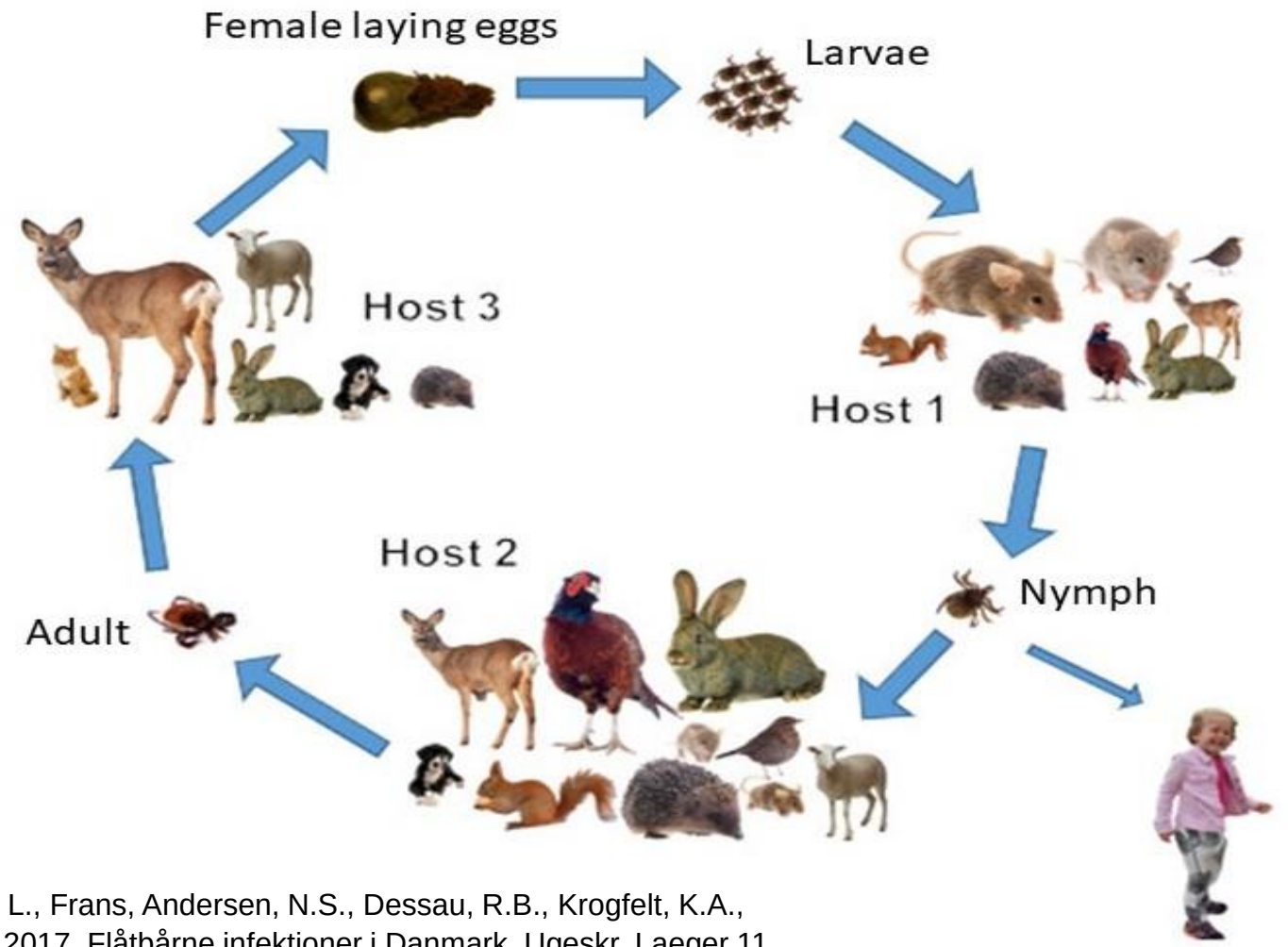
Skarphédinsson, S., Jensen, P.M., Kristiansen, K., 2005. Survey of tickborne infections in Denmark. Emerg. Infect. Dis. 11, 1055–1061. https://doi.org/10.3201/eid1107.041265

Tokkekøb Hegn Focus

Photograph: TBEV microfocus between the forest worker's house and a lake, Tokkekøb Hegn, North Zealand, Denmark

