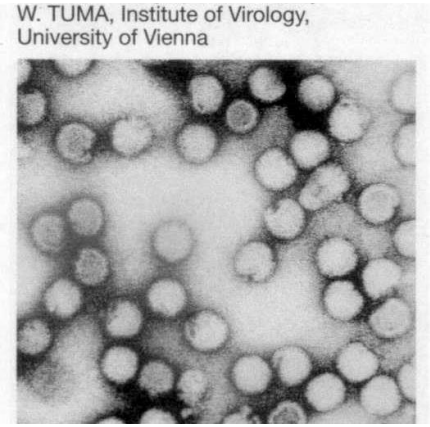
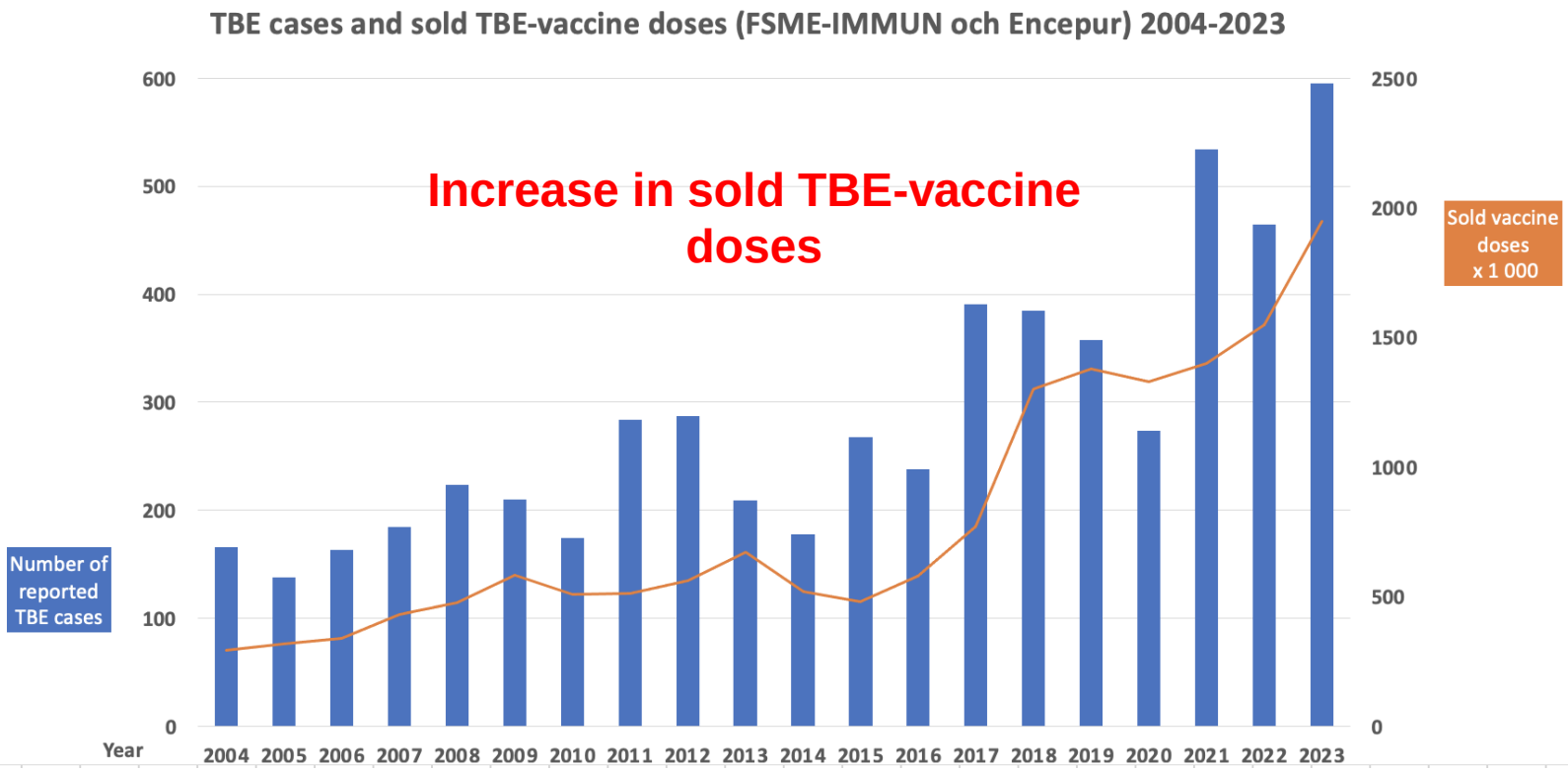
Tick-Borne Encephalitis Virus – More Widely Prevalent in Europe

Zoonosis Science Center





Åke Lundkvist
Zoonosis Science Center (ZSC)
IMBIM, Uppsala University
2024.04.23


TBE cases and sold TBE-vaccine doses (FSME-IMMUN och Encepur) 2004-2023
Increase in sold TBE-vaccine doses
Number of reported TBE cases
Sold vaccine doses x 1 000
Year
600
500
400
300
200
100
0
2500
2000
1500
1000
500
0
2004 2005 2006 2007 2008 2009 2010 2011 2012 2013 2014 2015 2016 2017 2018 2019 2020 2021 2022 2023

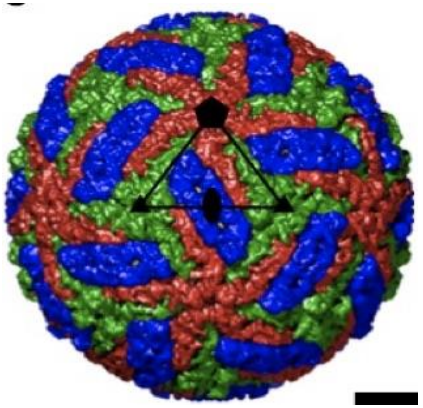
Flavivirus

Important human pathogens:

Dengue virus
Yellow fever virus
Japanese encephalitis virus
West Nile virus
Zika virus

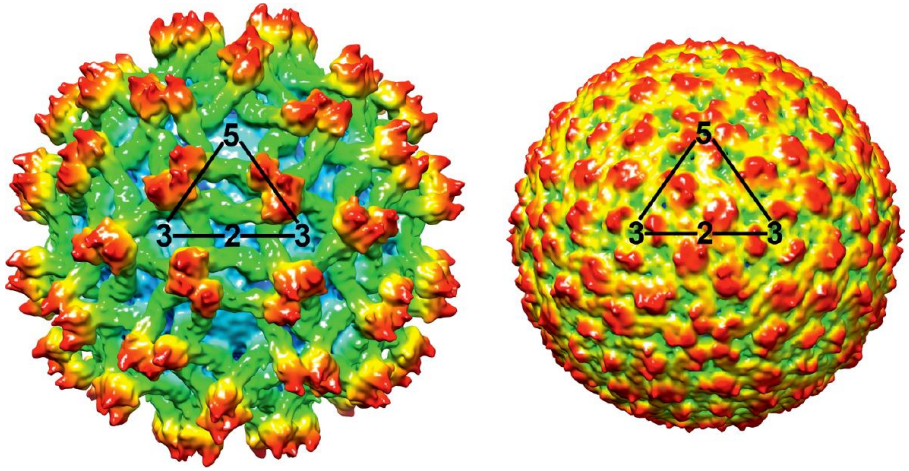
Tick-borne encephalitis virus (TBEV)
Powassan virus
Kyasanur Forest virus
Omsk Haemorhagic fever virus

