



Tick-borne encephalitis virus

and its **molecular epidemiology** in Europe

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Conflicts of interest?

- Reagentia – royalties for TBE serology test
- Pfizer – expert panel meeting fees



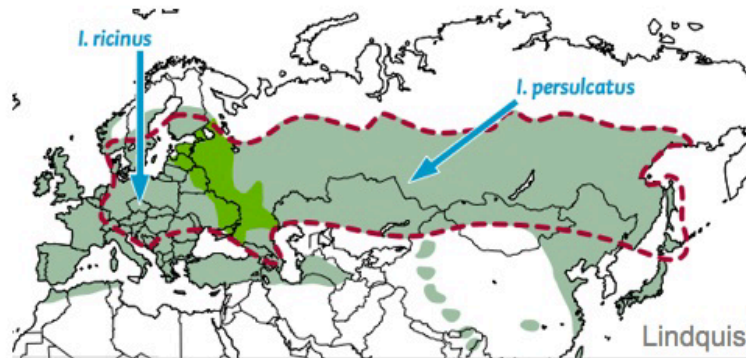
Tick-borne encephalitis virus

Genus *Flavivirus*, Family *Flaviviridae*

• TBEV VECTORS

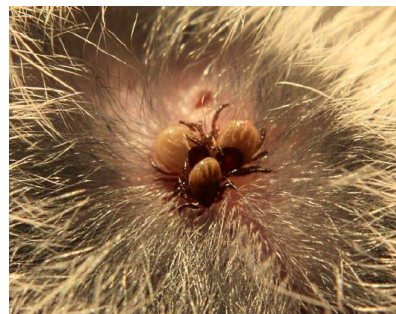
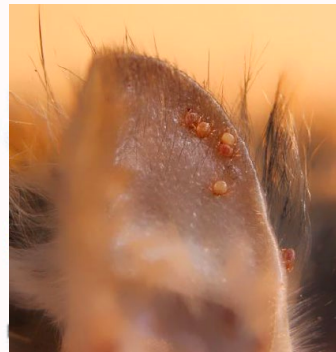
- Ixodes ricinus* - sheep tick → (TBEV European subtype)
- Ixodes persulcatus* - taiga tick → (TBEV - Siberian and Far Eastern subtypes)

1-2 % ↑



Lindquist & Vapalahti, Lancet 2008

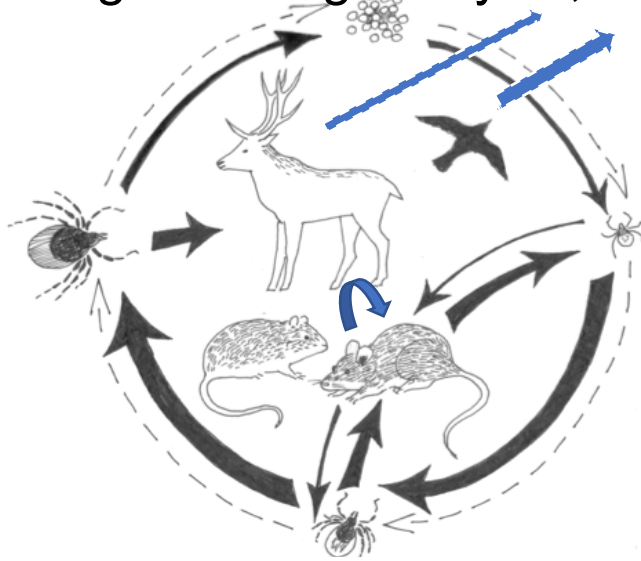
- virus transmitted within minutes from tick saliva, cycle in nature requires suitable climate, which favors "co-feeding"



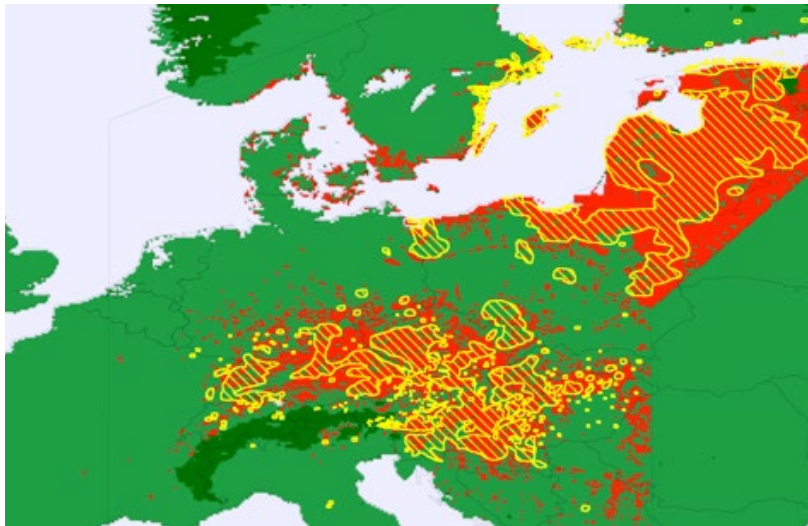
In endemic foci typically 1-2% of ticks TBEV positive

TBE - sensitive to climate

- Fragile ecological cycle, cofeeding

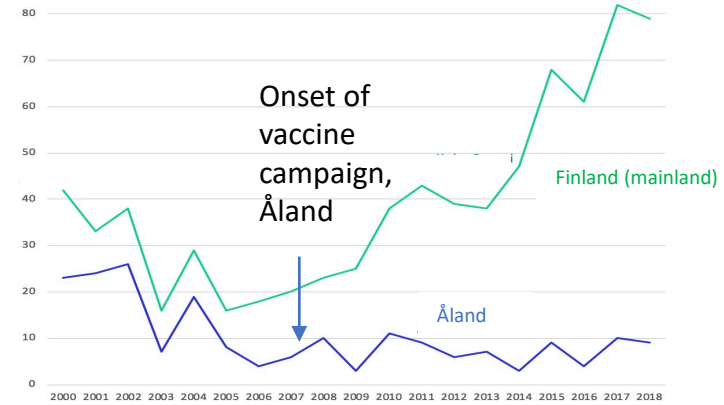


- “Focal” occurrence -climate influences

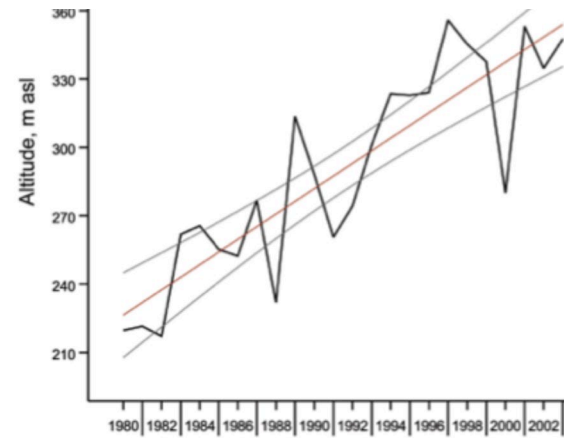


Randolph SE (2000), *Advances in Parasitology* 47, 217-243

- Case numbers rising in Finland and elsewhere in N Europe



- TBE risk areas are rising on the mountains in C Europe



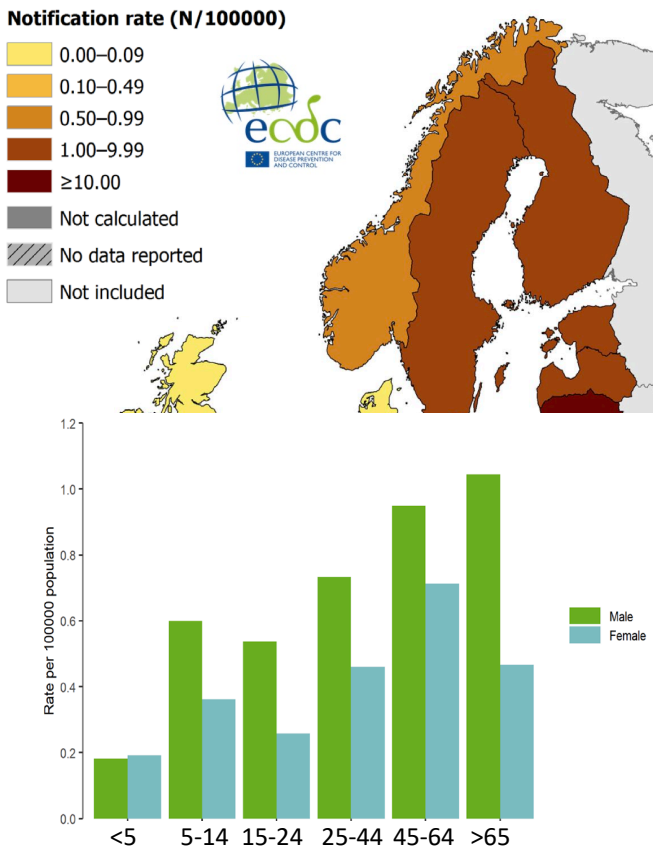
CLIMATE WARMING and TICK-BORNE ENCEPHALITIS, SLOVAKIA

Lukan et al, *Emerg Infect Dis*, 2010



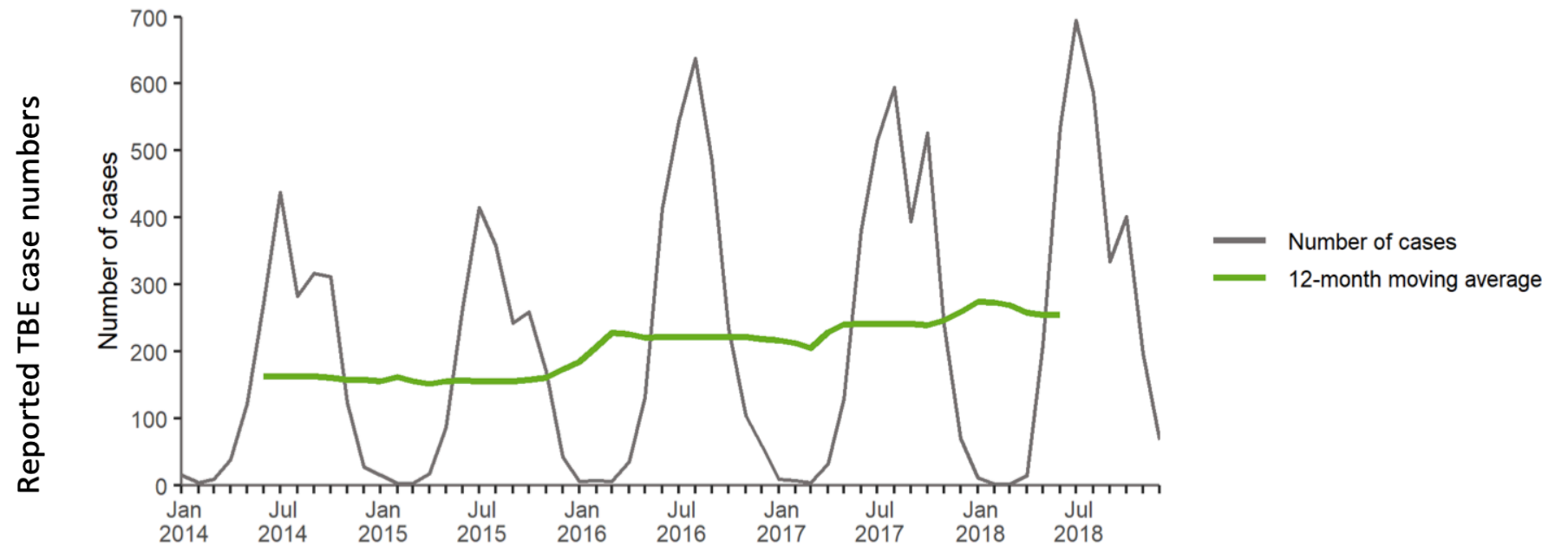
TBE in Europe

Incidence (2018)