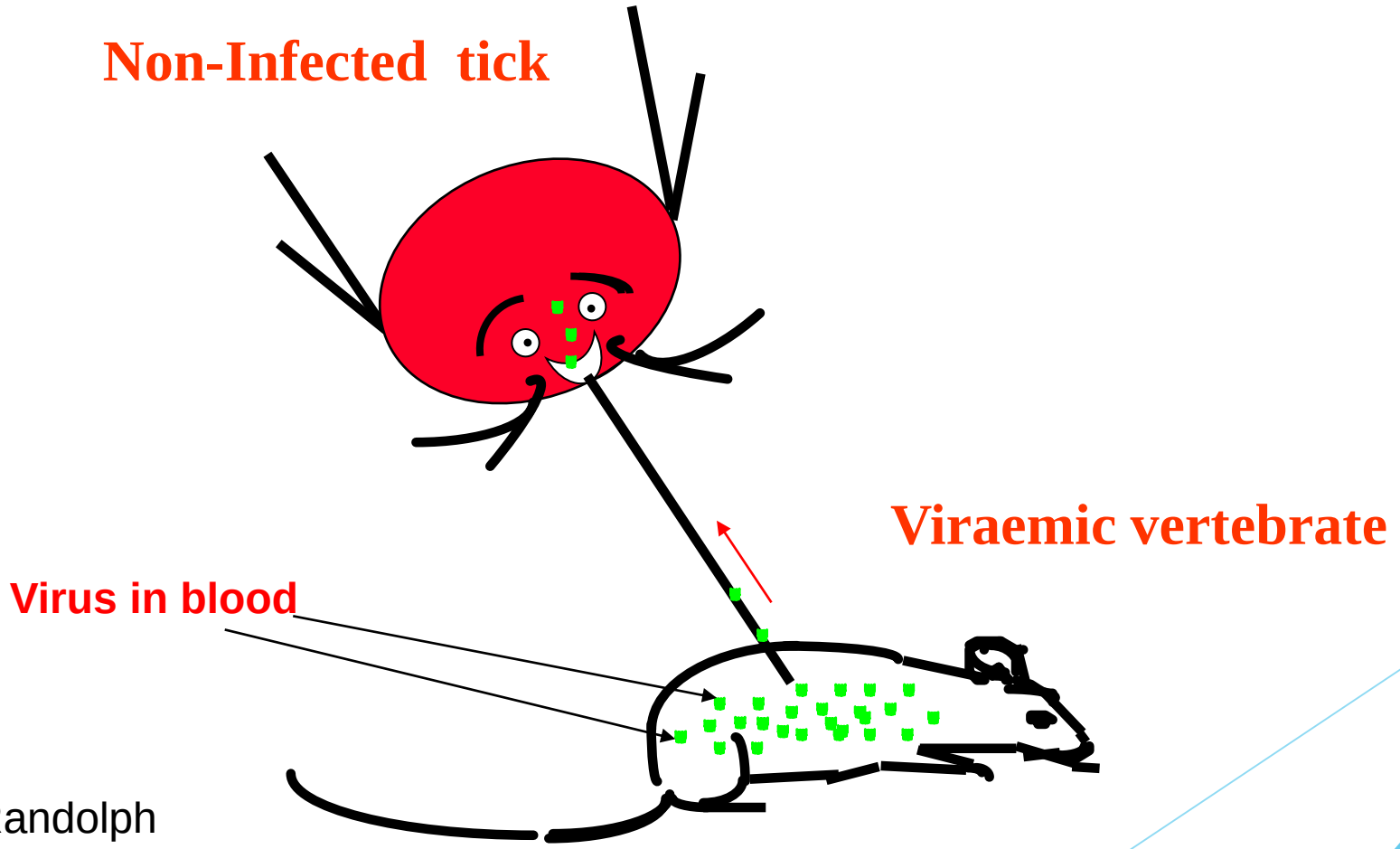
Fomsgaard, A., 2017. TBE in Denmark, in: Dobler, G., Erber, W., Schmitt, H.-J. (Eds.), TBE – The Book. Global Health Press, Singapore.

How come TBE is rare but neuroborreliosis is not?