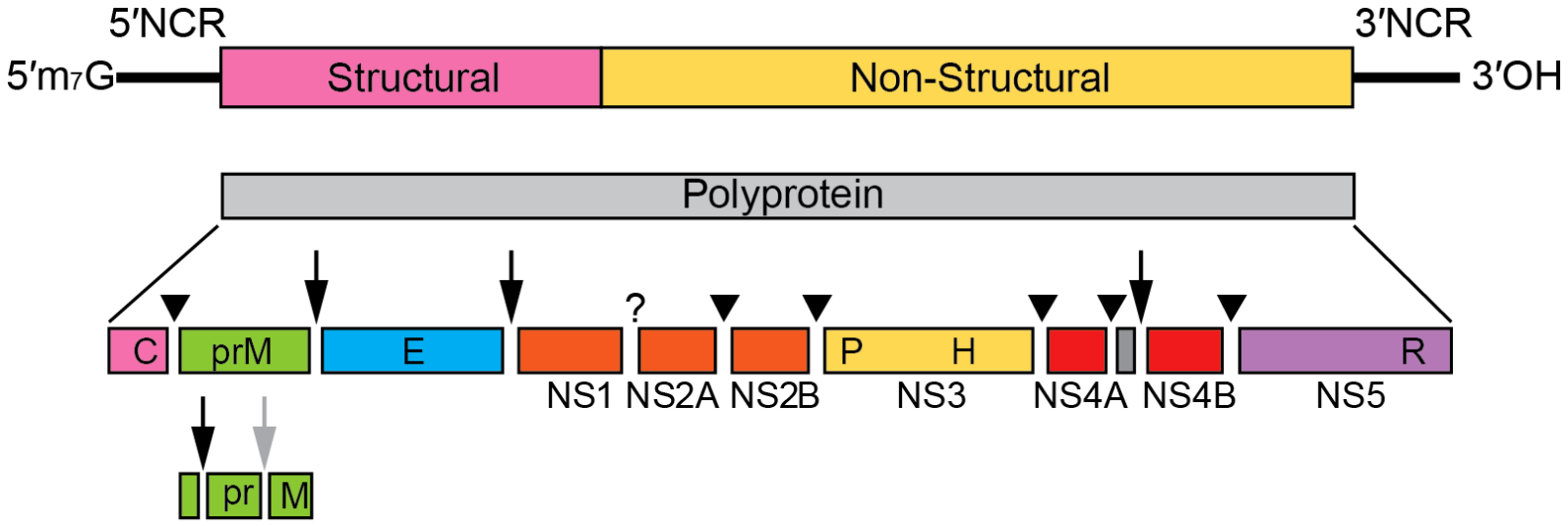
Hepatitis C virus



Füzik et al, Nature Com. 2018

Flavivirus/TBEV – Genome

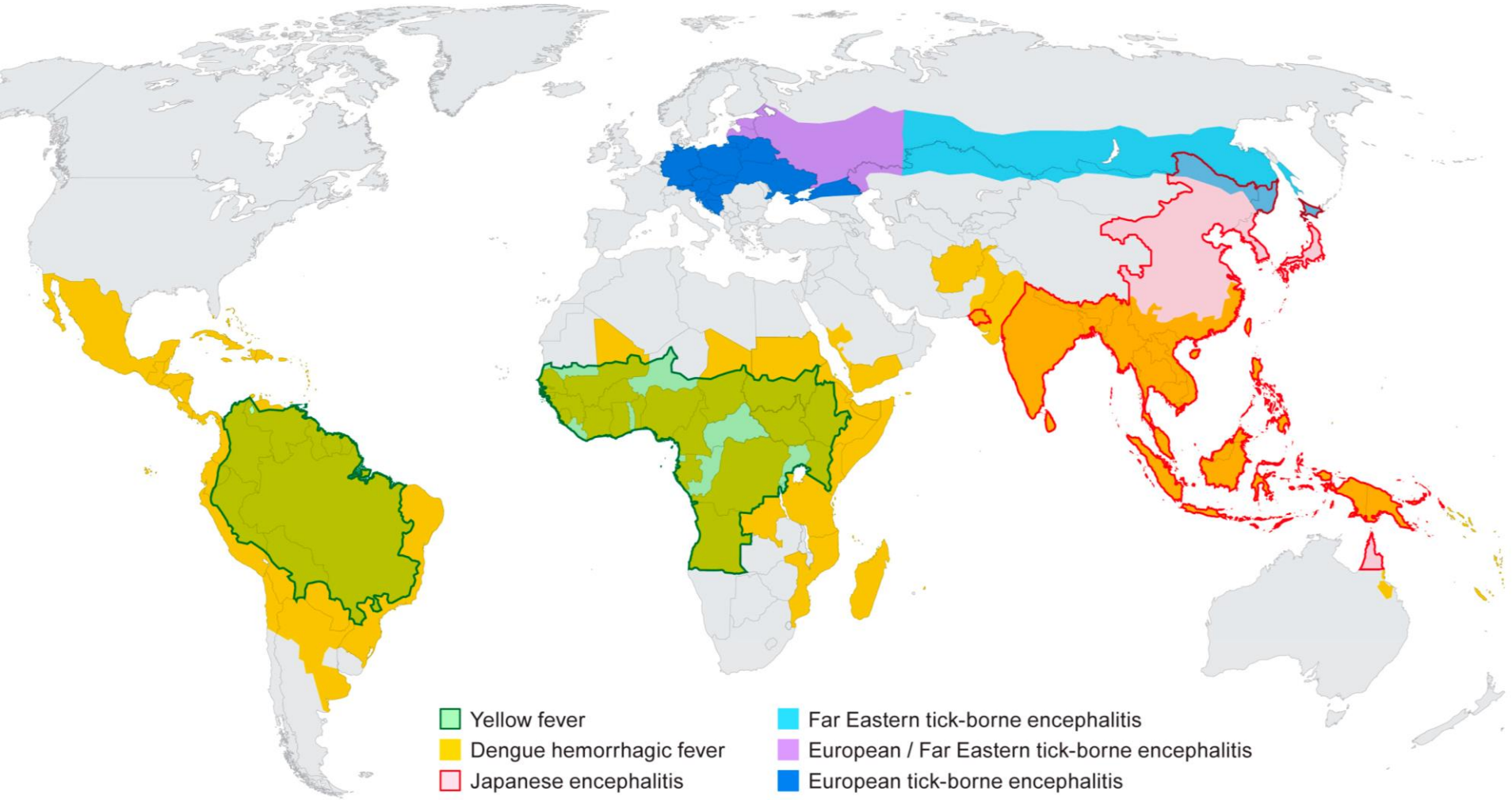




▼NS2B-3 protease ↓Signal peptidase ↓Golgi protease ? Unknown protease(s)

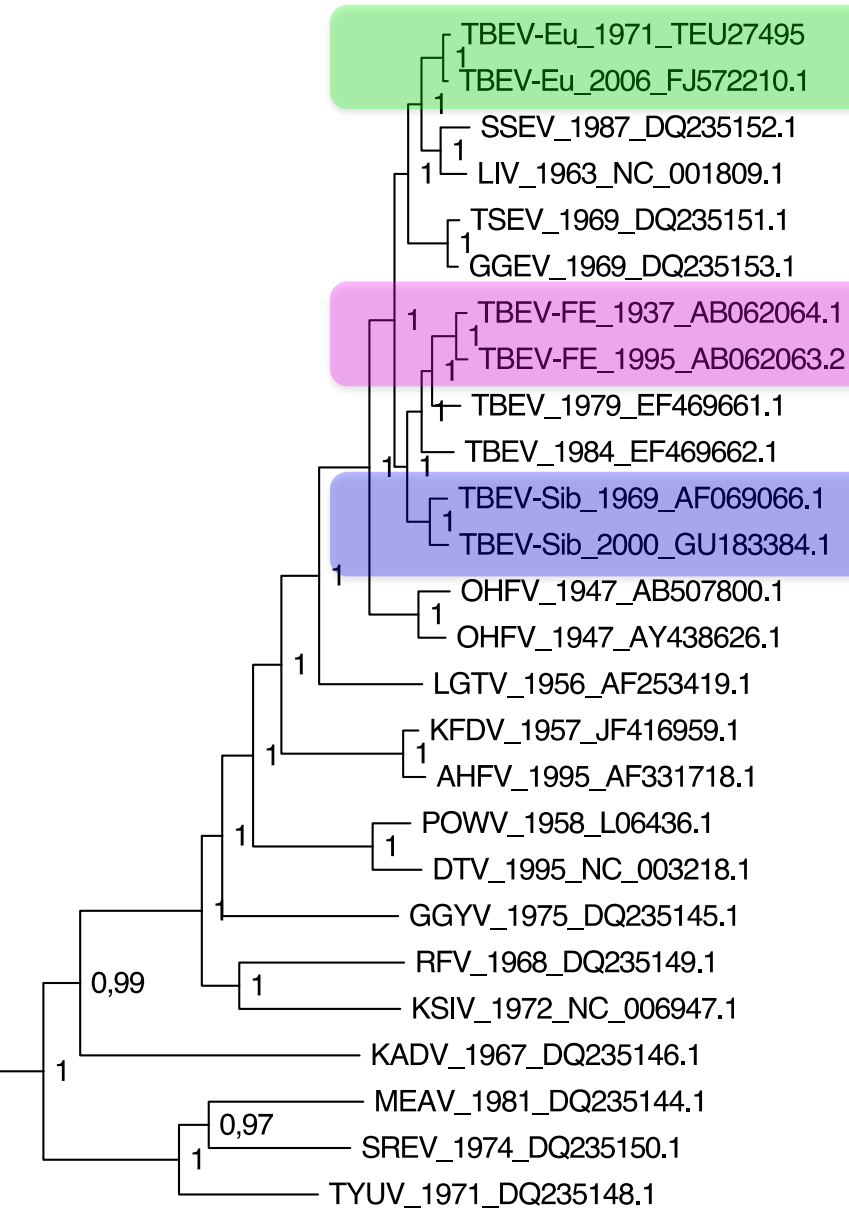
https://talk.ictvonline.org/ictv-reports/ictv_online_report/positive-sense-rna-viruses/w/flaviviridae/360/genus-flavivirus

Flavivirus distribution



Viruses 2017, 9(5), 97; https://doi.org/10.3390/v9050097

TBEV evolution



European subtype 1~2% mortality

Far-Eastern subtype ~5–35% mortality

Siberian subtype ~1–3% mortality

2 new subtypes proposed:
The Baikalian (TBEV-Bkl)
and the Himalayan (TBEV-Him)

TBEV vector distribution

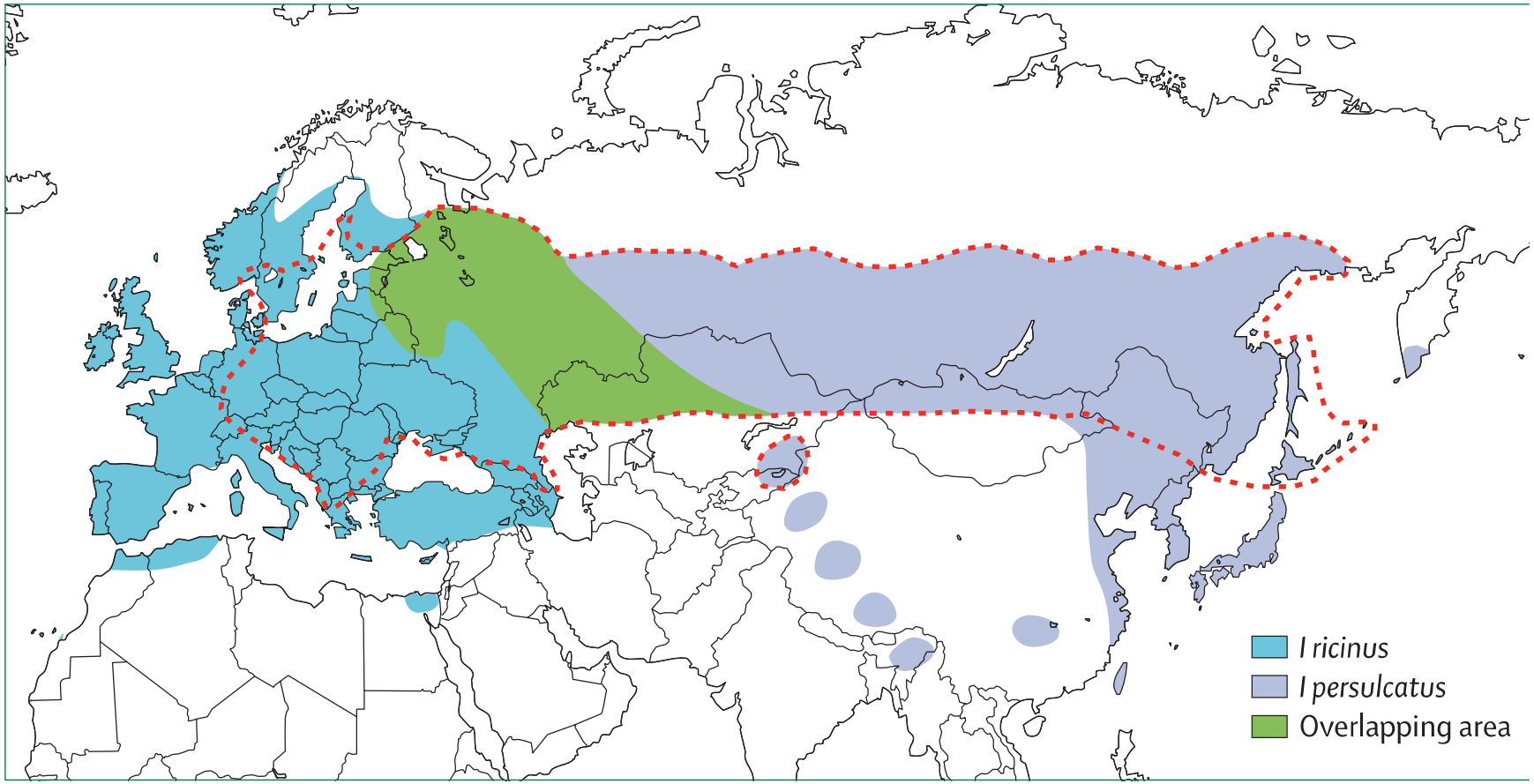


Figure 2: **The geographical distribution of *Ixodes* spp, with the western distribution for *I ricinus* and the eastern distribution for *I persulcatus***

The distribution for these two vectors overlaps in the green area. The dotted line defines the border for the tick-borne encephalitis endemic area. Note that the disease is very focally distributed within its endemic zone. Ixodes distribution in China is uncertain.