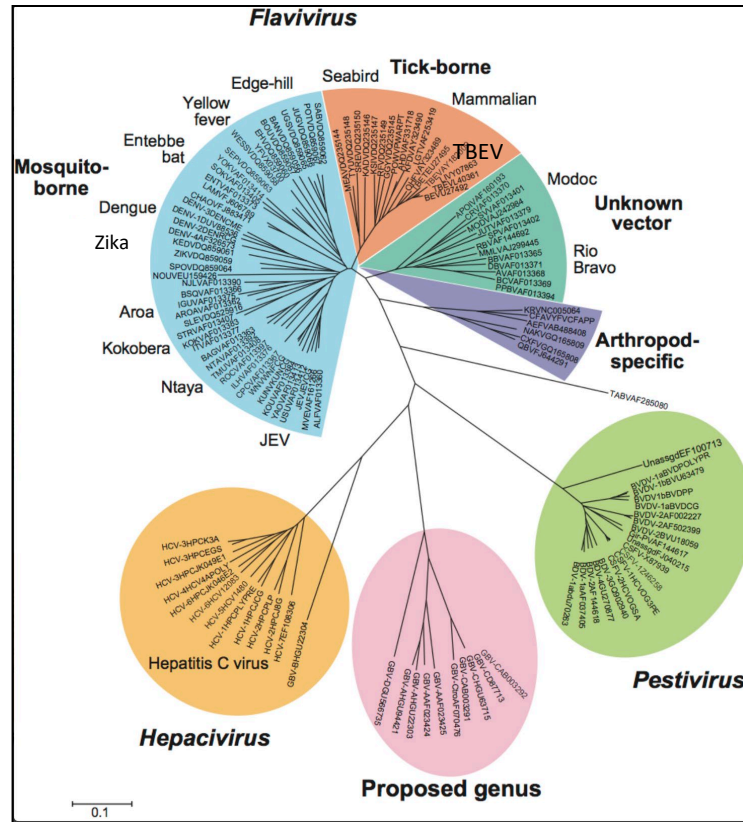
Cases (N, 2015-2020)

Figure 3. Distribution of confirmed tick-borne encephalitis cases by month, EU/EEA, 2014–2018

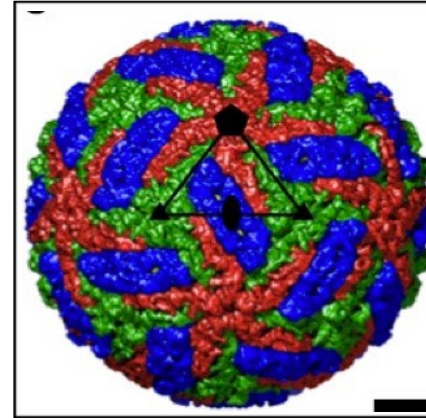


TBEV, Genus Flavivirus, family *Flaviviridae*

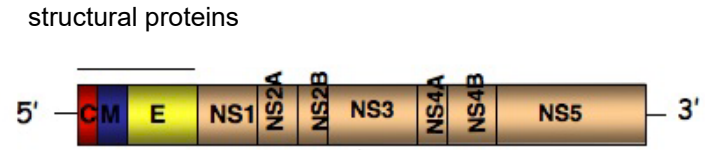
• Flavivirus phylogeny



• TBEV particle



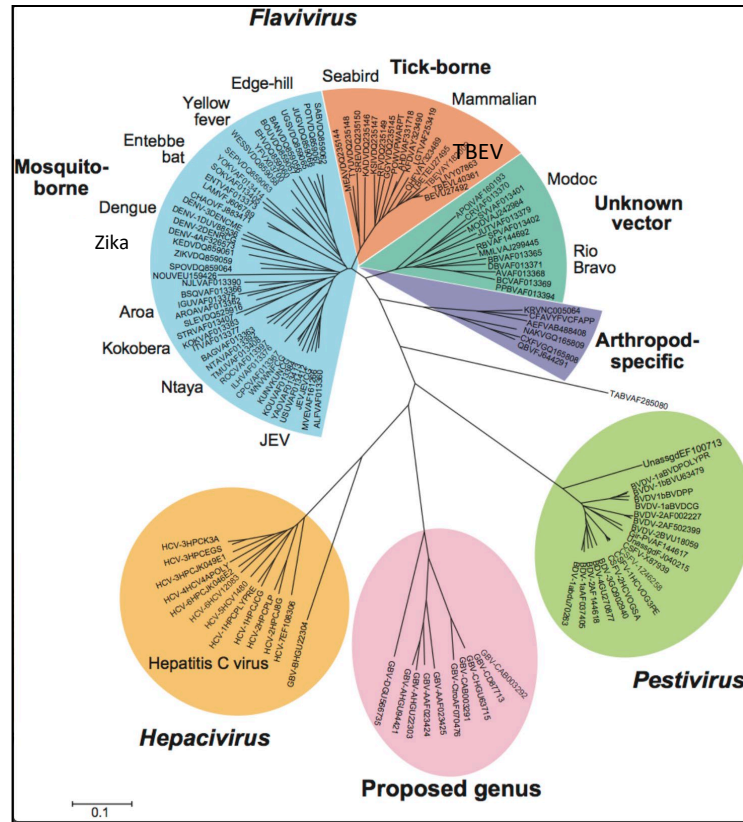
• RNA-genome



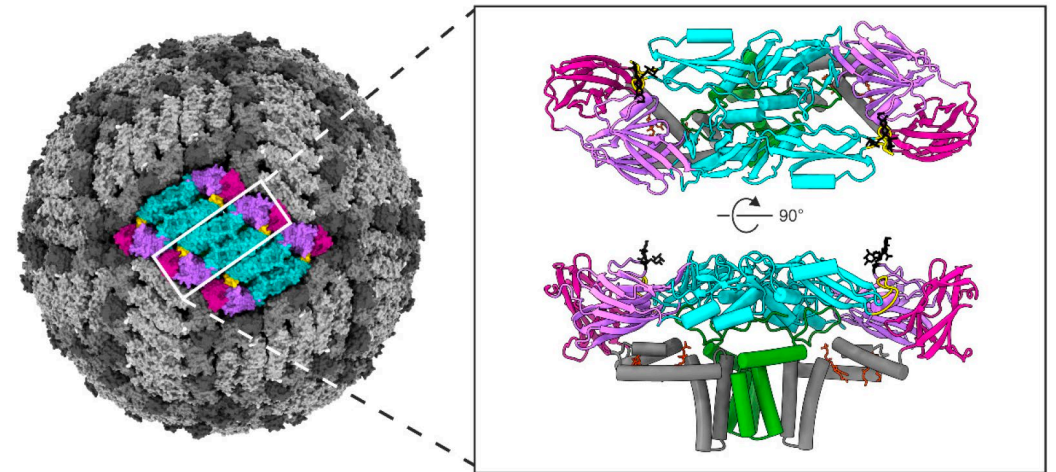
Füzük et al,
Nat Comm
2018

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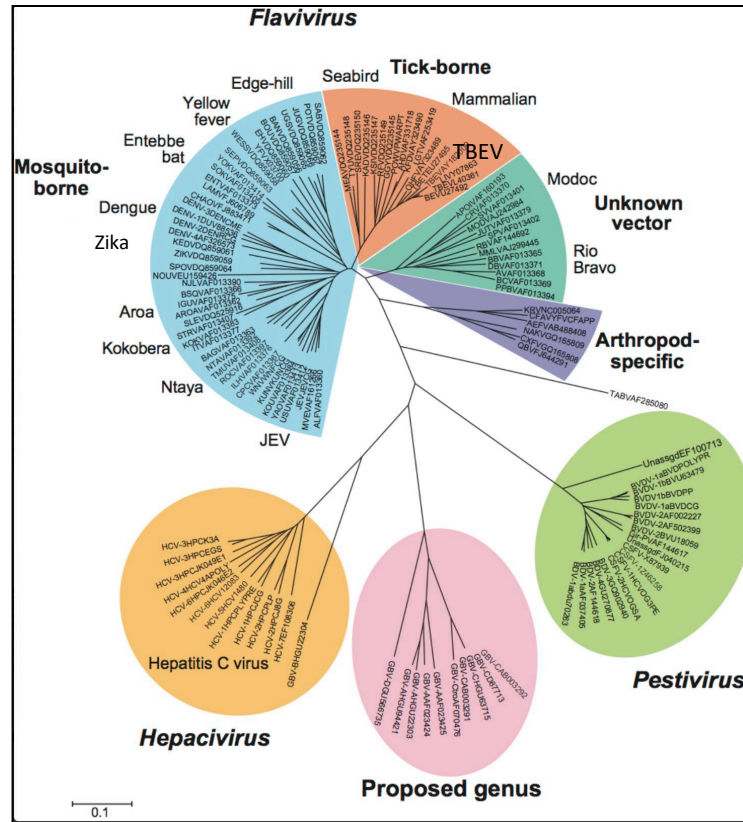
• TBEV particle



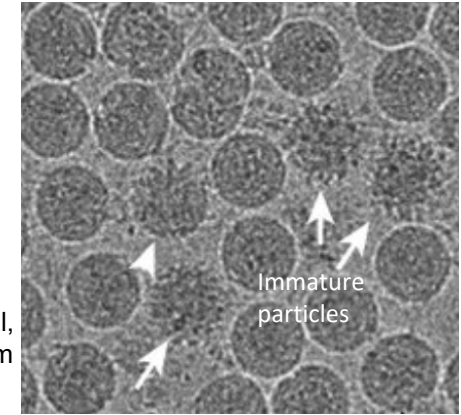
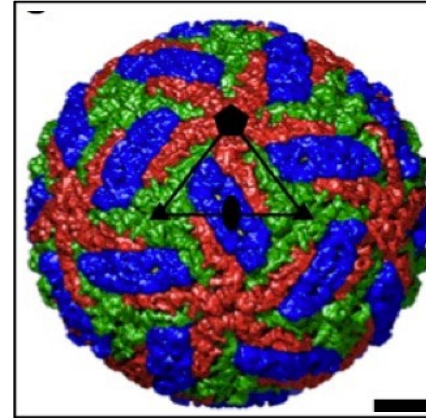
Pulkinen et al, Viruses 2022

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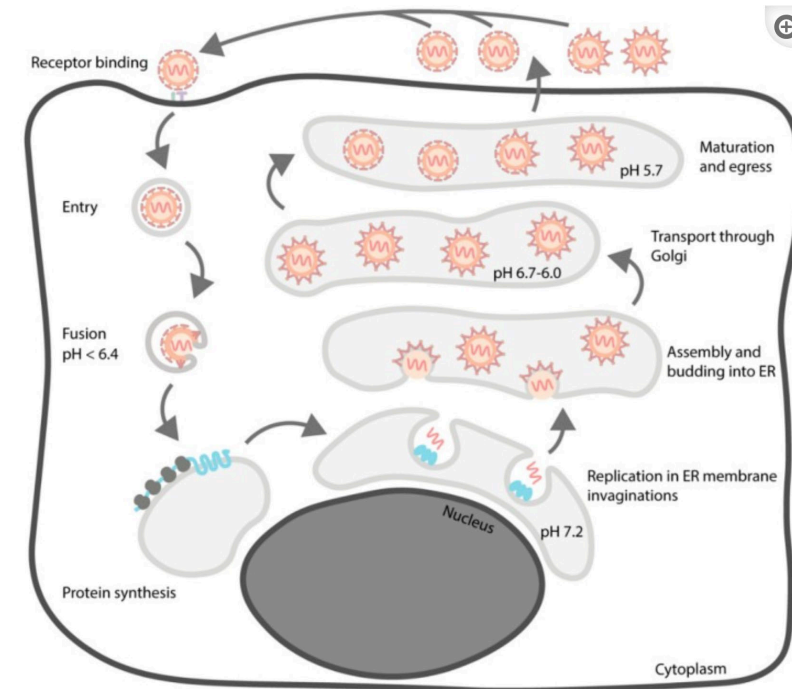