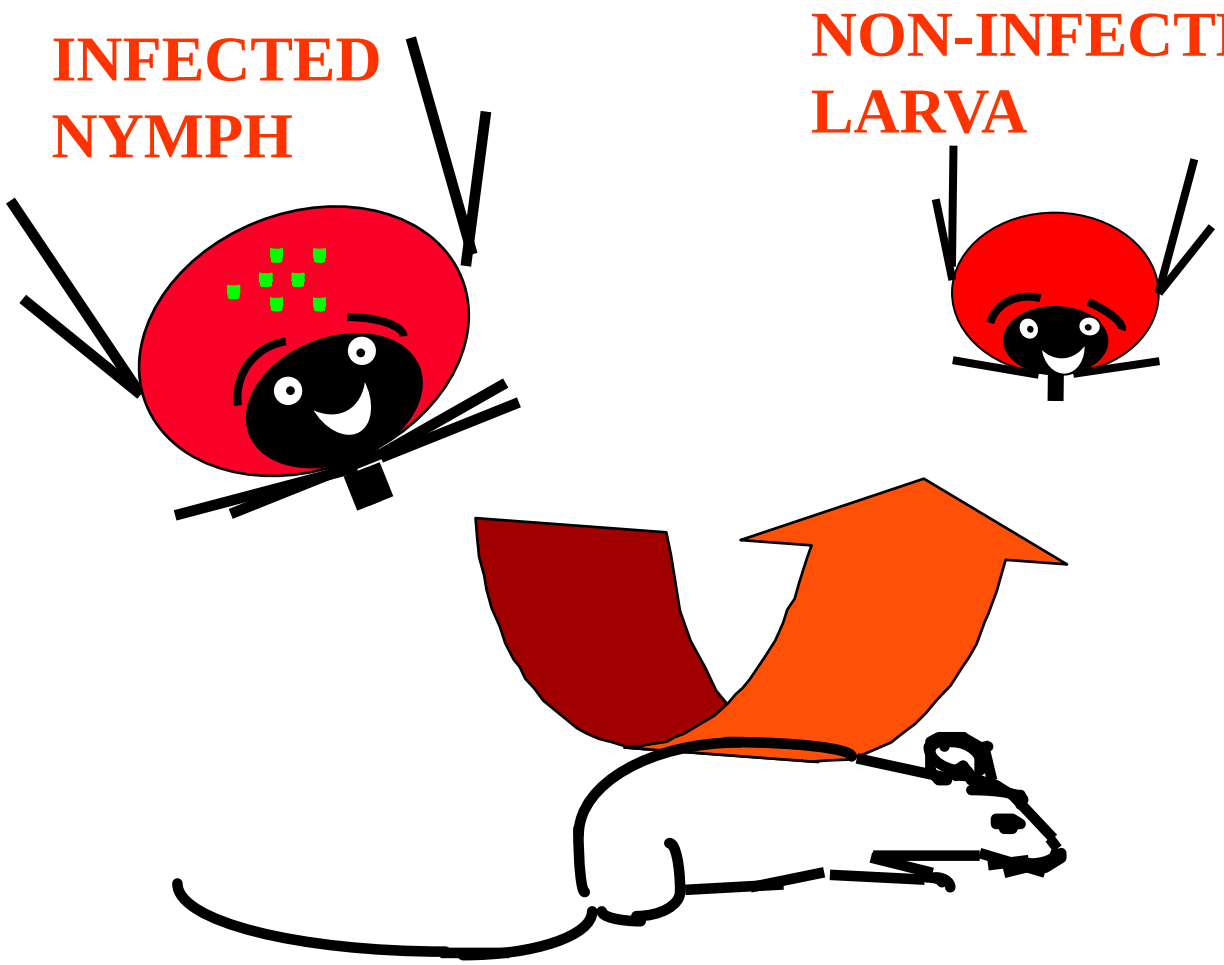
Jensen, B.B., Ocias, L., Frans, Andersen, N.S., Dessau, R.B., Krogfelt, K.A., Skarphédinsson, S., 2017. Flåtbårne infektioner i Danmark. Ugeskr. Laeger 11.