Lancet 2008; 371: 1861–71

TBEV prevalence in Sweden

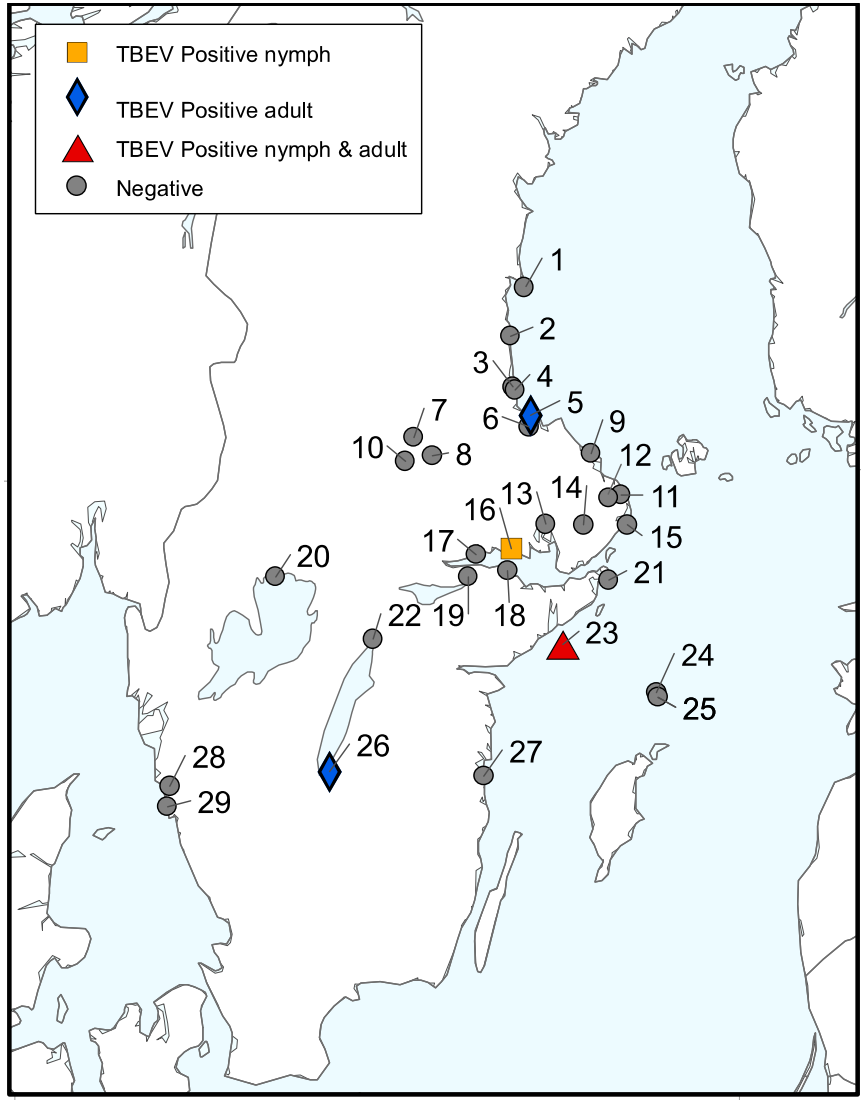
Collection from Hudiksvall to Jönköping,

>4500 ticks collected

- 1576 larvae
- 2118 nymphs
- 873 adults

Results

- 7 out 2980 ticks collected
- ≈ 0.23% for central/southern Sweden
- Lower in nymphs (0.10%) than in adult ticks (0.55%)