• TBEV particle

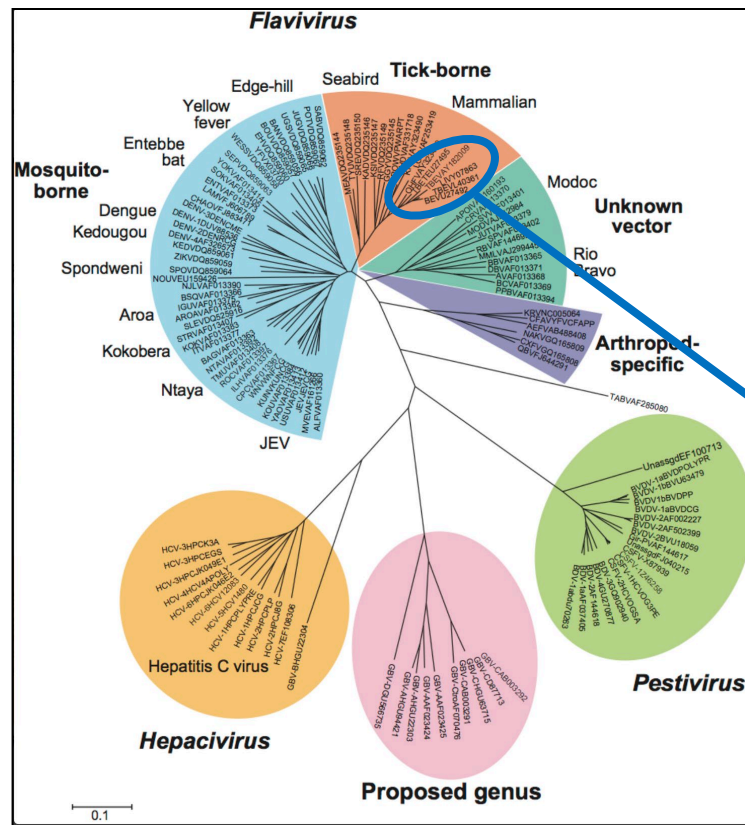


Füzük et al, Nat Comm 2018

• Virus buds in ER and matures while transported



Pulkkinen et al, Viruses 2018



Kuivanen, Smura, Vapalahti,
TBEV, Encyclopedia of Virology 2021

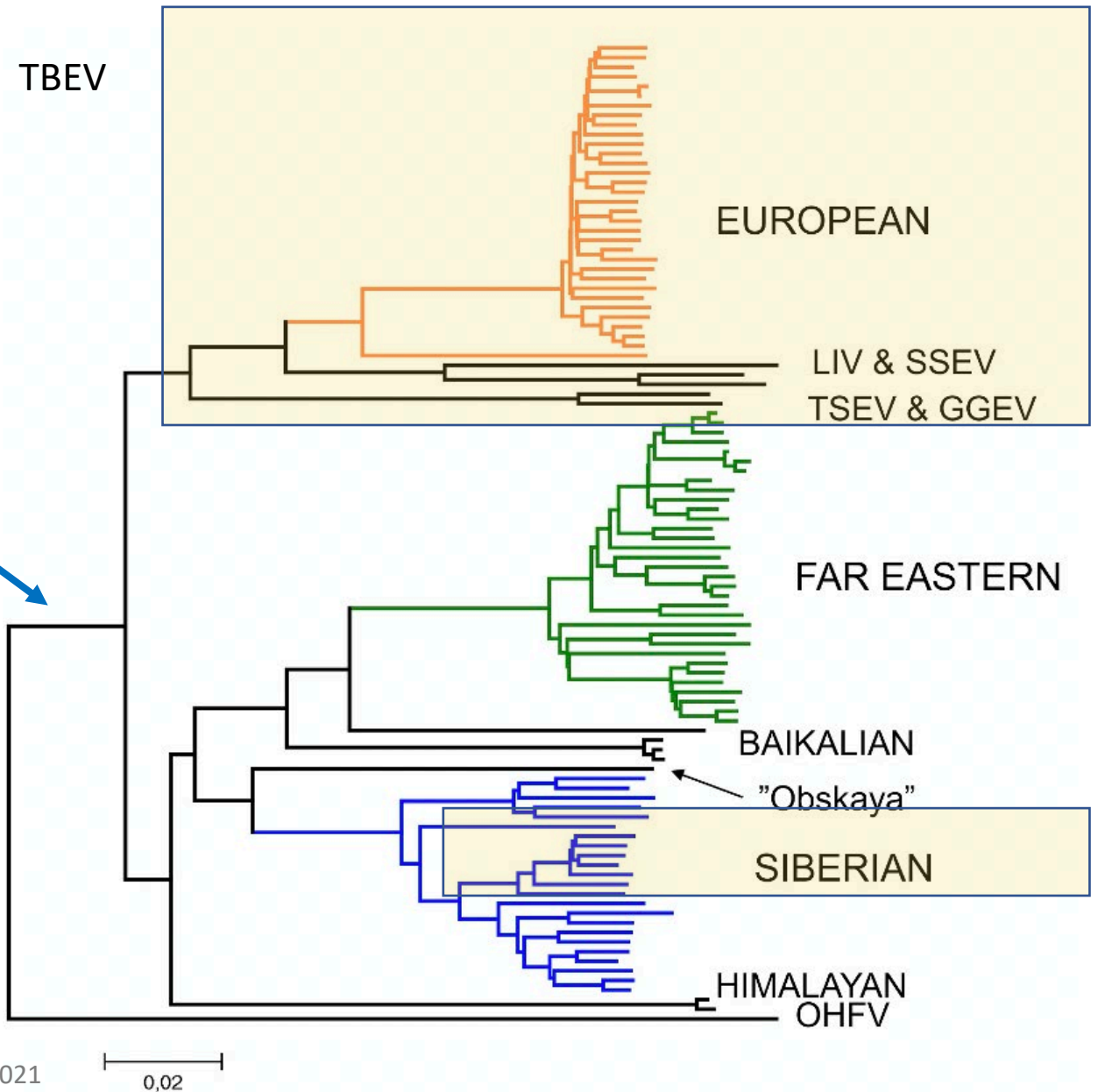
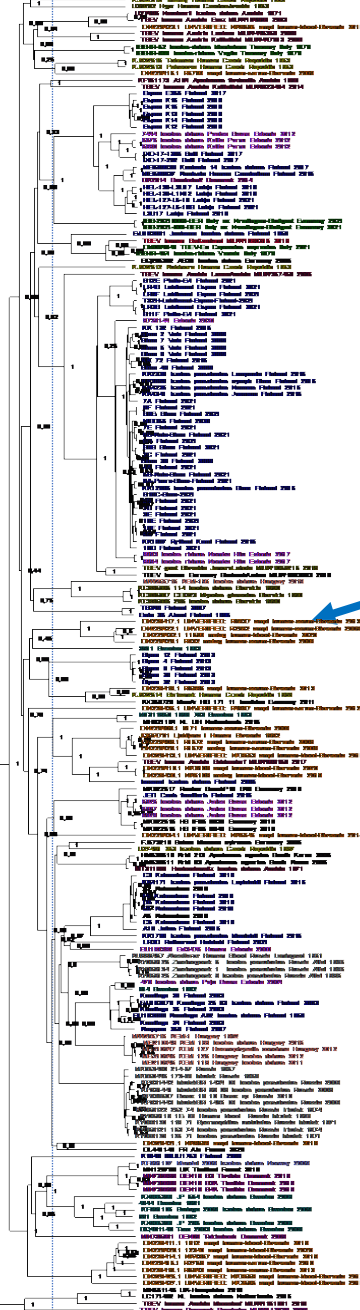


Figure 1. A phylogenetic tree based on the complete coding regions of TBEV. Omsk hemorrhagic fever virus (OHFV) that is the closest relative to TBEV was included as an outgroup. The three



No large-scale geographic clustering

FIN
SLN

mutation rate 2.32×10^{-5}
[95%HPD 1.76-2.90 $\times 10^{-5}$]
Smura et al
In preparation
EVD-LabNet collaboration