Viraemic transmission



Maps from S. Randolph

Non-viraemic transmission of tick-borne encephalitis virus between ticks co-feeding on wildlife species



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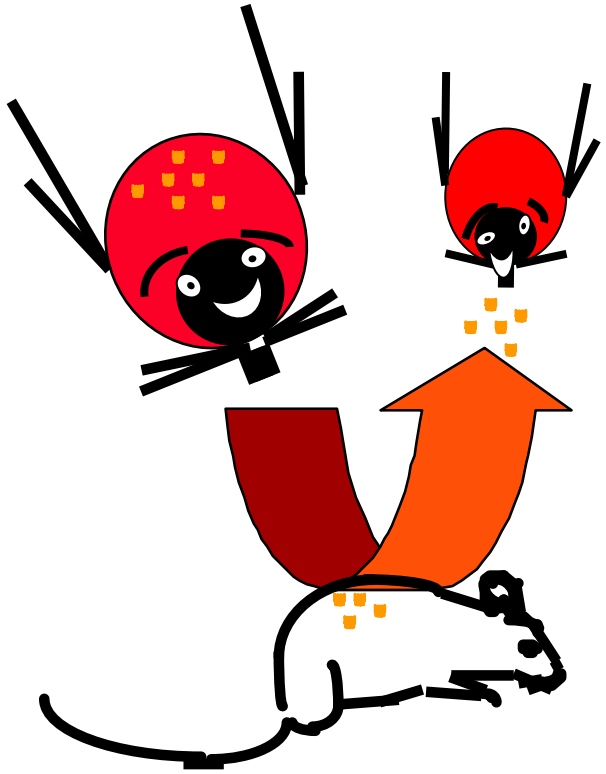
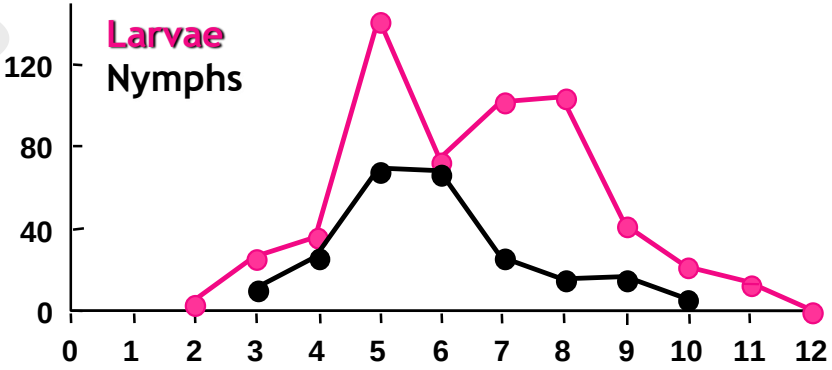
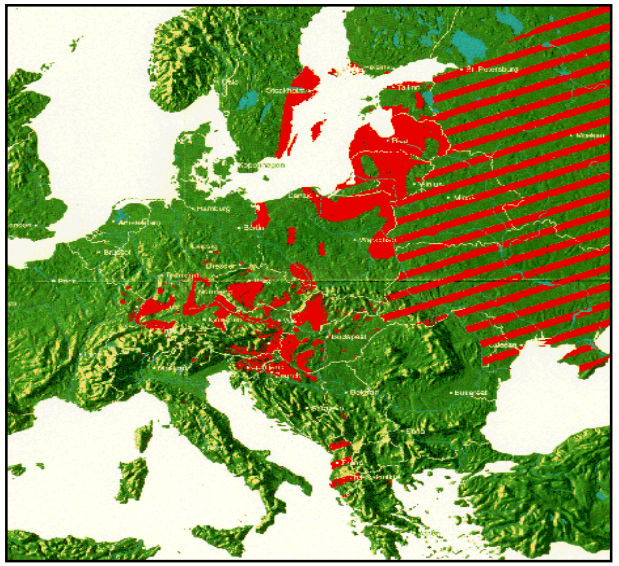