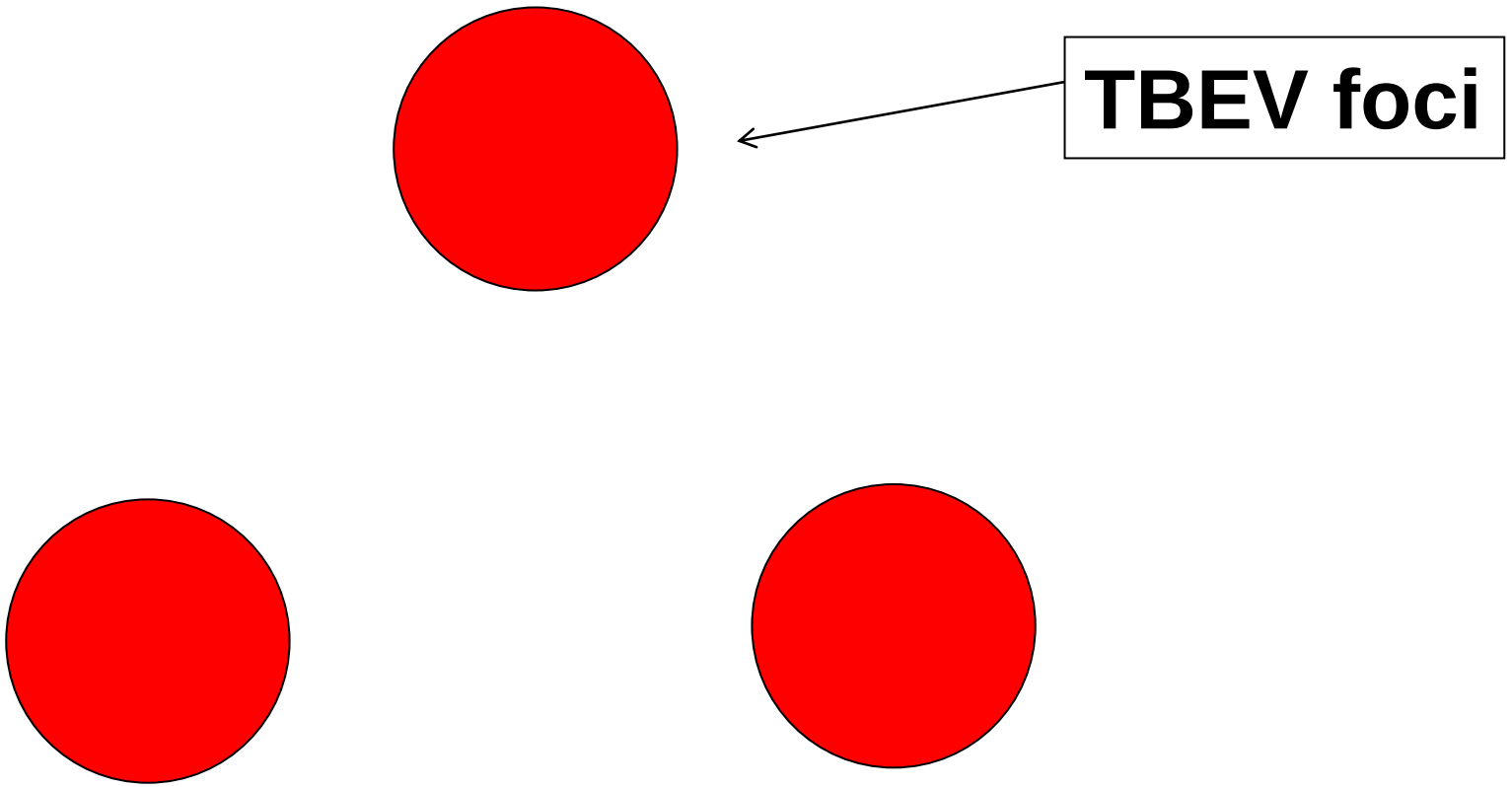
J. Pettersson and T. Jaensson, 2014

TBEV prevalence in Sweden and neighbouring countries

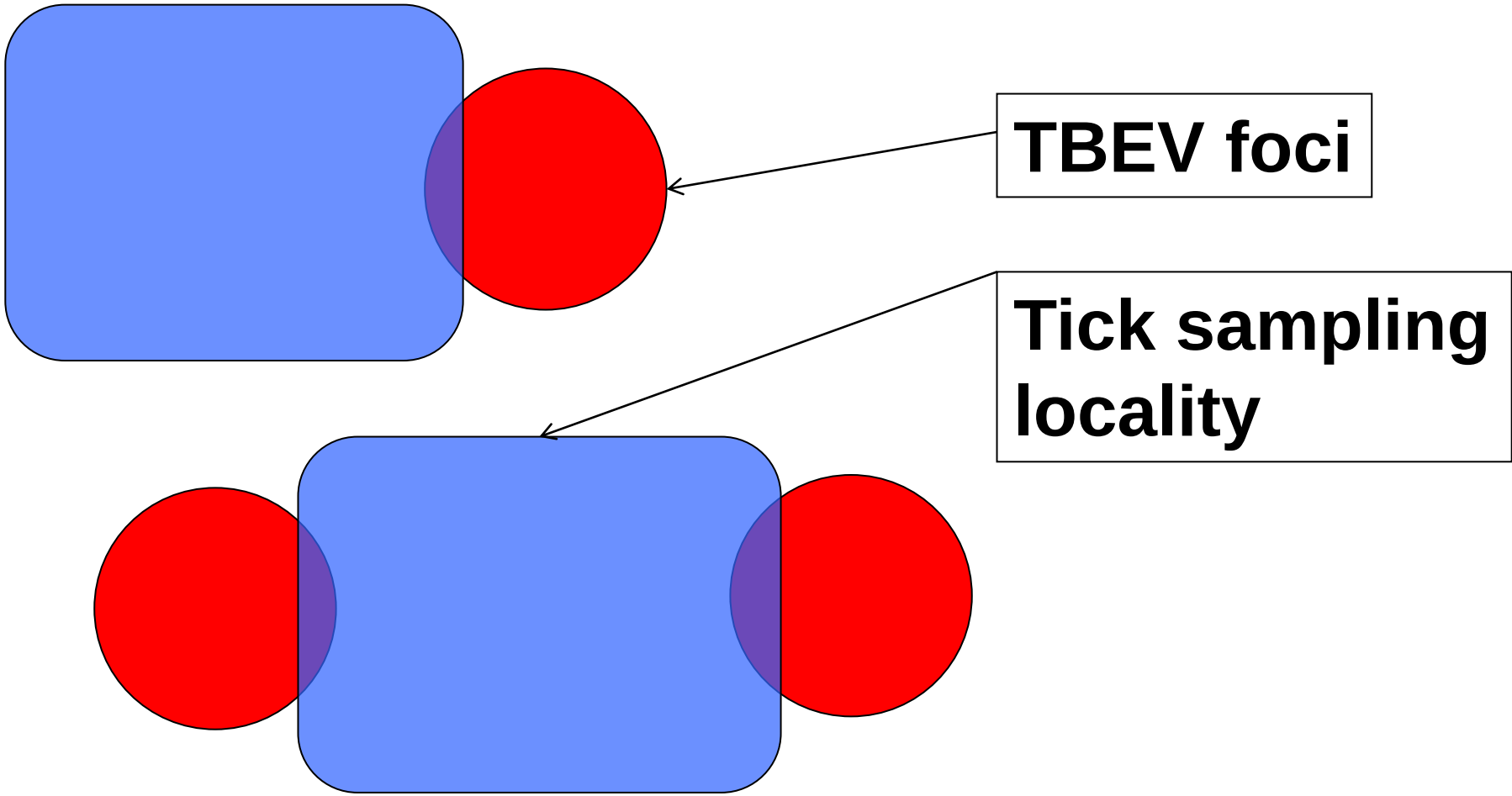
Country	Collection year	# Studies, # sites	N. of collected ticks		N. of TBEV-positive	
			Total	Pools collected	Pools positive	MIR %
Sweden	1958–2008	4 studies, 45 sites	11733	1510	30	**0.26**
Finland	1957–2008	4 studies, ≥ 27 sites	14320	2490	42	**0.29**
Norway	2003–2009	2 studies, 9 sites	6440	≥ 563	26	**0.40**
Denmark	1999–2011	3 studies , ≥ 18 sites	6865	≥ 70	11	**0.16**
SE+FI+NO+DE	**1957–2011**	**All sites (≥ 99)**	**39358**	**≥ 4633**	**109**	**0.28**

J. Pettersson and T. Jaensson, 2014

Why the low TBEV prevalence in *Ixodes ricinus?*



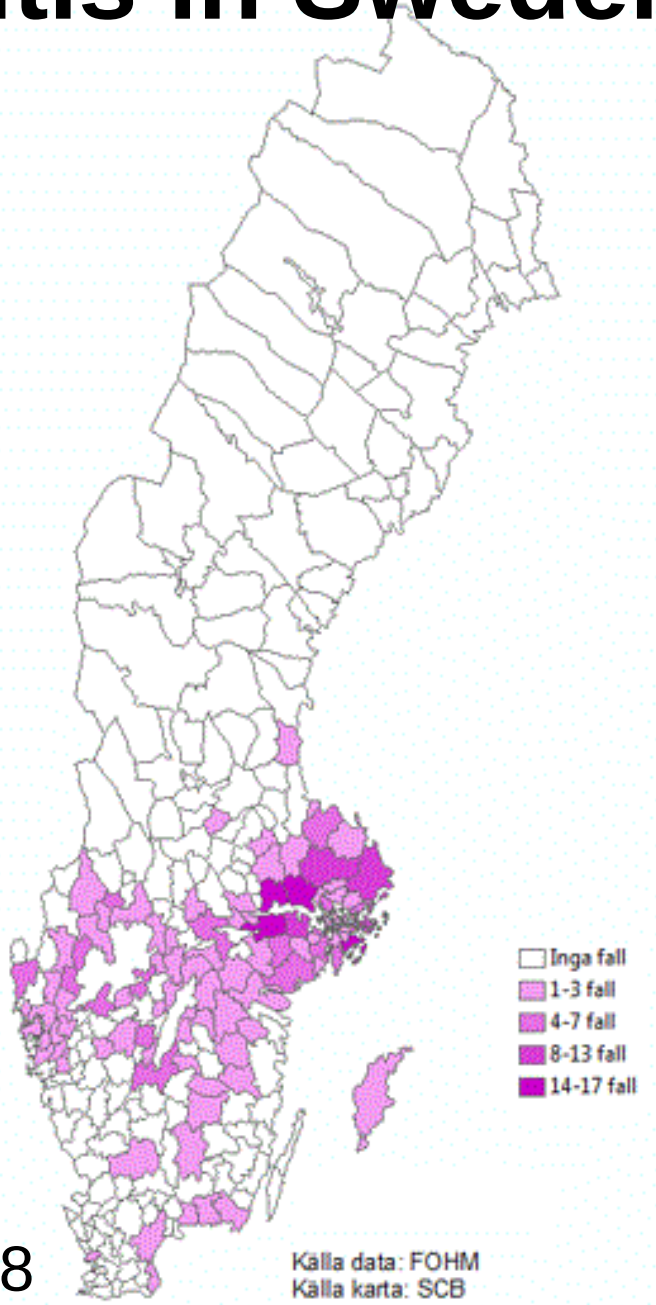
Why the low TBEV prevalence in *Ixodes ricinus?*



Tick-borne encephalitis in Sweden

> 75% of all cases in central Sweden

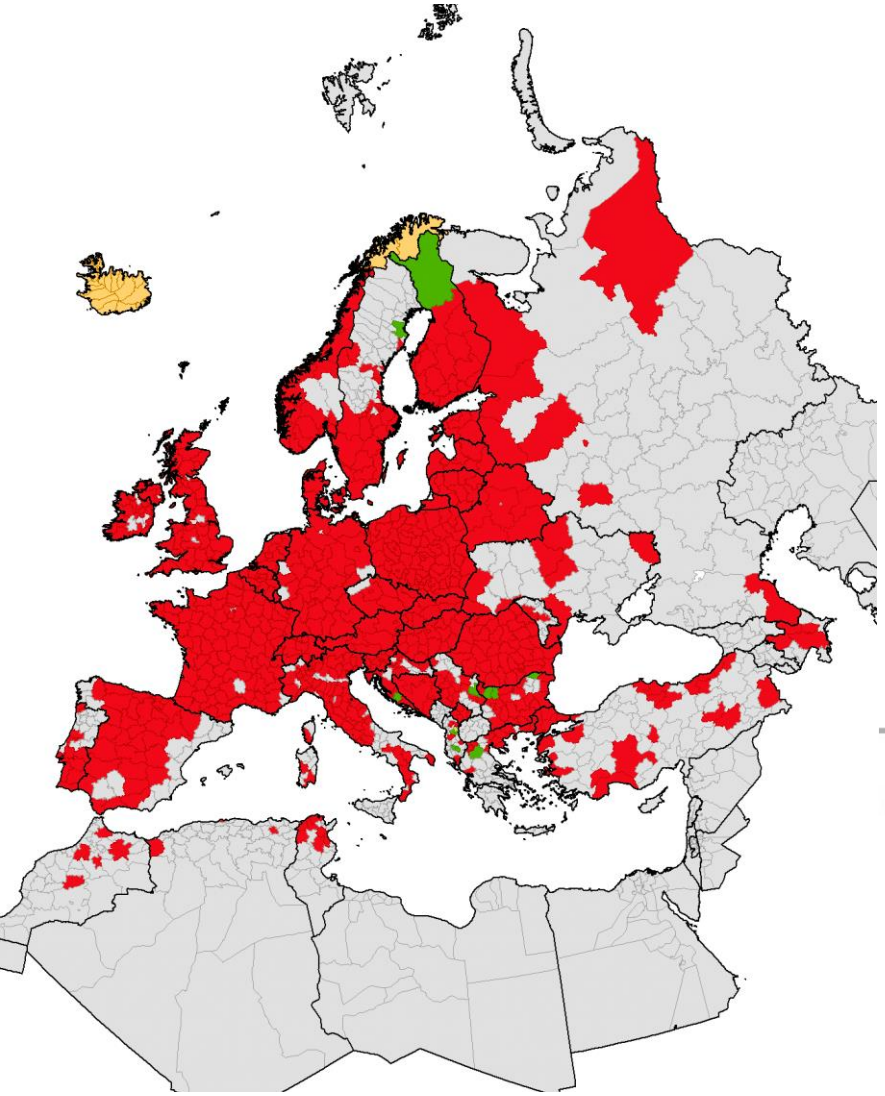
Centred around coastal regions and big lakes