TBEV

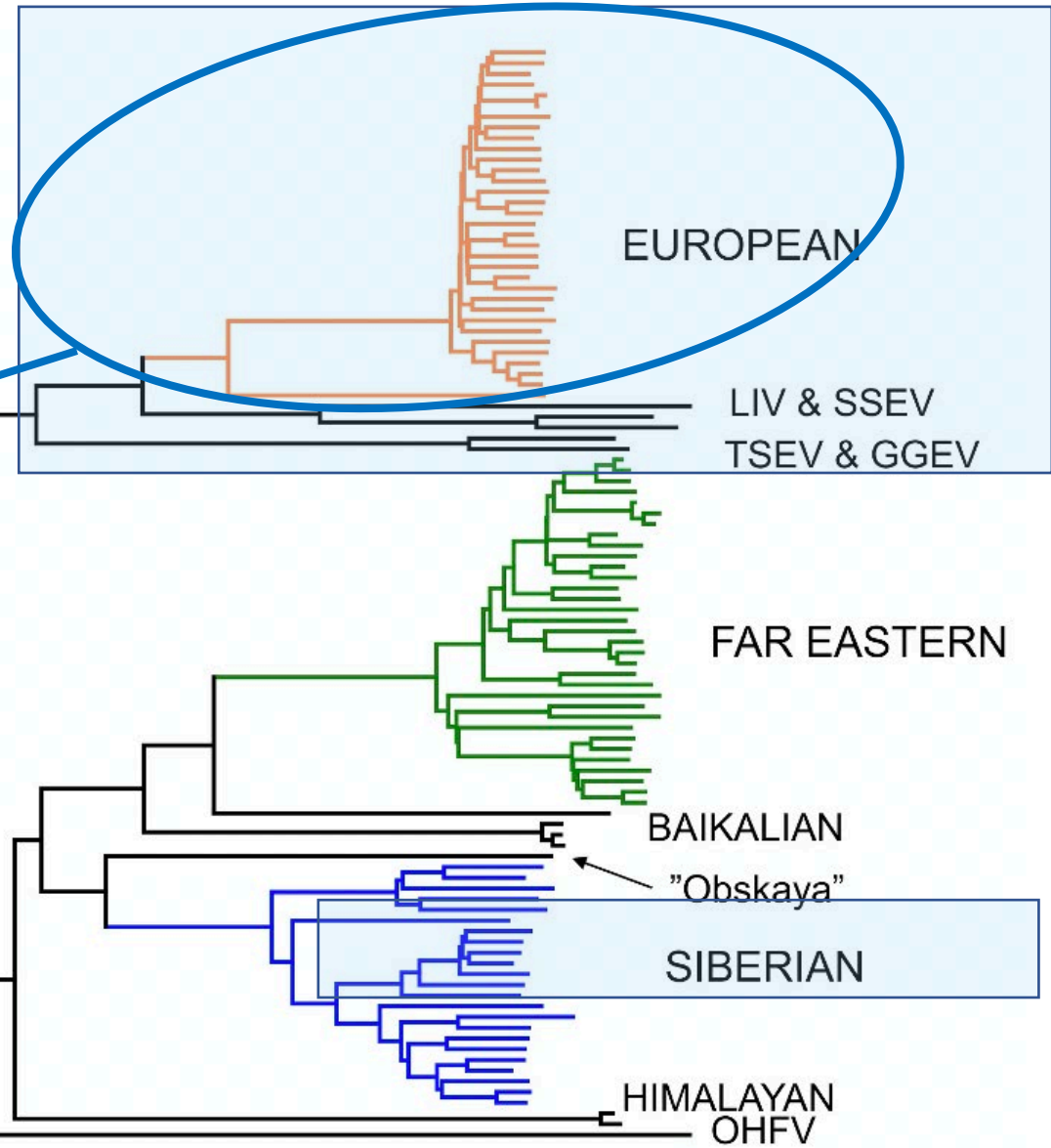


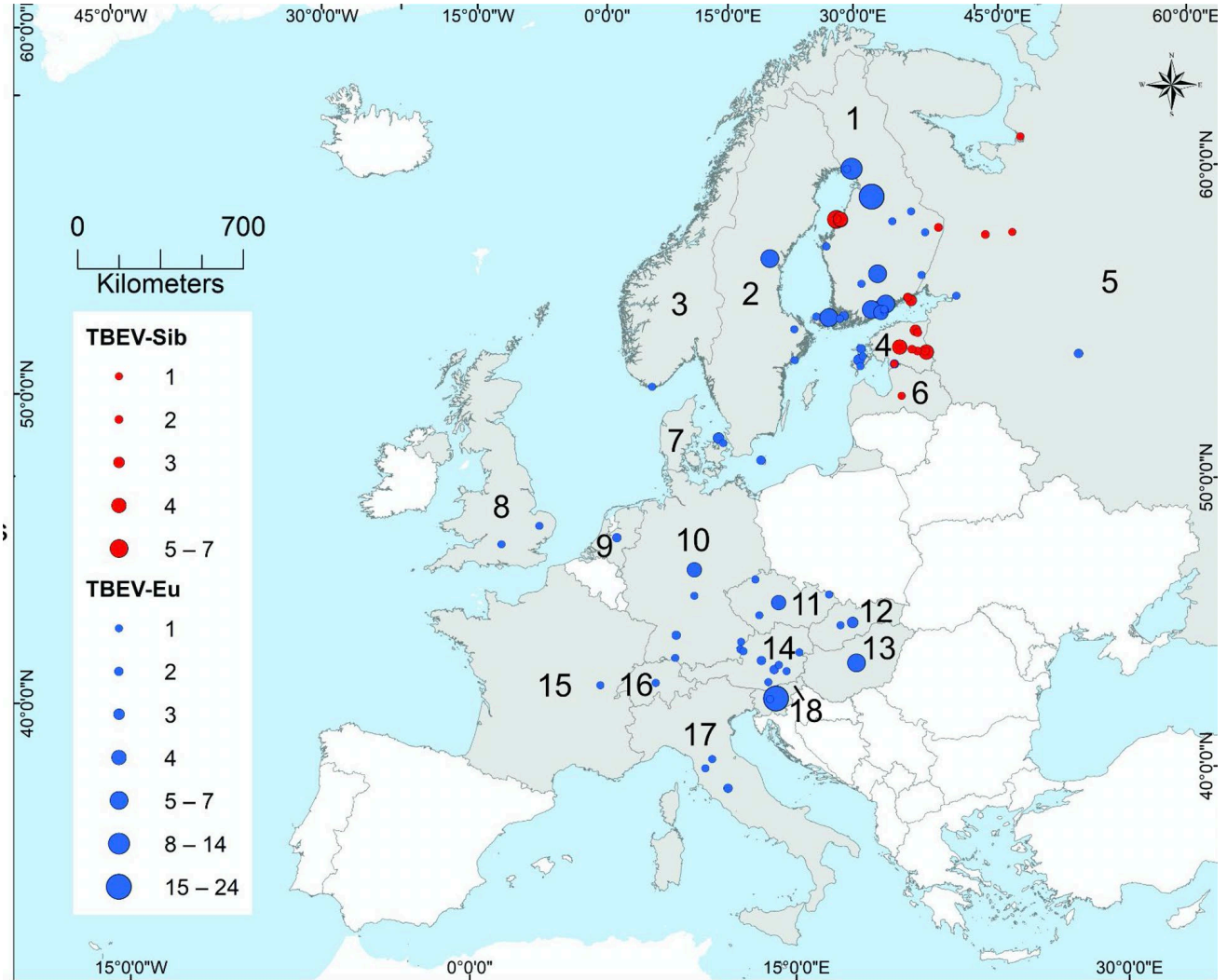
Figure 1. A phylogenetic tree based on the complete coding regions of TBEV. Omsk hemorrhagic fever virus (OHFV) that is the closest relative to TBEV was included as an outgroup. The three

Molecular epidemiology of TBEV in Europe

based on full genomes - strains available for the study



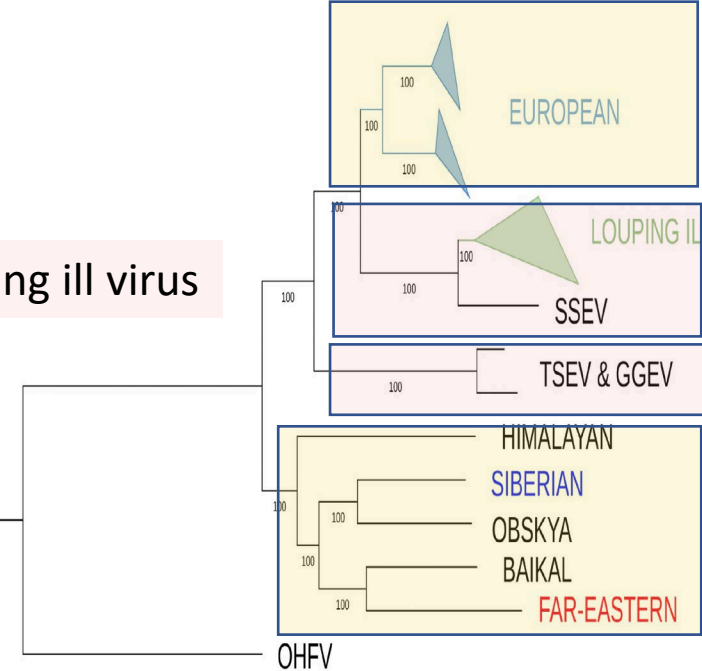
		Number of sequences		Samples pending re-sequencing
		New	Genbank	
TBEV-Eur	Austria	7	3	
	Czech Republic		7	3
	Denmark	1	5	
	Estonia	10	1	53
	Finland	65	18	
	France	1		
	Germany	3	6	
	Hungary		6	
	Italy	3	1	
	Netherlands		2	
	Norway		1	
	Poland			44
	Russia		15	
	Slovakia	1	2	
	Slovenia	9	23	
South Korea	2			
Sweden	4	5	41	
United Kingdom		2		
Total		103	100	141
TBEV-Sib Baltic clade	Estonia	19	2	
	Finland	22	2	
	Latvia		1	
	Russian Karelia	2	2	
	Total	43	7	
TBEV-Sib (all)			96	



TBEV and LIV taxonomy

ICTV: Tick-borne encephalitis virus

ICTV: Louping ill virus

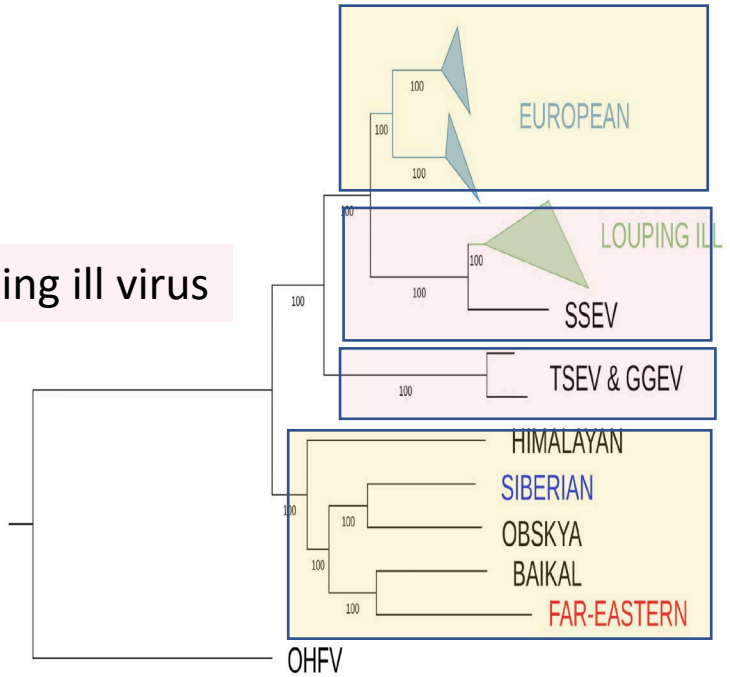


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TBEV and LIV taxonomy

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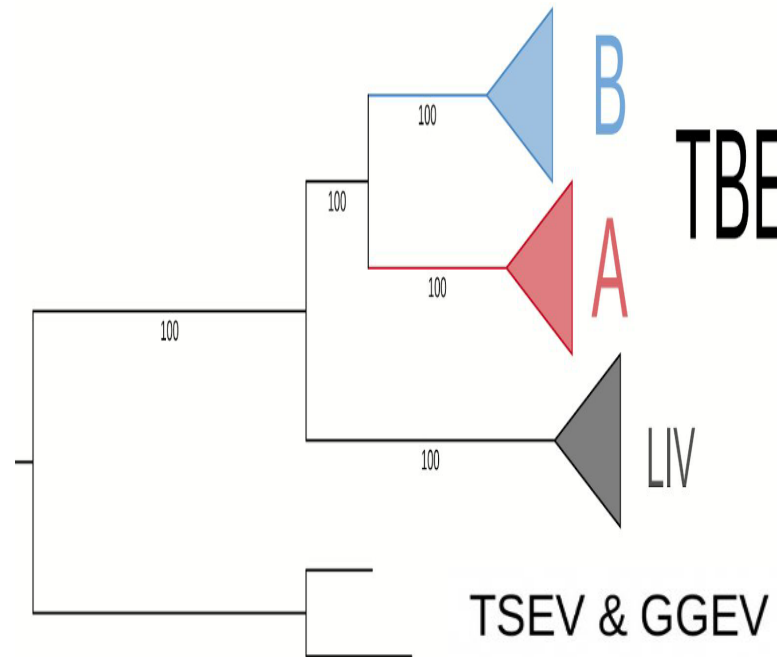


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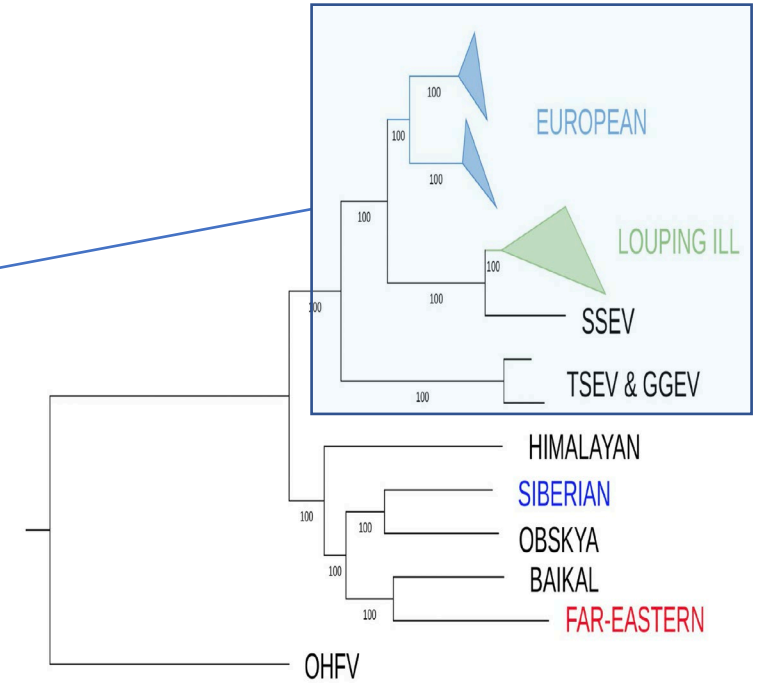
European Subtype



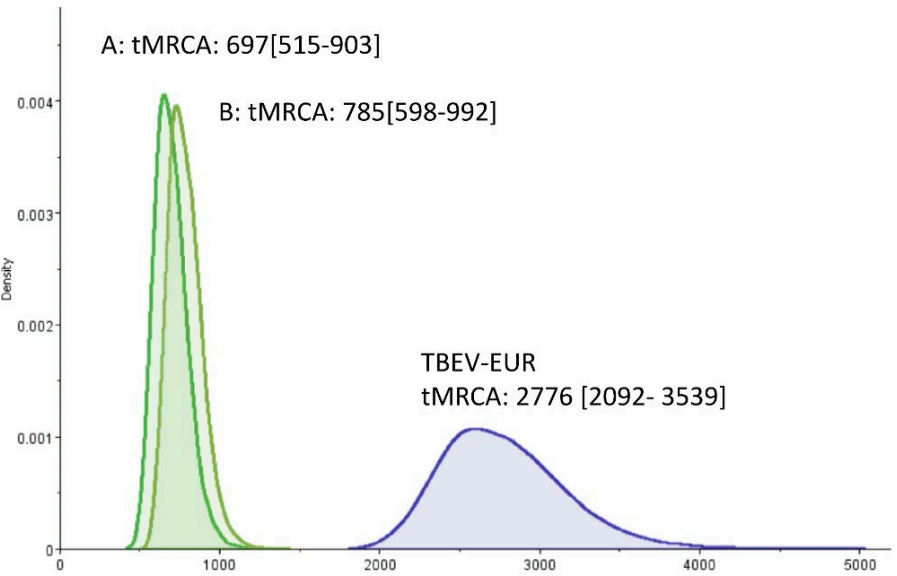
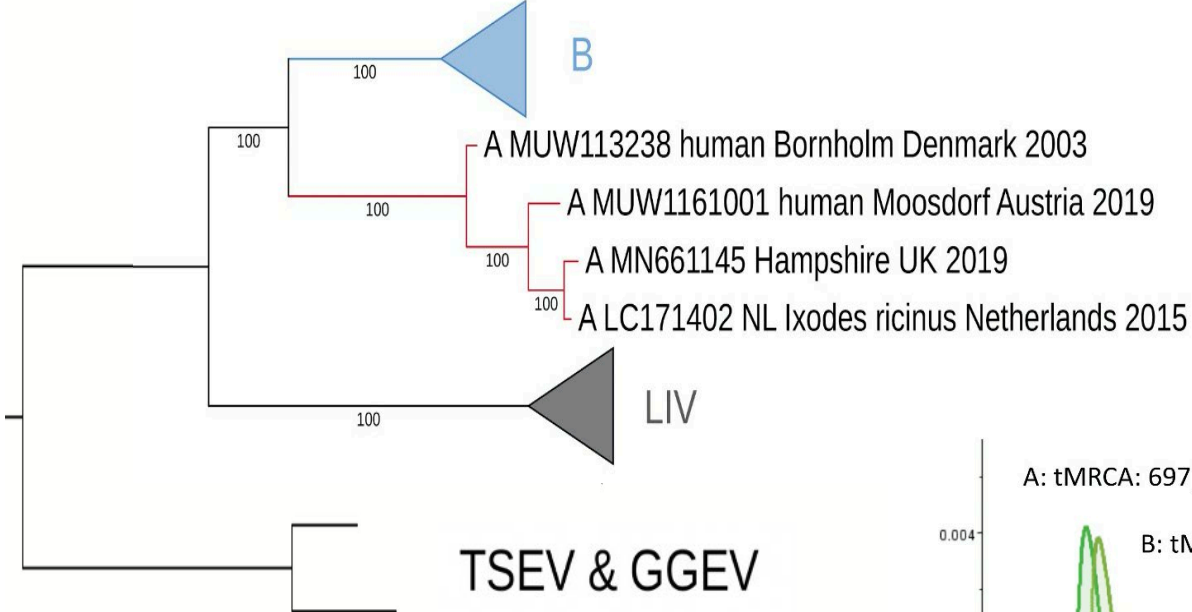
Teemu Smura