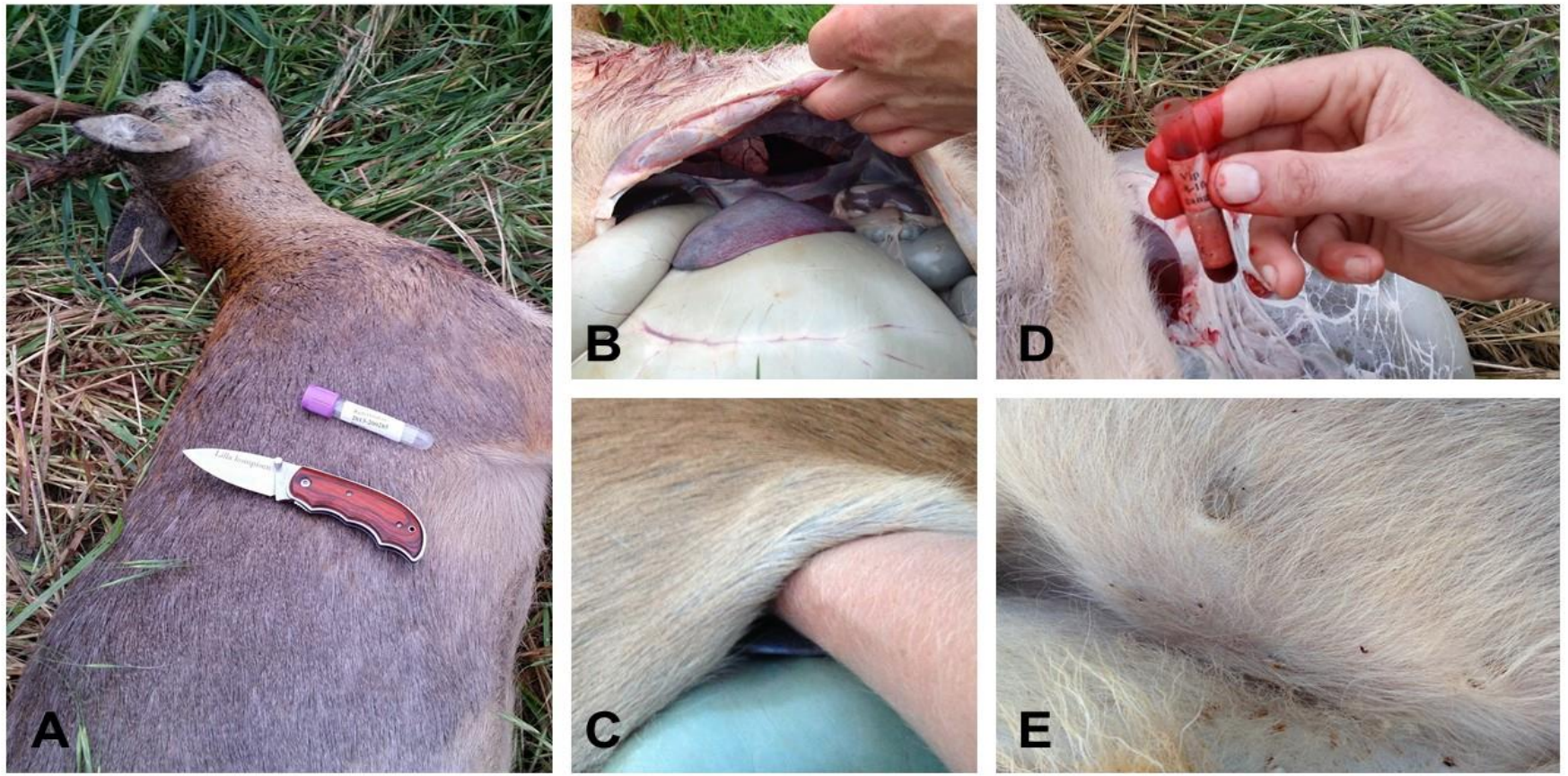
Climate





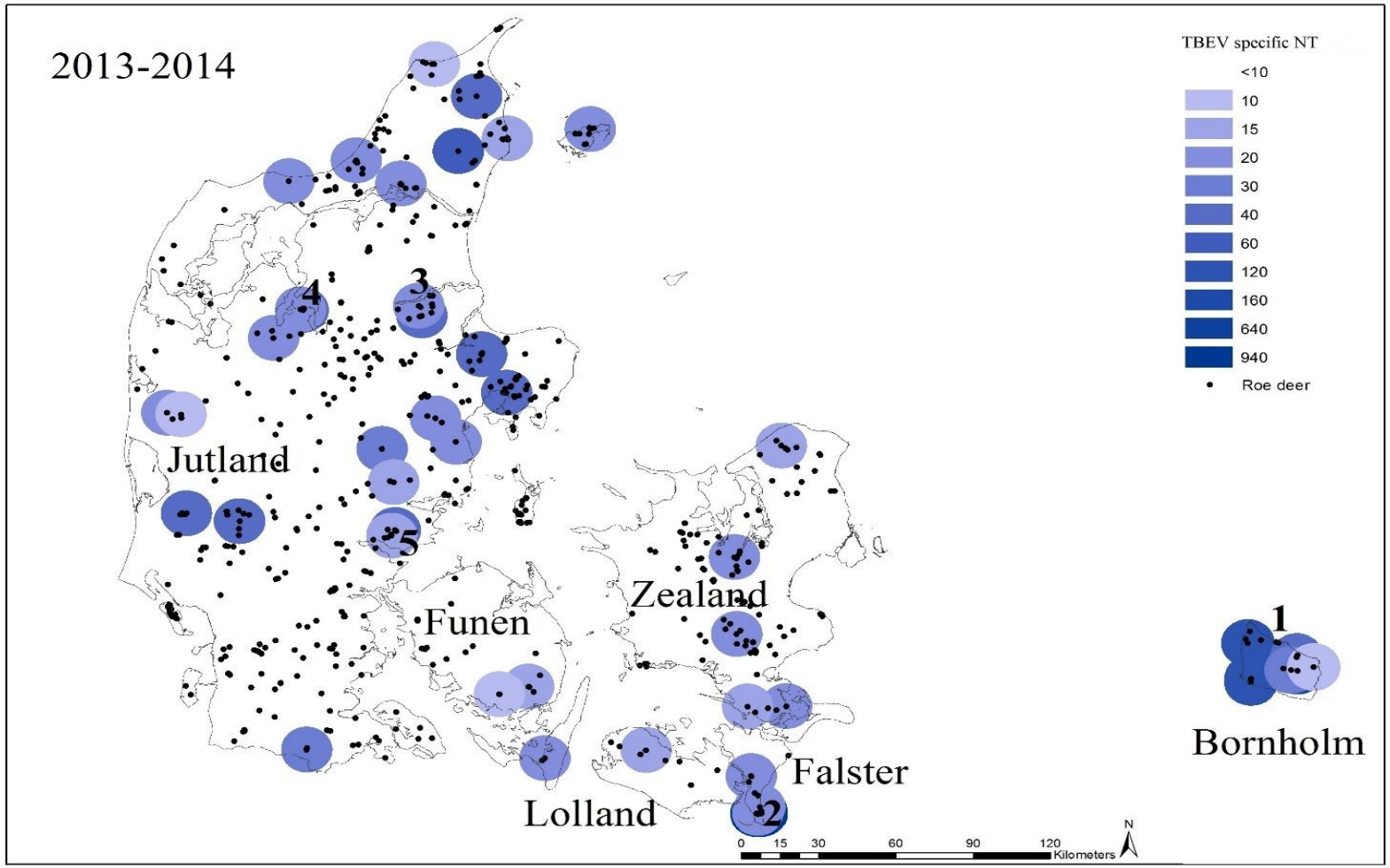
Maps from S. Randolph

Looking for TBEV microfoci outside of Bornholm – Sentinel serosurvey



Andersen, N.S., Larsen, S.L., Olesen, C.R., Stiasny, K., Kolmos, H.J., Jensen, P.M., Skarphédinsson, S., 2018. Continued expansion of tick-borne pathogens: Tick-borne encephalitis virus complex and Anaplasma phagocytophilum in Denmark. Ticks Tick-Borne Dis. pii: S1877-959X(18)30192-4. https://doi.org/10.1016/j.ttbdis.2018.09.007

Looking for TBEV microfoci outside of Bornholm – Sentinel serosurvey in roe deer



TBEV in hunters and blood donors

- 2/443 Hunters from all of Denmark
- 1/180 Blood donor

Take home message

- TBE is rare in Denmark, but relatively common in our neighbouring countries.
- Most cases of TBE in childhood will present similarly as in adults. However, a more diffuse clinical picture is seen specially in preschool children.
- Anti-TBEV serology are needed to establish the diagnosis.
- There is no specific treatment for TBE. Supportive care are needed based on the individual clinical course.
- Long term sequelae are common regardless of severity of the initial symptoms
- Protective immunity can be elicited in children by TBE vaccines.

Tank you