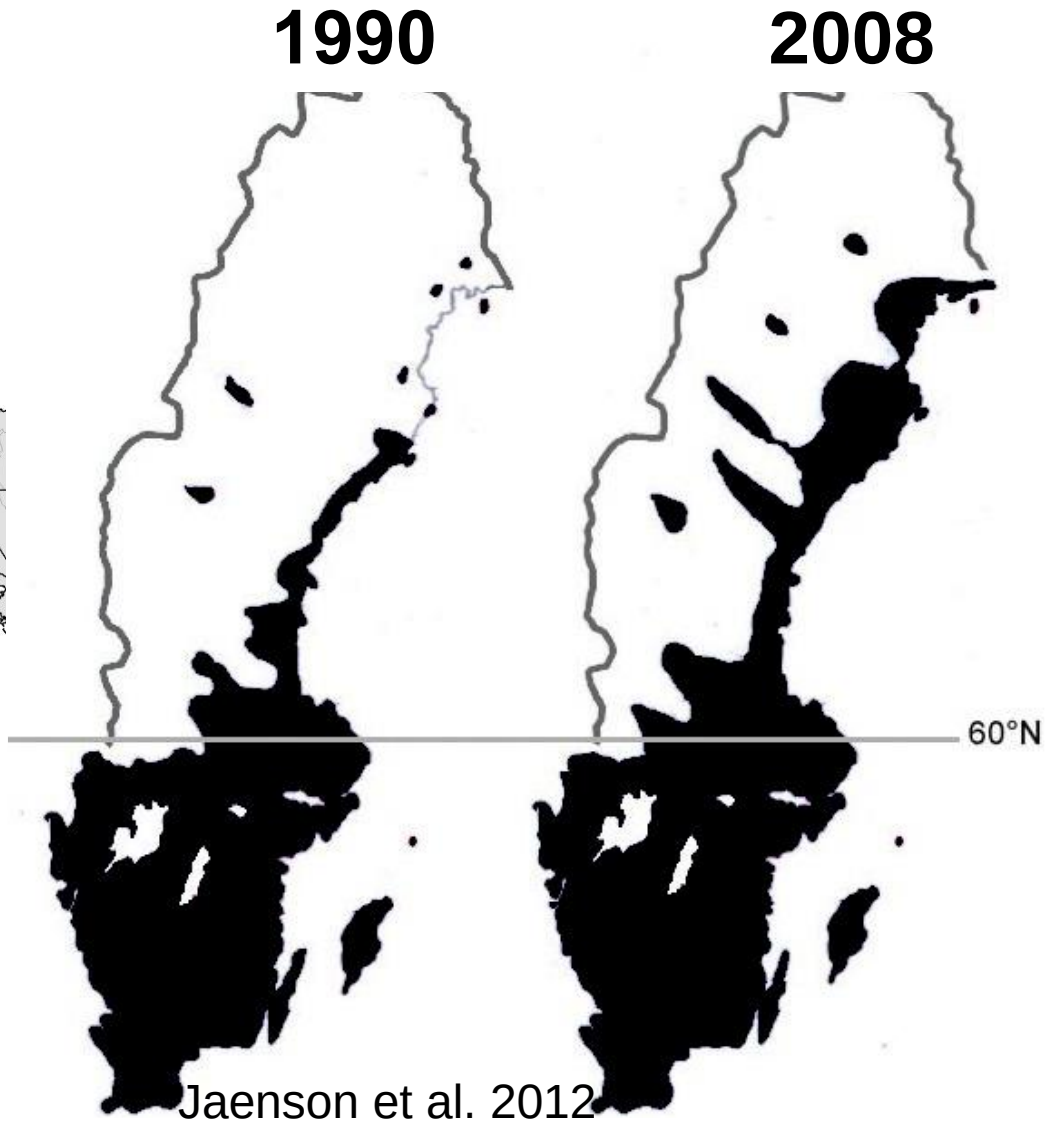


Public Health Agency of Sweden, 2018


N O R G E
STOCKHOLM
KØBENHAVN
HAMBURG
MINSK

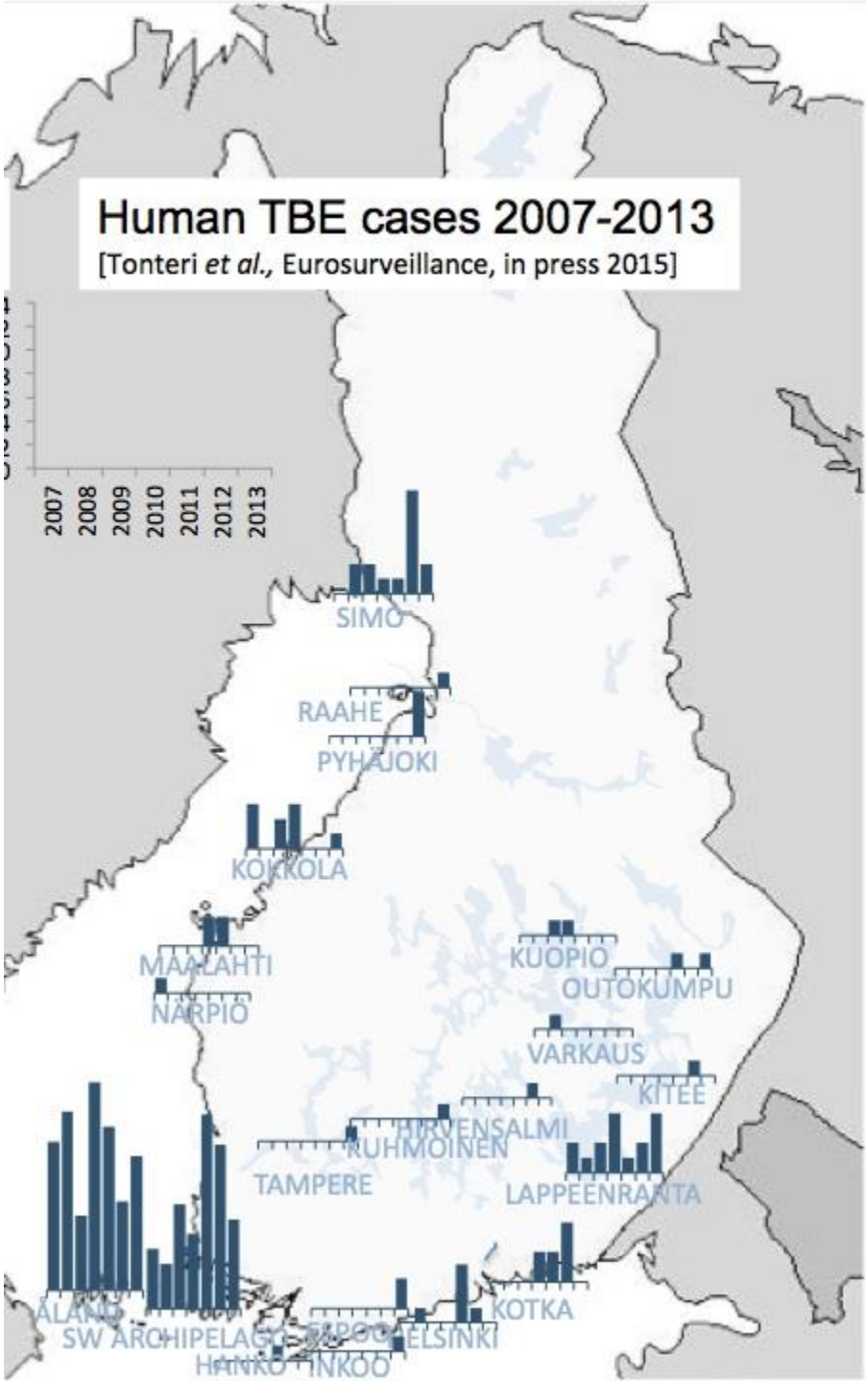
Ixodes ricinus ticks in Europe/Sweden





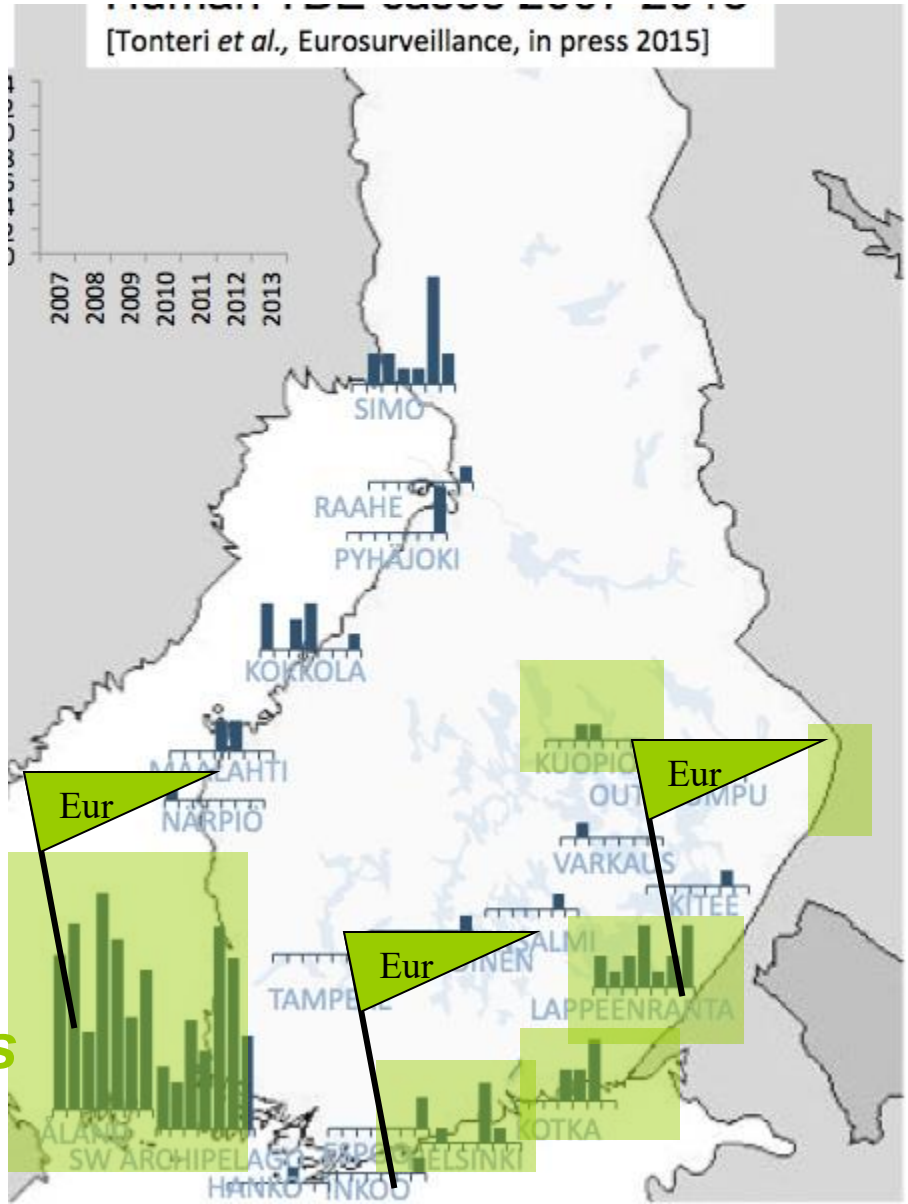
Jaenson et al. 2012

https://ecdc.europa.eu/en/publications-data/ixodes-ricinus-current-known-distribution-june-2018