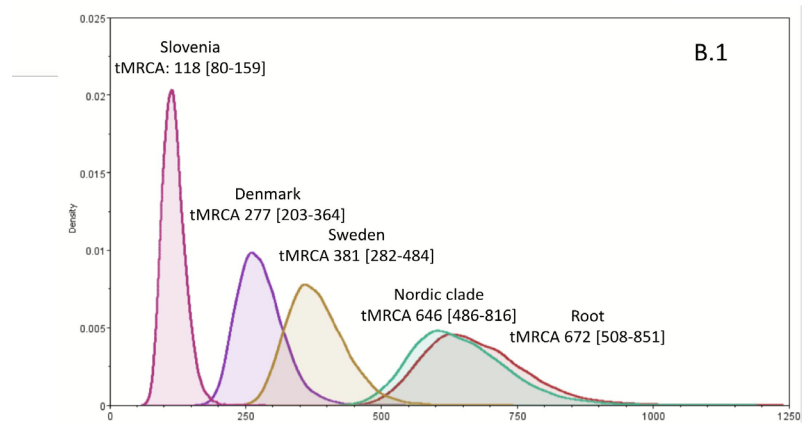
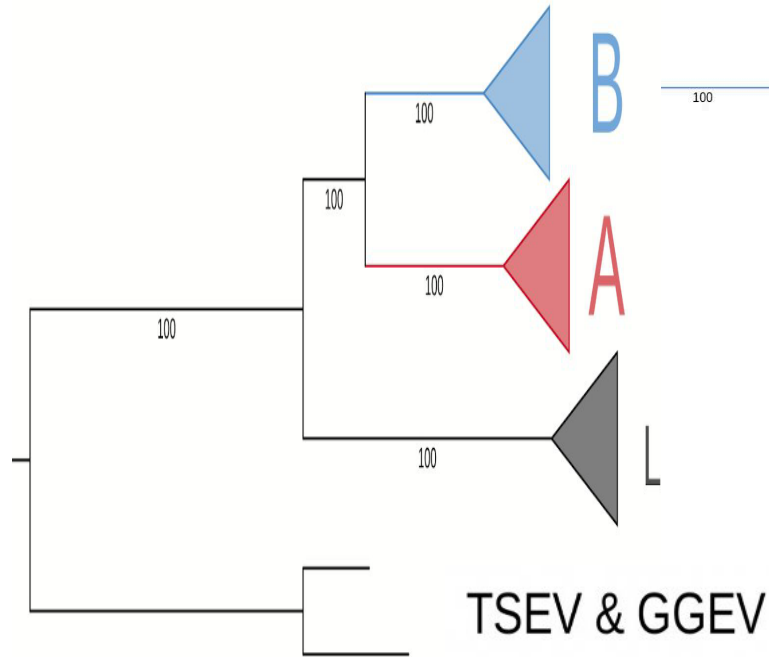
TBEV-EUR



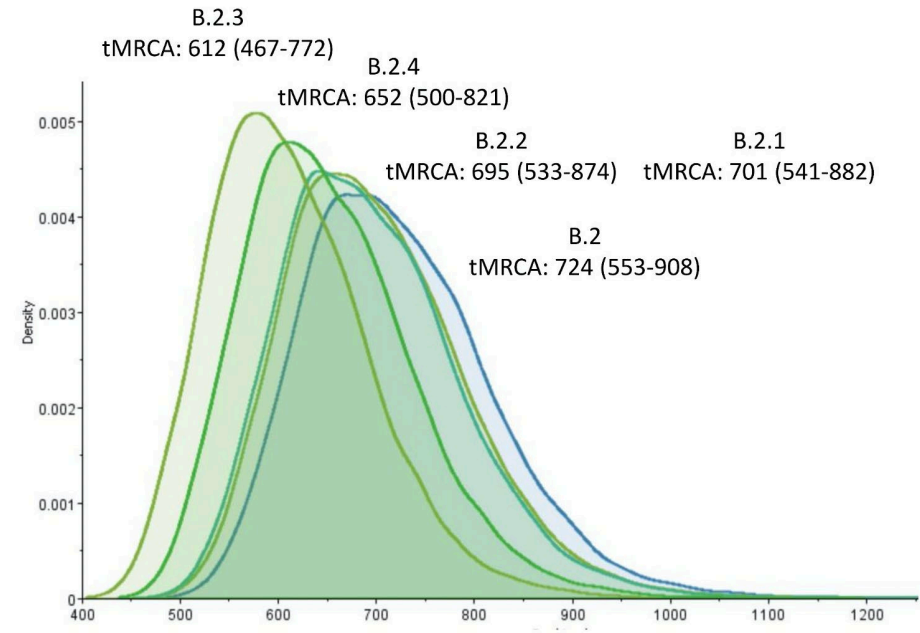
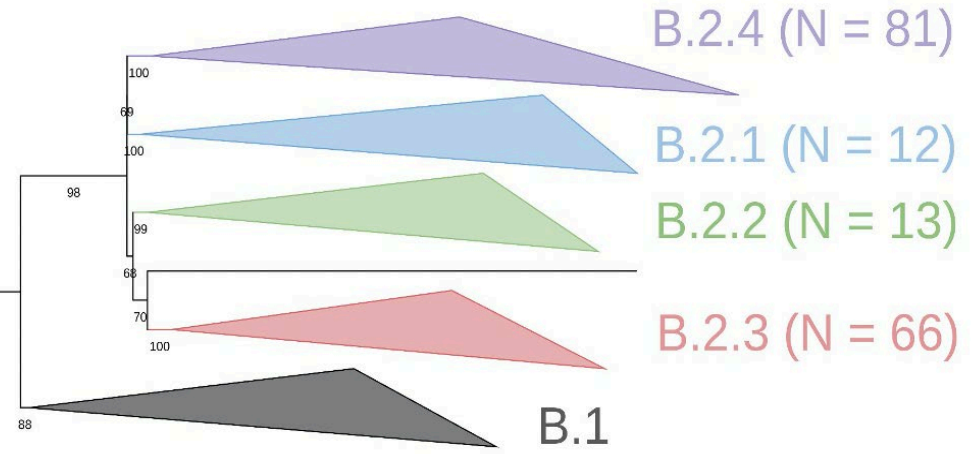
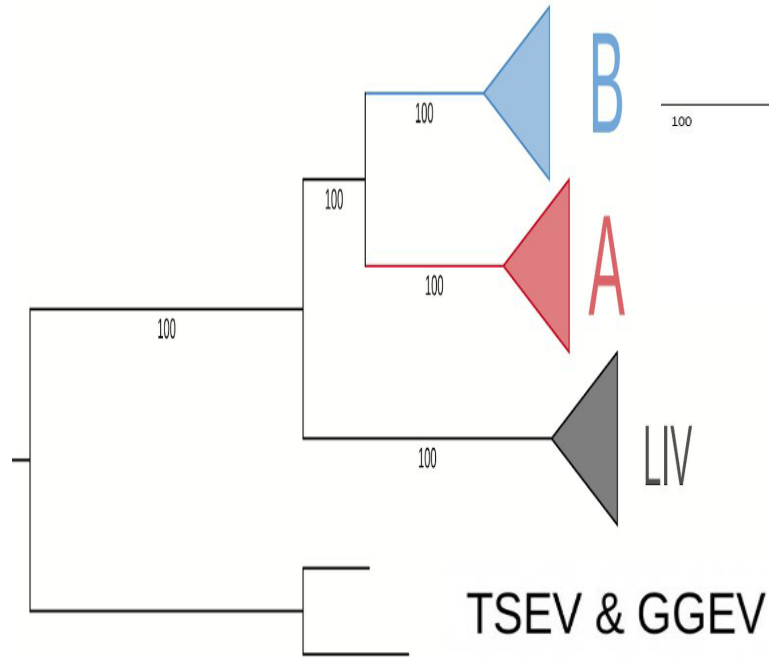
European Subtype, Time of most recent ancestor (tMRCA)