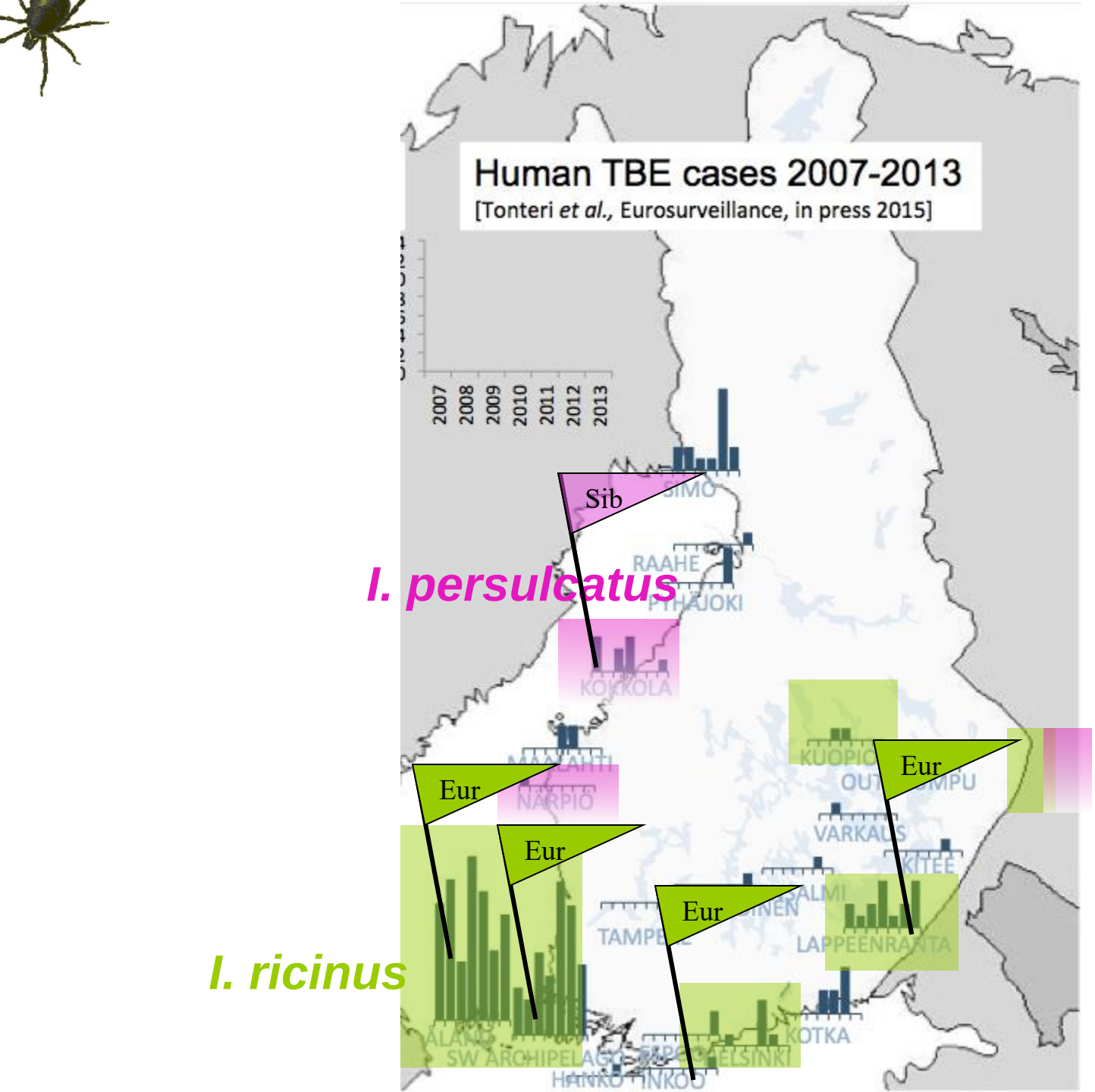

Human TBE cases 2007-2013
[Tonteri et al., Eurosurveillance, in press 2015]
2007
2008
2009
2010
2011
2012
2013
SIMO
RAAHE
PYHÄJOKI
KOKKOLA
MAARIAHTI
NÄRPIÖ
KUOPIO
OUTOKUMPU
VARKAUS
KITEE
HIRVENSALMI
RUHMOINEN
TAMPERE
LAPPEENRANTA
KOTKA
ÅLAND
SW ARCHIPELAGO
HELSINKI
HANKO
INKOO