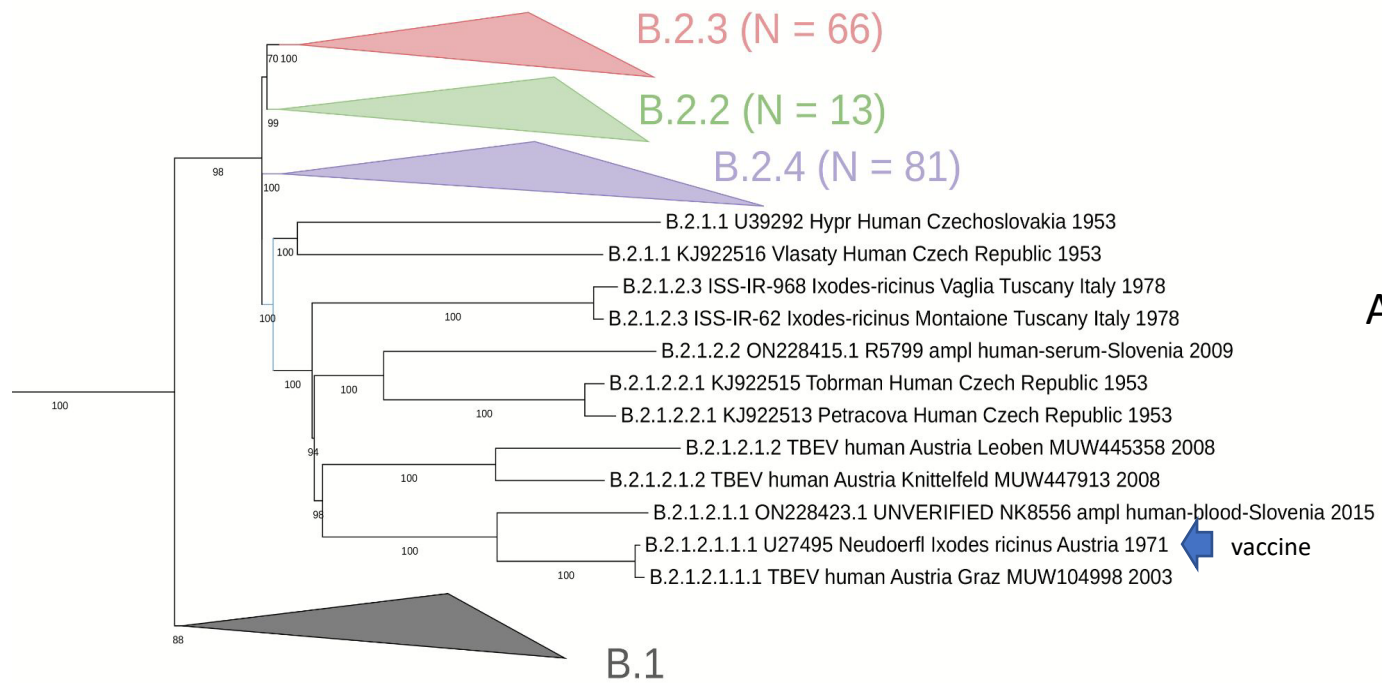
TBEV-Eur sublineage B.1



TBEV-Eur sublineage B.2

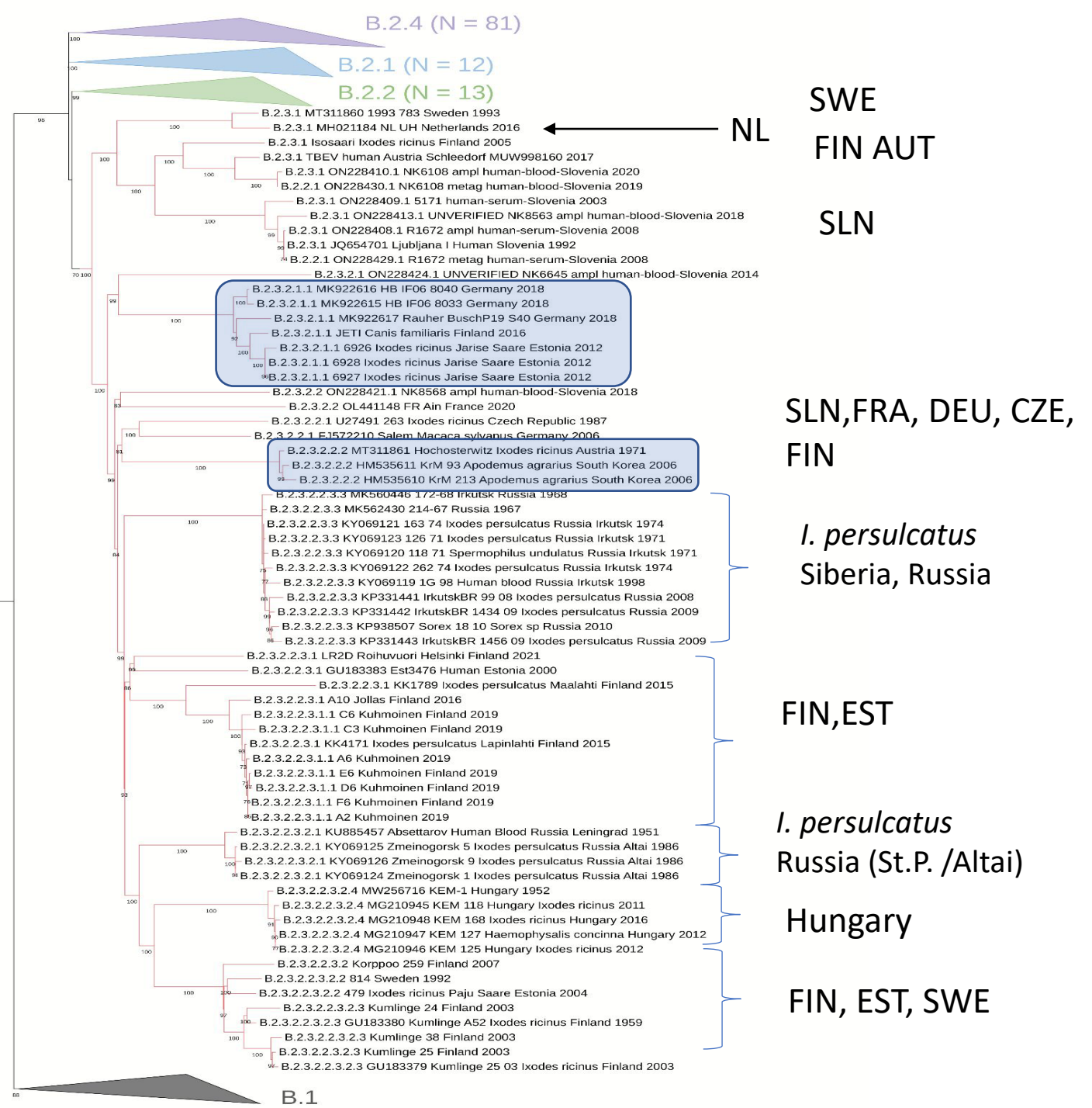


B.2.1

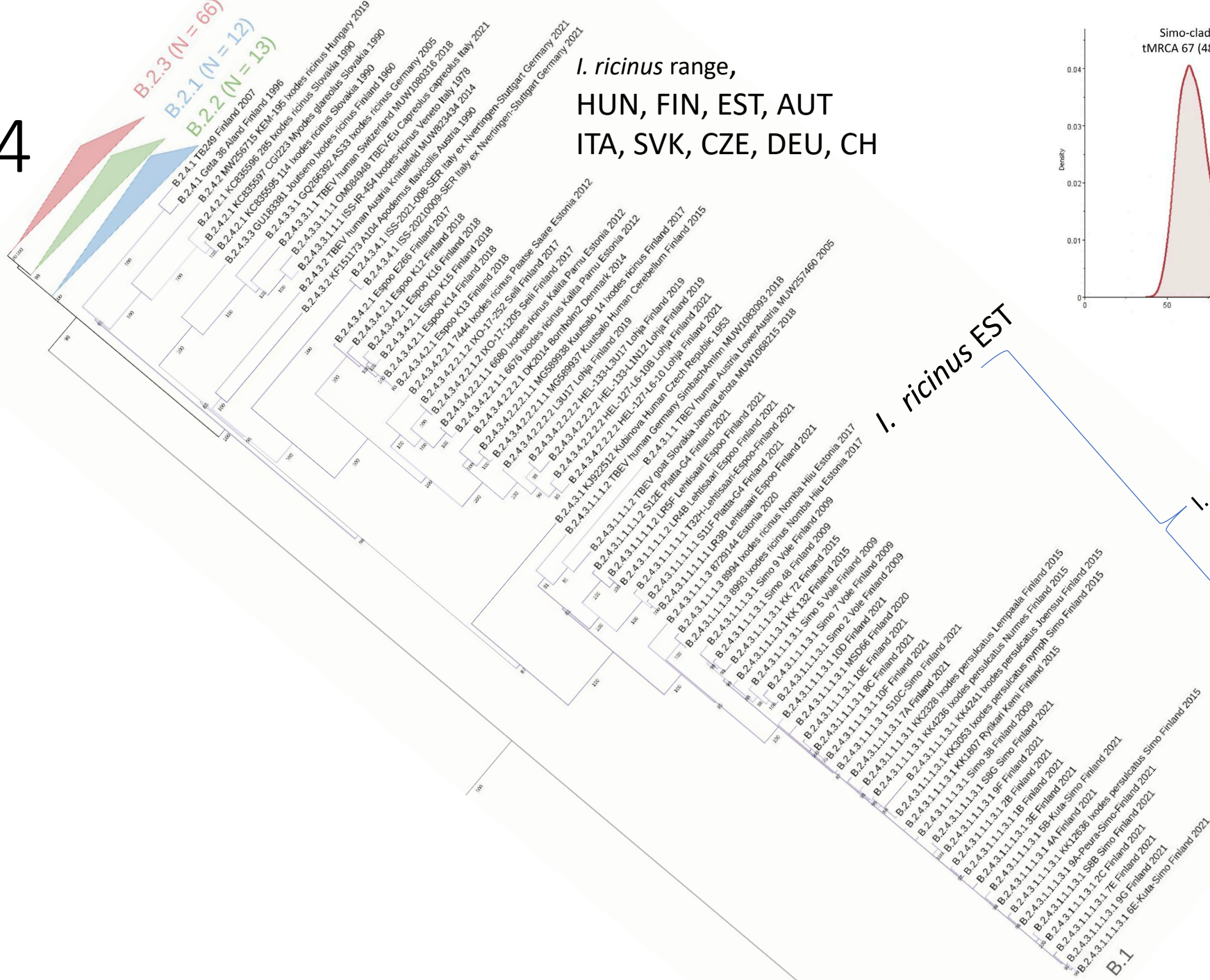


Austria, Slovenia, Czech Rep, Italy

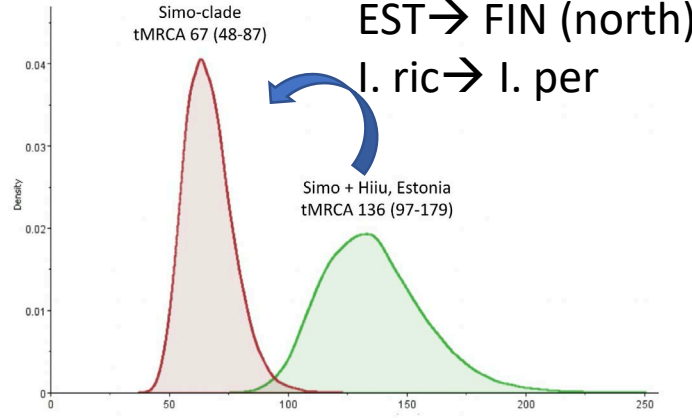
B.2.3



B.2.4

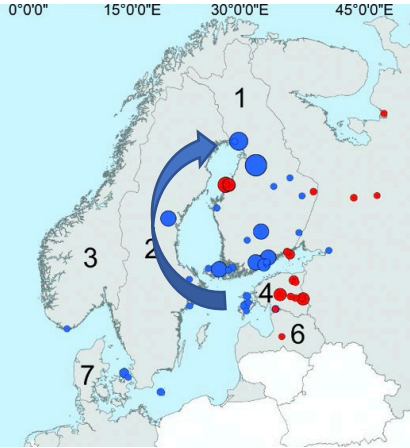


I. ricinus range,
HUN, FIN, EST, AUT
ITA, SVK, CZE, DEU, CH

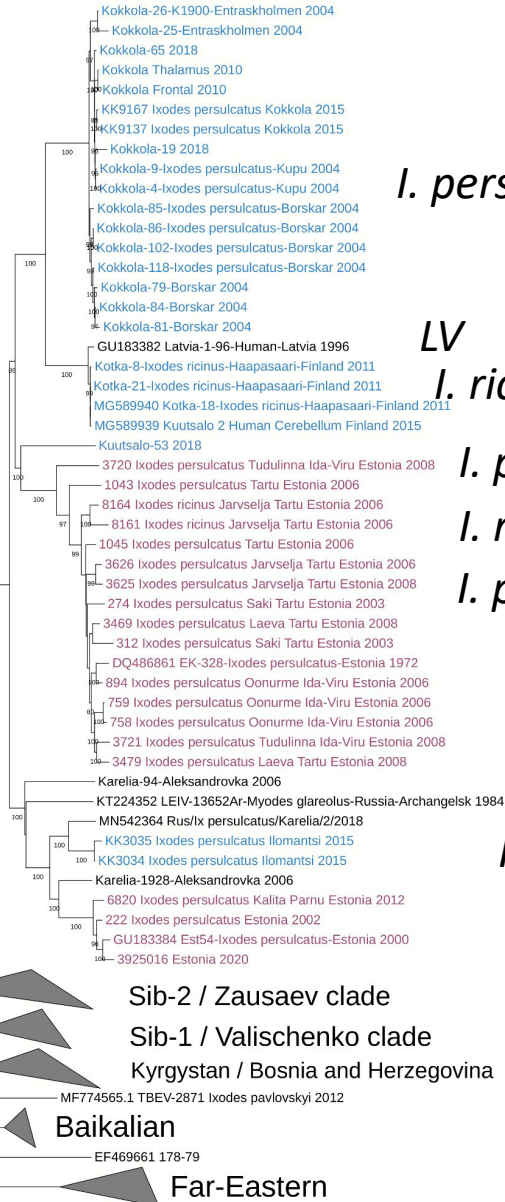
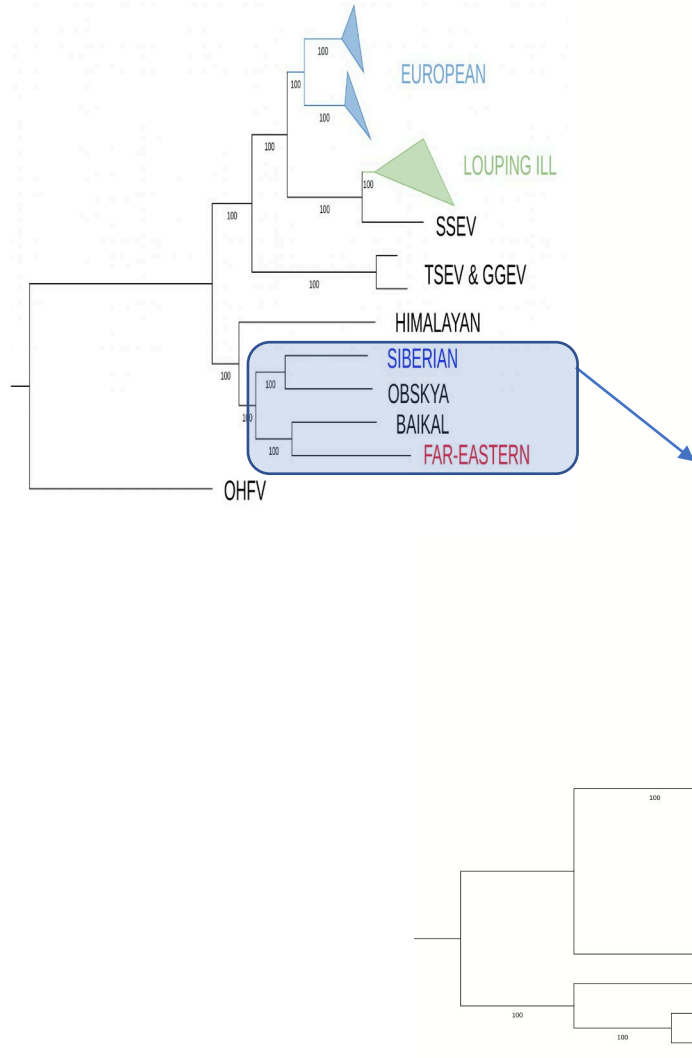