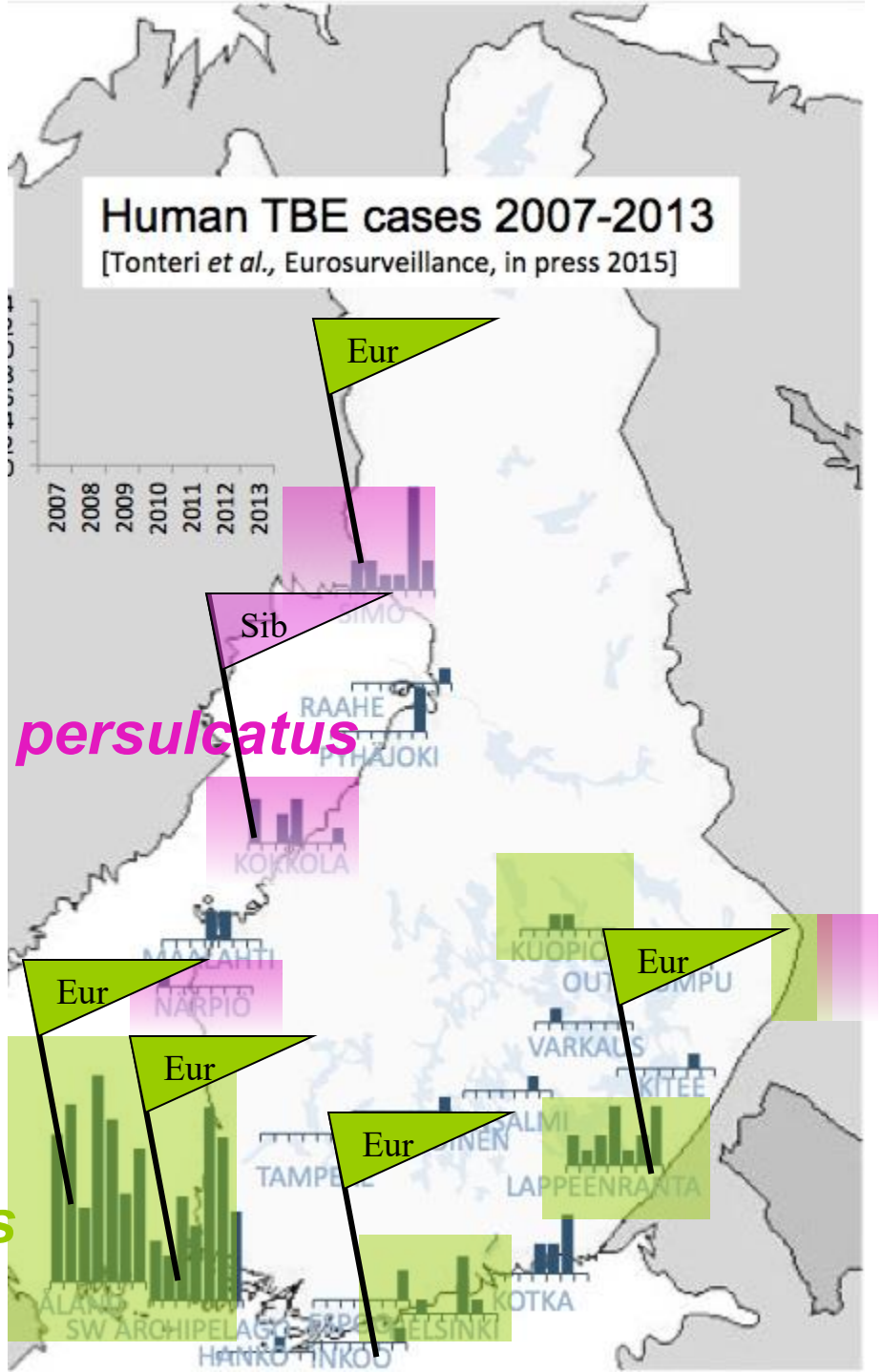
TBE virus vectors and subtypes

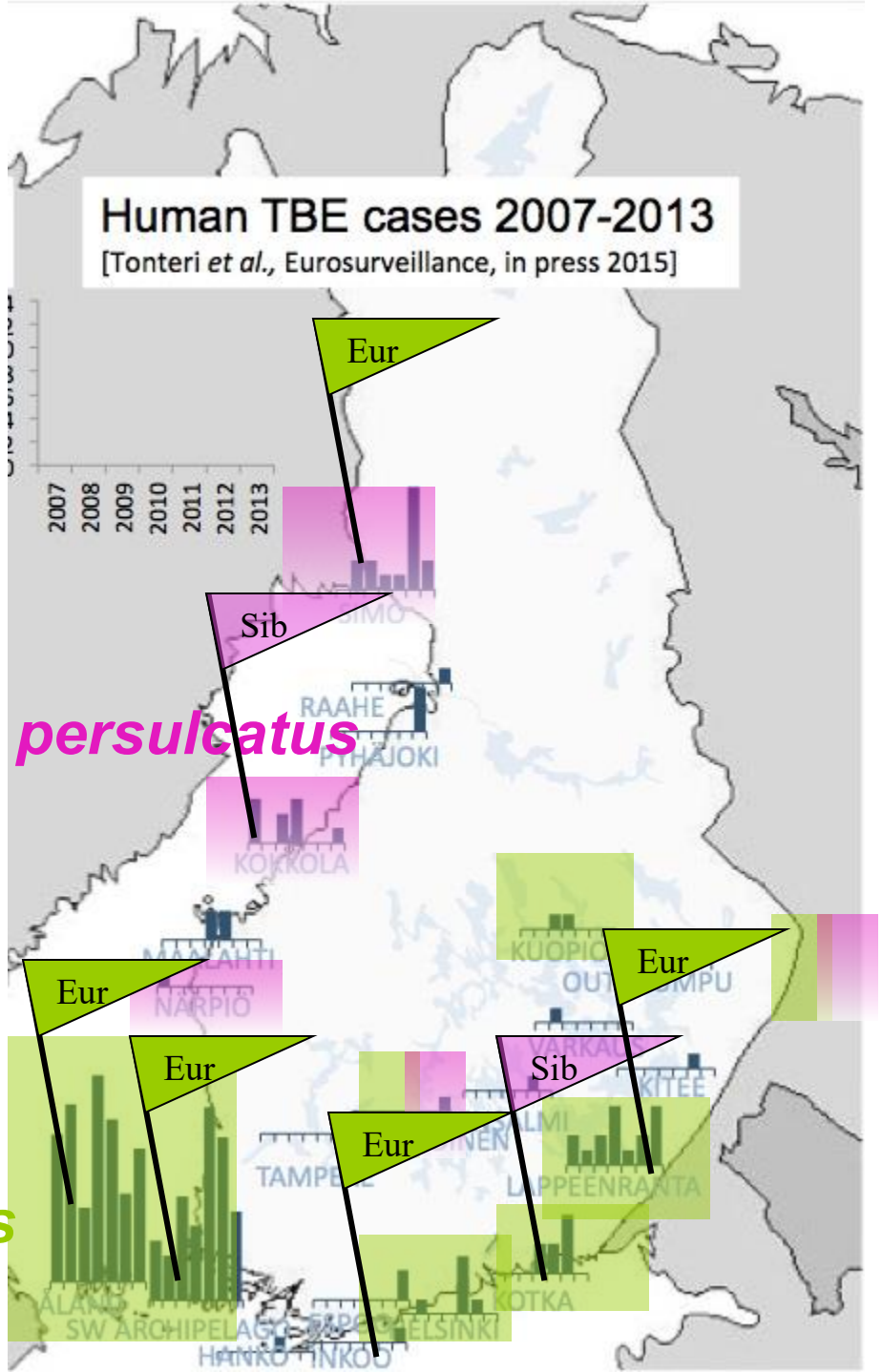
in Finland

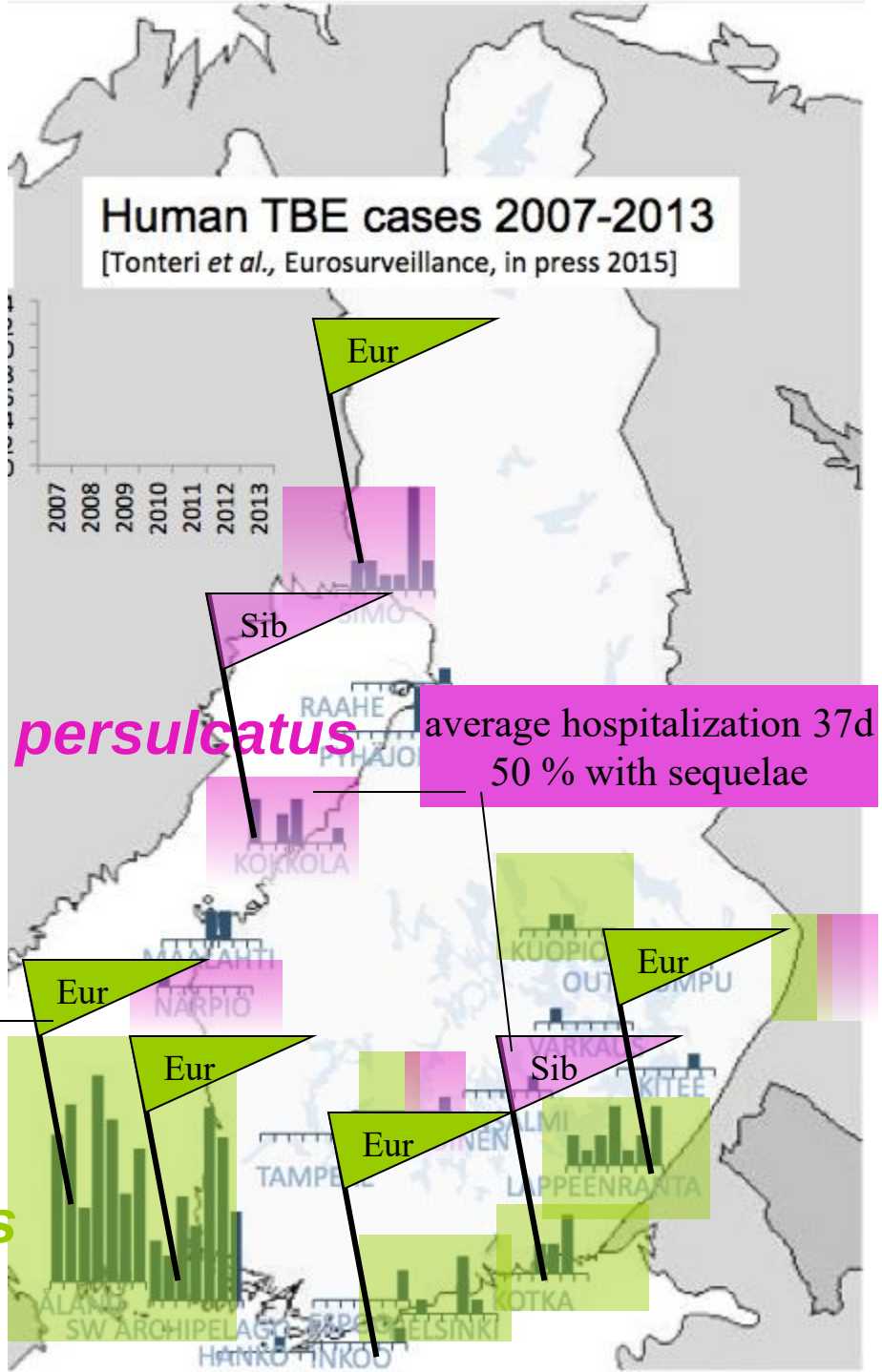


I. ricinus


Human TBE cases 2007-2013
[Tonteri et al., Eurosurveillance, in press 2015]
2007
2008
2009
2010
2011
2012
2013
Sib
Eur
Eur
Eur
Eur
I. persulcatus
I. ricinus
RAAHE
KOKKOLA
NÄRPIÖ
VARKAUS
LAPPEENRANTA
KOTKA
HANKO


Human TBE cases 2007-2013
[Tonteri et al., Eurosurveillance, in press 2015]
2007
2008
2009
2010
2011
2012
2013
Eur
Sib
Eur
Eur
Eur
Eur
RAAHE
PYHÄJOKI
KOKKOLA
KUOPIO
VARKAUS
LAPPEENRANTA
KOTKA
HANKO
I. persulcatus
I. ricinus


Human TBE cases 2007-2013
[Tonteri et al., Eurosurveillance, in press 2015]
2007
2008
2009
2010
2011
2012
2013
Eur
Sib
Eur
Eur
Eur
Sib
Eur
RAAHE
PYHÄJOKI
KOKKOLA
KUOPIO
LAPPEENRANTA
KOTKA
HANKO
I. persulcatus
I. ricinus



Jääskeläinen EID 2006, 2011, 2018, JGV 2010
Uzcategui JGV 2012

Contents lists available at ScienceDirect

Ticks and Tick-borne Diseases

journal homepage: www.elsevier.com/locate/ttbdis

Original article

Siberian subtype tick-borne encephalitis virus in *Ixodes ricinus* in a newly emerged focus, Finland

Anu Jääskeläinen[a,*], Elina Tonteri[a], Ilkka Pieninkeroinen[b], Tarja Sironen[a], Liina Voutilainen[a,c], Markku Kuusi[d], Antti Vaheri[a,e], Olli Vapalahti[a,e,f]

[a] *Department of Virology, University of Helsinki, P.O. Box 21, FI-00014 Helsinki, Finland*
[b] *Kymenlaakso Central Hospital, Kotkantie 41, FI-48210 Kotka, Finland*
[c] *Natural Resources Institute, Vantaa Unit, P.O. Box 18, FI-01301 Vantaa, Finland*
[d] *Department of Infectious Diseases, National Institute for Health and Welfare, P.O. Box 30, FI-00271 Helsinki, Finland*
[e] *Department of Virology and Immunology, HUSLAB, Helsinki University Hospital, P.O. Box 400, FI-00029 Helsinki, Finland*
[f] *Department of Veterinary Biosciences, University of Helsinki, P.O. Box 66, FI-00014 Helsinki, Finland*

Jaenson *et al. Parasites & Vectors* (2016) 9:377
DOI 10.1186/s13071-016-1658-3

Parasites & Vectors

RESEARCH Open Access

First evidence of established populations of the taiga tick *Ixodes persulcatus* (Acari: Ixodidae) in Sweden

Thomas G. T. Jaenson[1*], Kairi Värv[2], Isabella Fröjdman[3], Anu Jääskeläinen[4], Kaj Rundgren[5], Veerle Versteirt[6], Agustín Estrada-Peña[7], Jolyon M. Medlock[8,9] and Irina Golovljova[2]

TBE - Risk and increase in Sweden

Red fox and tick-borne encephalitis (TBE) in humans: can predators influence public health?

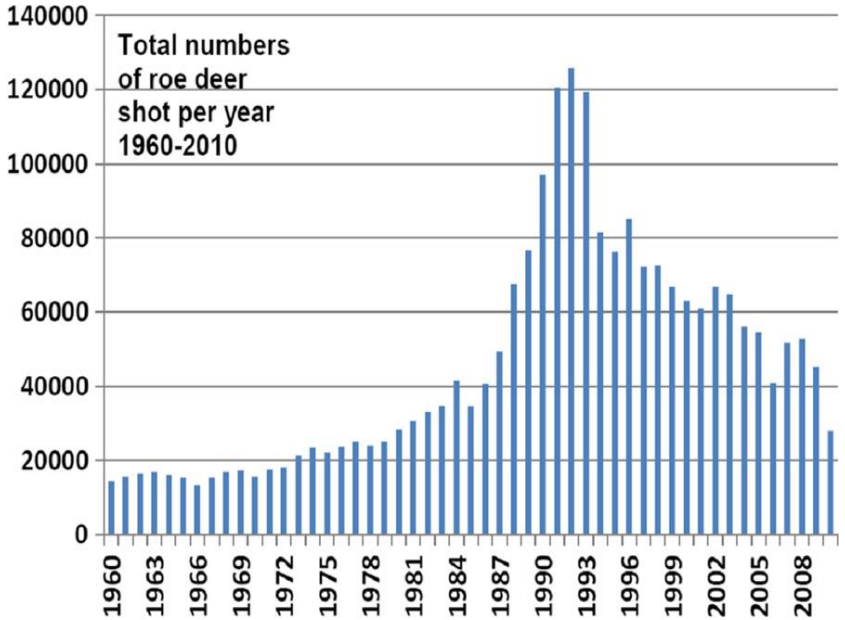
Haemig PD, Lithner S, Sjostedt De Luna S, Lundkvist Å, Waldenström J, Hansson L, Arneborn M, Olsen B.
Scand J Infect Dis. 2008;40(6-7):527-32.