I. ricinus EST

I. persulcatus, FIN



TBEV-Sib/Baltic lineage: FIN/EST/LV/RUS



I. persulcatus (NW FIN)

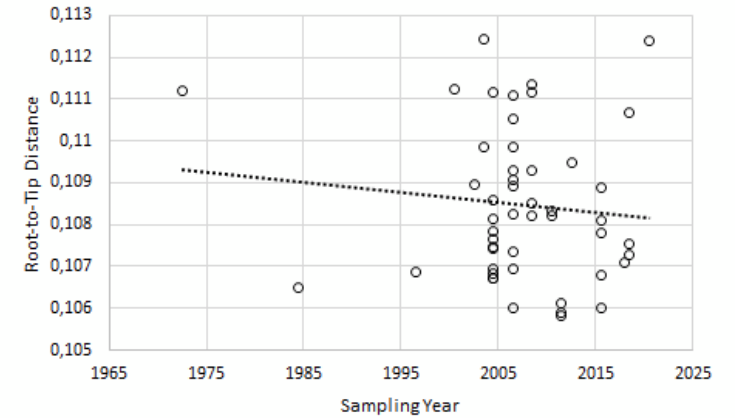
LV
I. ricinus (SE FIN)

I. persulcatus
I. ricinus
I. persulcatus

I. persulcatus (RUS; E FIN, EST)

TBEV-Sib/Baltic lineage:

correlation between root-to-tip distance & time of sampling



No clock! -> tMRCA?

Conclusions of TBEV phylogeography

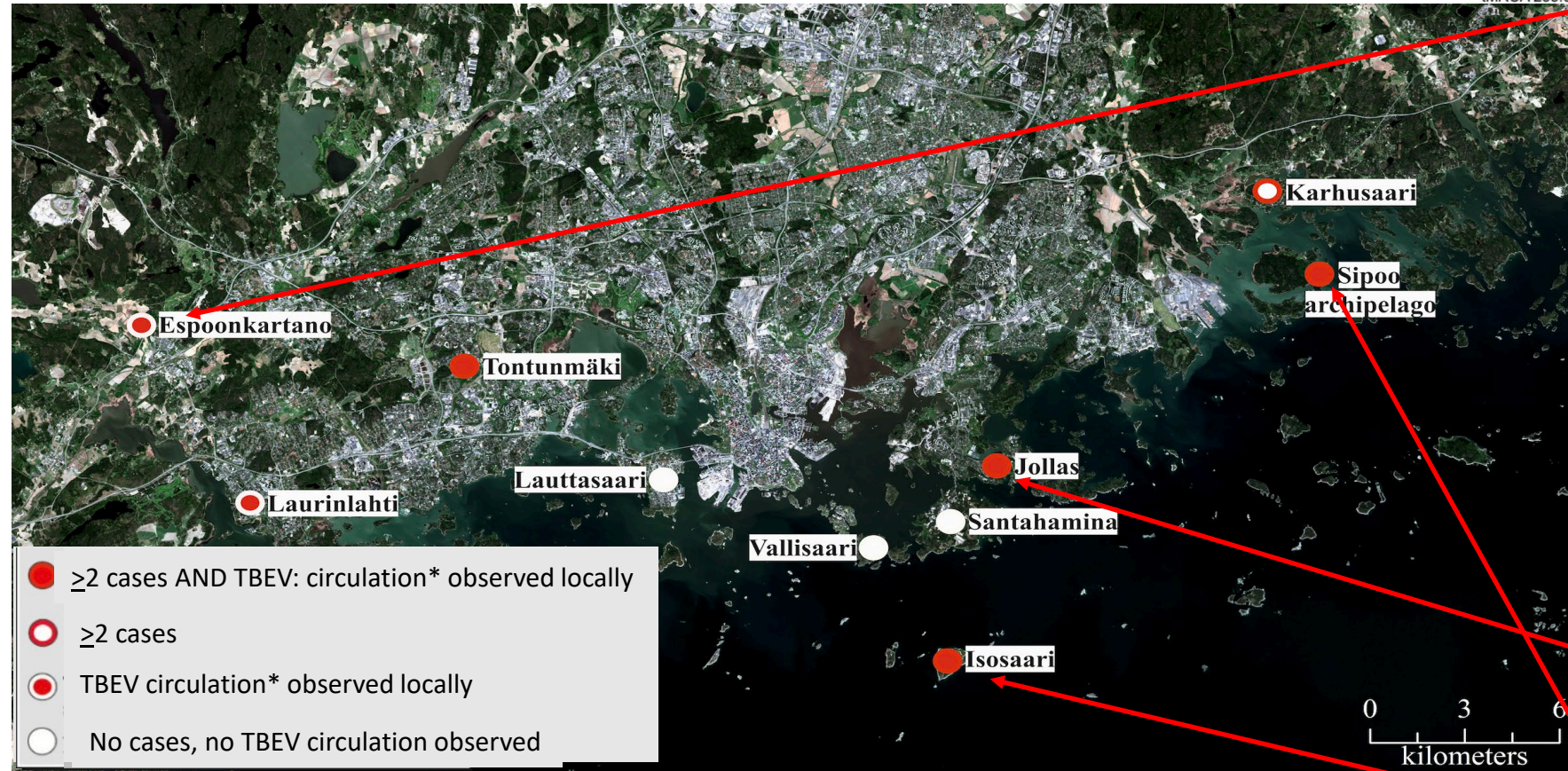
- Limited large-scale geographical clustering
- Both Eur and Sib subtypes had “vector-jumps” to the other tick species (*I. ricinus* & *I. persulcatus*)
- Both north, south and west long-distance movements of foci
- Foci in “new emerging areas” in W and N Europe particularly diverse genetically
- Isolated foci originating from single introductions decades ago

TBEV-Eur subclusters (A and B) Diverged ~2700 years ago

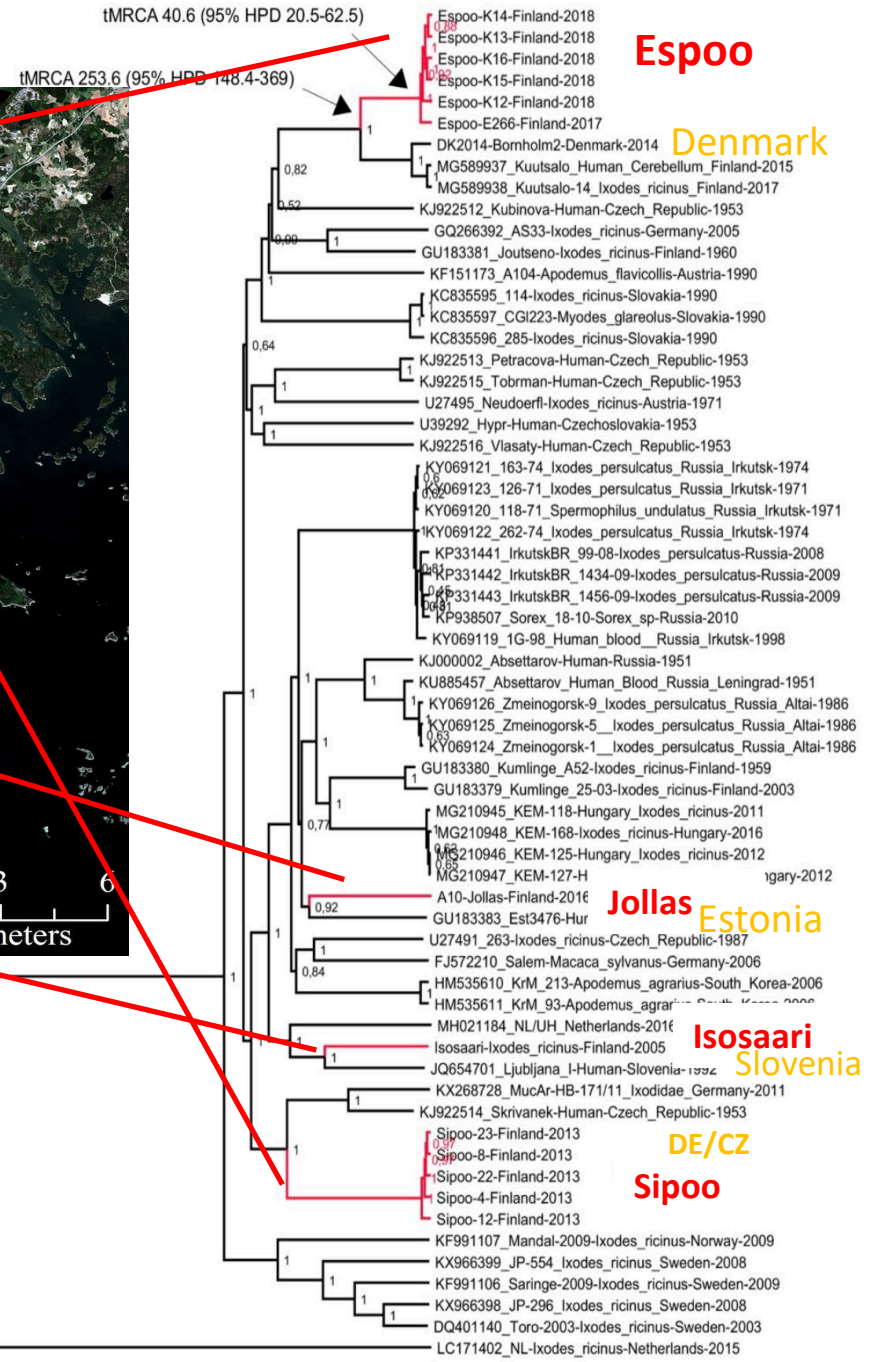
Strains in both A and B diverged independently ca ~700 years ago. (What happened in the 14th century?)

Taxonomic definition of TBEV and LIV “wrong”

TBEV arrival and spread in Helsinki



- ≥2 cases AND TBEV: circulation* observed locally
- ≥2 cases
- TBEV circulation* observed locally
- No cases, no TBEV circulation observed



• TBEV in foci spread decades ago – introduced earlier several times by (?) migratory birds

- Needed for TBE emergence:**
- 1) Introduction
 - 2) Suitable environmental conditions and exposure
 - 3) Lack of control means



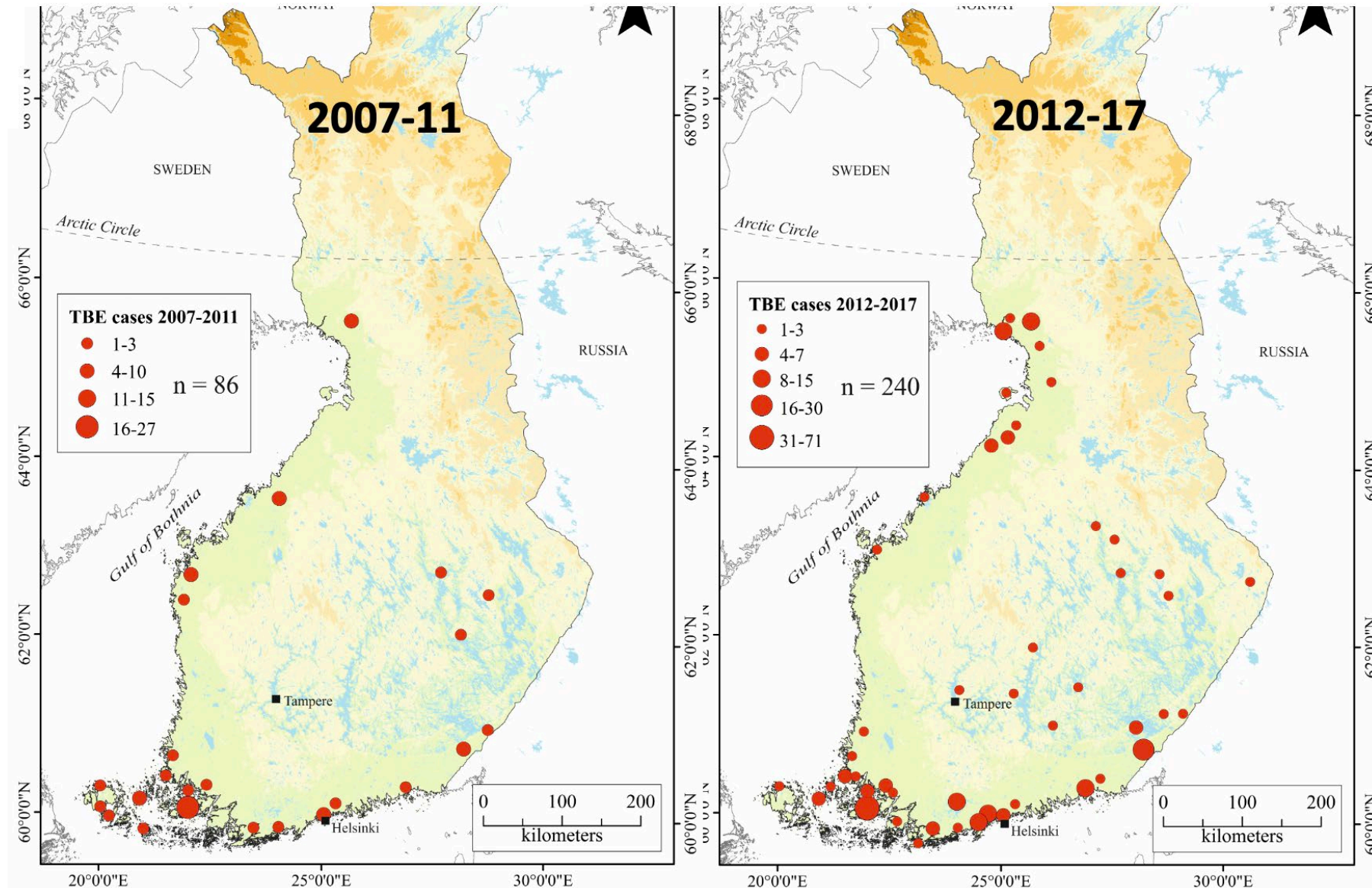
TBEV full genomes, Phylogeny

SMURA YM, EMERG MICROB & INFECT 2019, 1: 675-683

3000,0 2500,0 2000,0 1500,0 1000,0 500,0 0,0



TBE in Finland 2007-17



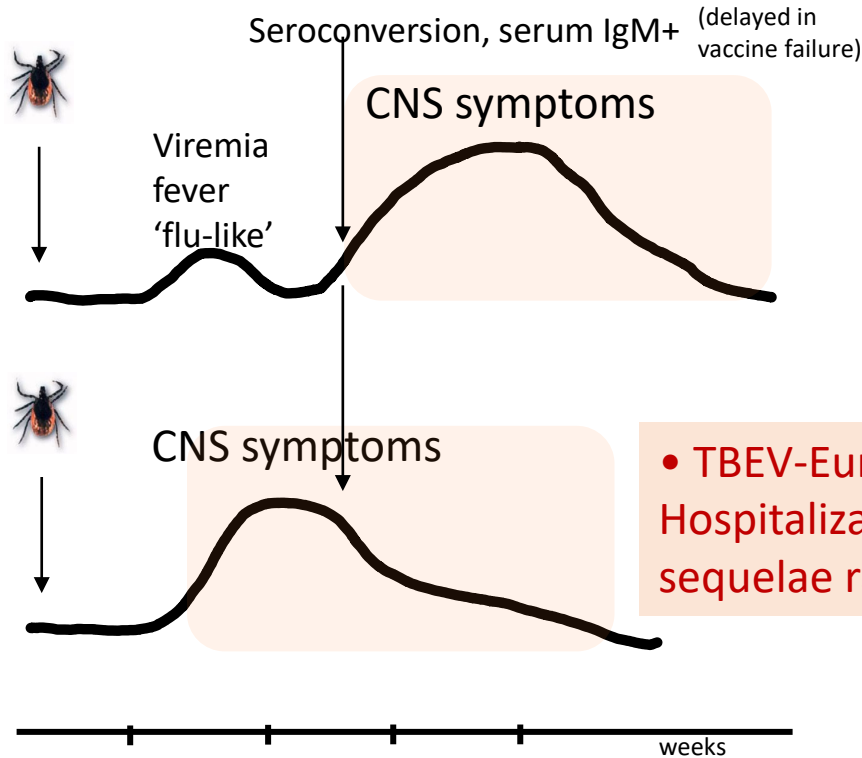


TBE in Finland 2007-17

→ Siberian vs European subtype

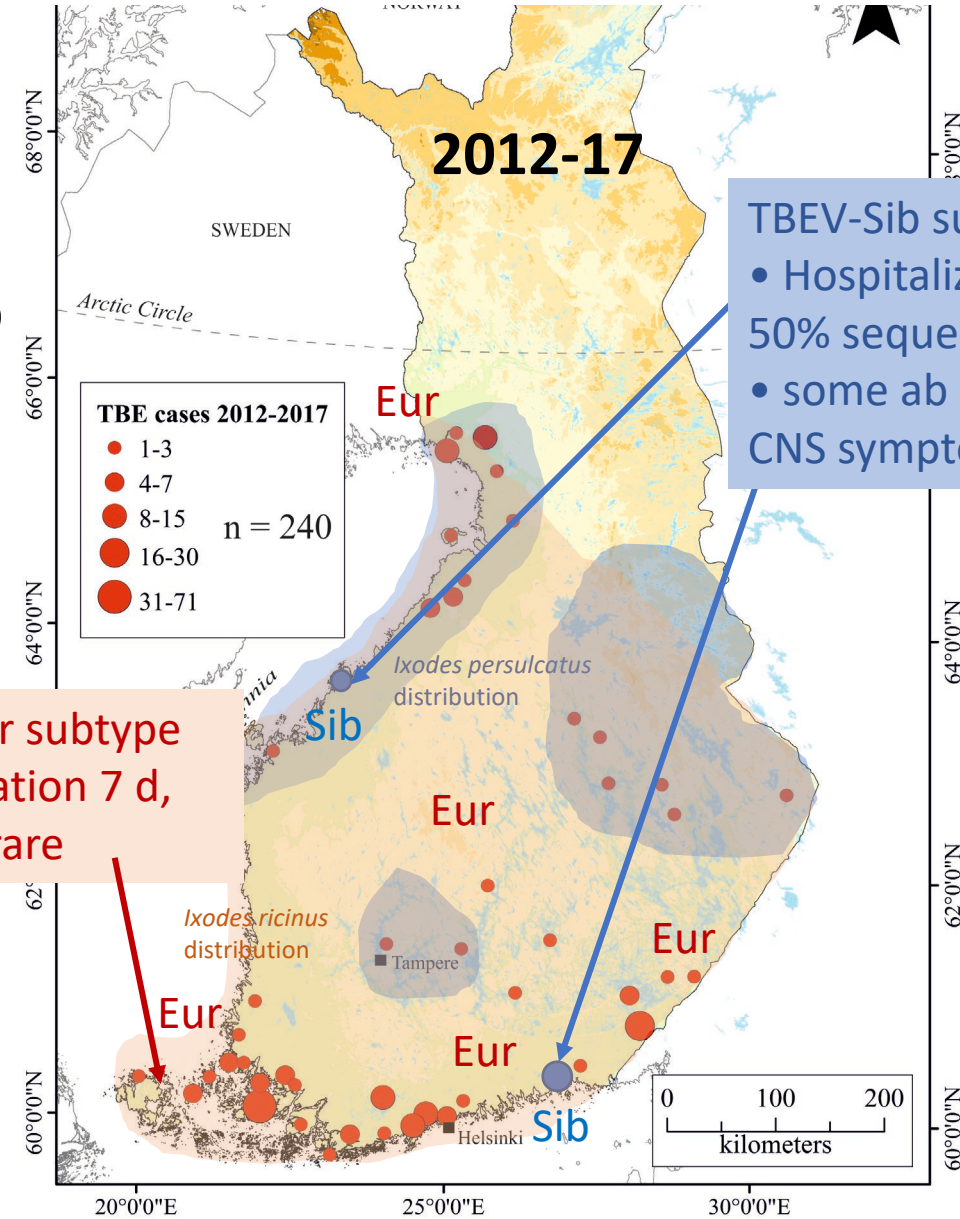
2007-11

Biphasic
Typical in European subtype



Monophasic
More common with Siberian subtype

2012-17



TBEV-Sib subtype

- Hospitalization 37d, 50% sequelae
- some ab neg when CNS symptoms

TBEV-Eur subtype
Hospitalization 7 d, sequelae rare

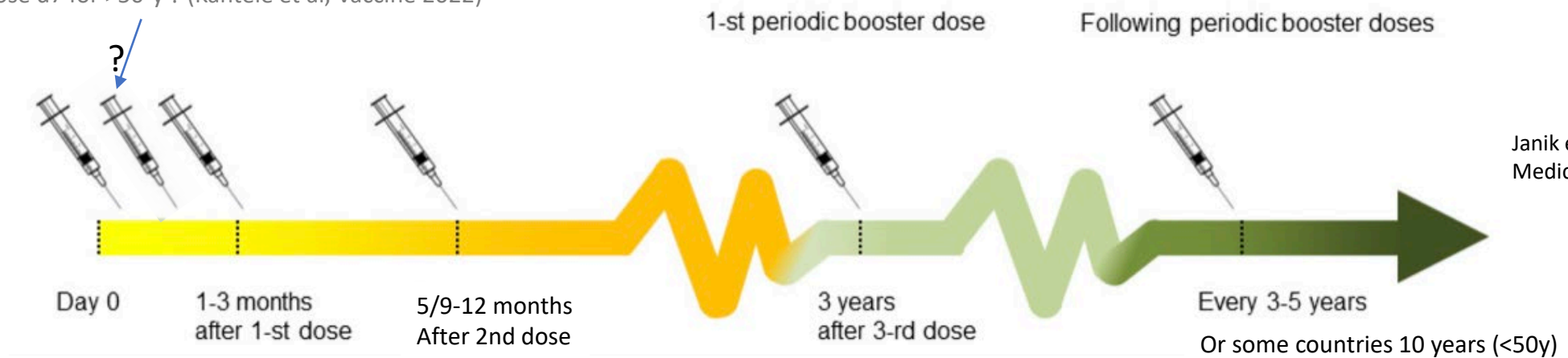
Control:

- Tick control
- Avoiding unpasteurized milk
- TBE vaccination

Transmission occurs soon after attachment, unlike for borrelia, tick removal usually too late

Formalin-inactivated, purified TBEV-Eur viral particles
Pfizer: FSME-immun; Novartis: Encepur

Rapid dose d14 (instead of 1-3 mo) for faster immunisation
Extra dose d7 for >50-y ? (Kantele et al, Vaccine 2022)



- Who should be vaccinated?

THANK YOU!



- 1) **Teemu Smura, Viktor Olander, Tarja Sironen, Mert Erdin, Ruut Uusitalo, Olli Vapalahti**, Viral Zoonoses Research Unit, Departments of Virology and Veterinary Biosciences, University of Helsinki & Department of Virology and Immunology, Helsinki University Hospital and University of Helsinki, Helsinki, Finland
- 2) **Julia Geller**, Department of Virology and Immunology, National Institute for Health Development, Tallinn, Estonia
- 3) **Samo Zakotnik, Miša Korva, Tatjana Avšič-Županc** University of Ljubljana, Slovenia
- 4) **John Petterson**, Folkhälsomyndigheten, Sweden
- 5) **Maciej Grzybek, Martyna Krupińska** Division of Tropical Parasitology, Institute of Maritime and Tropical Medicine, Medical University of Gdańsk, Poland
- 6) **Jeremy Camp, Stephan Aberle**, Department of Virology, Medical University of Vienna, Austria
- 7) **Giulietta Venturi**, National Reference Laboratory for Arboviruses, Department of Infectious Diseases, Istituto Superiore di Sanità, Rome, Italy
- 8) **Haná Zelena**, University of Ostrava, Czech Republic
- 9) **Kamelia Stanoeva**, RIVM, The Netherlands
- 10) **Åke Lundkvist** University of Uppsala, Sweden