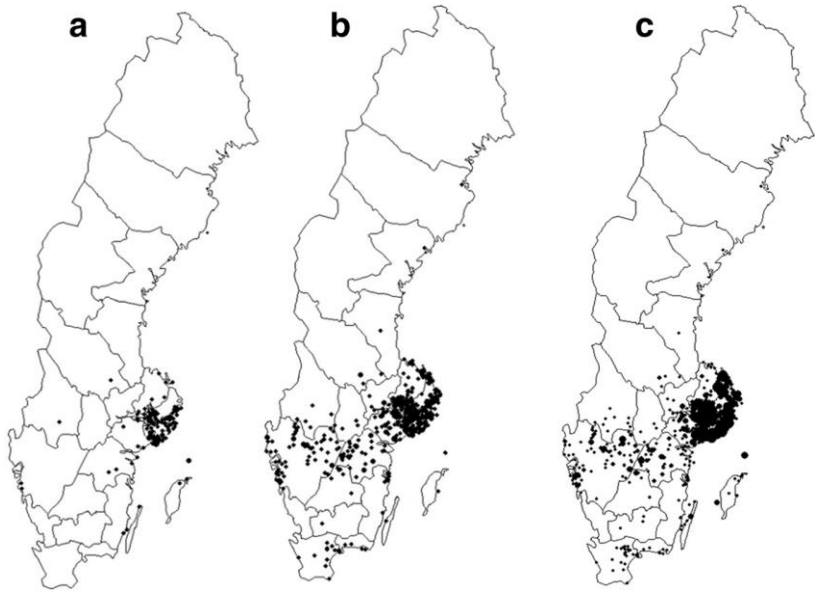
Forecasting risk of tick-borne encephalitis (TBE): using data from wildlife and climate to predict next year's number of human victims.

Haemig PS, Sjöstedt de Luna S, Grafström A, Lithner S, Lundkvist Å, Waldenström J, Kindberg J, Stedt J, Olsen B.
Scand J Infect Dis. 2011 May;43(5):366-72.

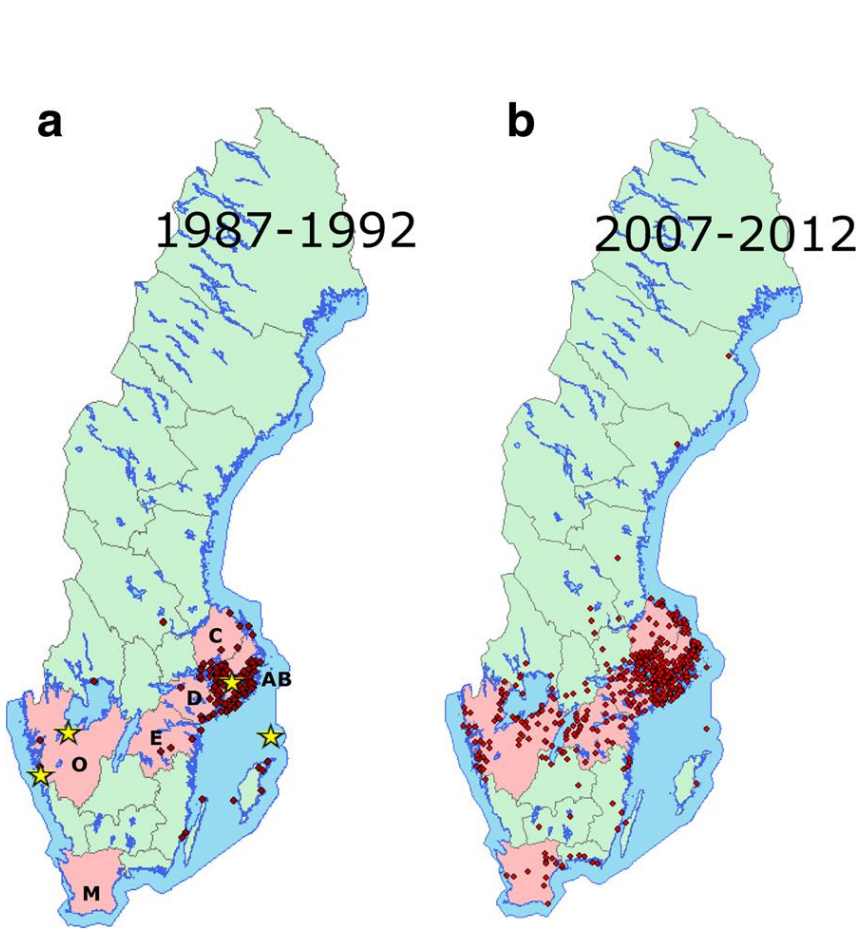
Why is tick-borne encephalitis increasing? A review of the key factors causing the increasing incidence of human TBE in Sweden.

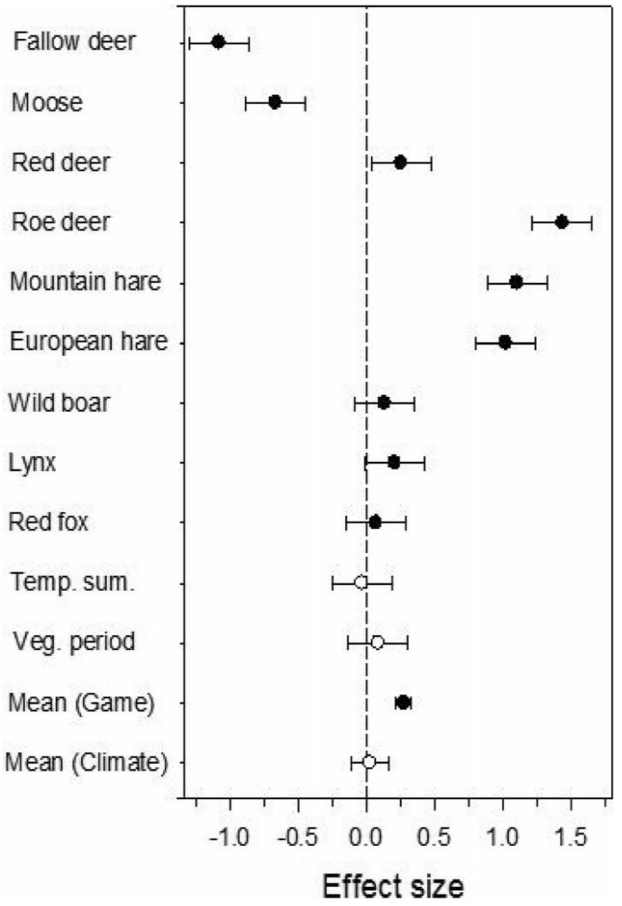
Jaenson TG, Hjertqvist M, Bergström T, Lundkvist Å
Parasit Vectors. 2012 Aug 31;5:184. doi: 10.1186/1756-3305-5-184.





TBE – Increase in Sweden



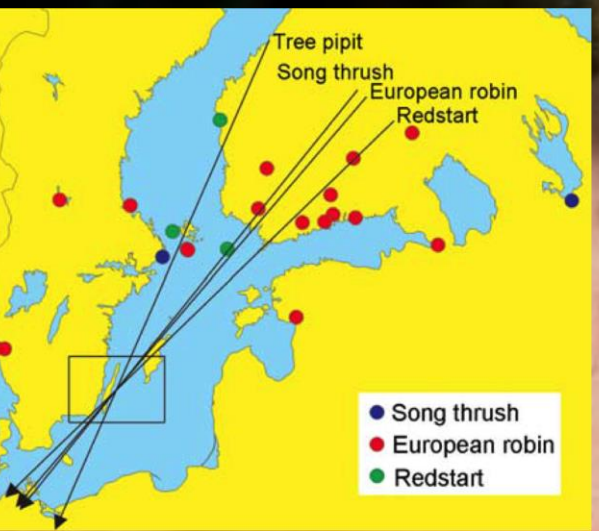


T. Jaensson et al., 2018

Fig. 4 Meta-analysis of the effect of number of killed game animals (filled symbols) and climatic variables (open symbols) on incidences of TBE. For each entry (except the mean values) the values for six counties in Sweden were included. A positive value means that a high number of killed animals or high values of the environmental variables in one year results in increased numbers of cases of human TBE recorded the following year (i.e. a lag period of one year). The dots show the mean effect sizes, the bars the 95% confidence intervals.

photo: Ola Nordsteien. Jomfruland bird observatory Sept 2003

Greenfinch, *Carduelis chloris*,

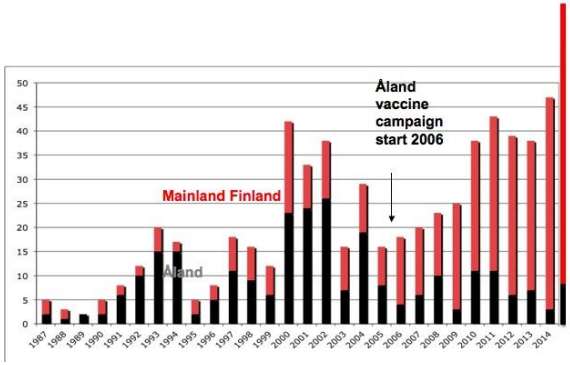


Migrating Birds and Tickborne Encephalitis Virus
Waldenström J, Lundkvist Å, Falk KI, Garpmo U, Bergström S, Lindegren G, Sjöstedt A, Mejlon H, Fransson T, Haemig P, Olsen B. Emerg Infect Dis. 2007 Aug;13(8):1215-8.

TBEV ecology - Gaps

- Trans-ovarial transmission.
- Trans-stadial transmission.
- Viremic transmission vs. co-feeding?
- Tick species?
- Reservoir hosts. Rodents vs. roe deer, red deer?
- Rodent species?
- Birds, hedgehogs, insectivors?

Why increase of TBE in some areas?





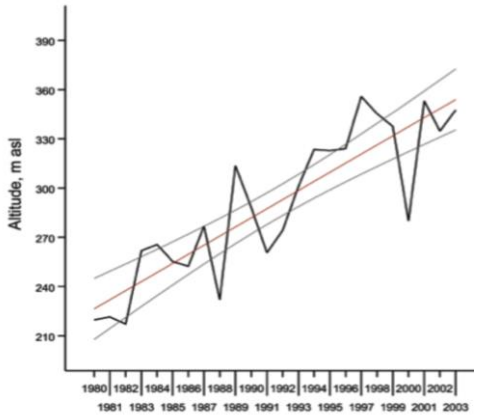
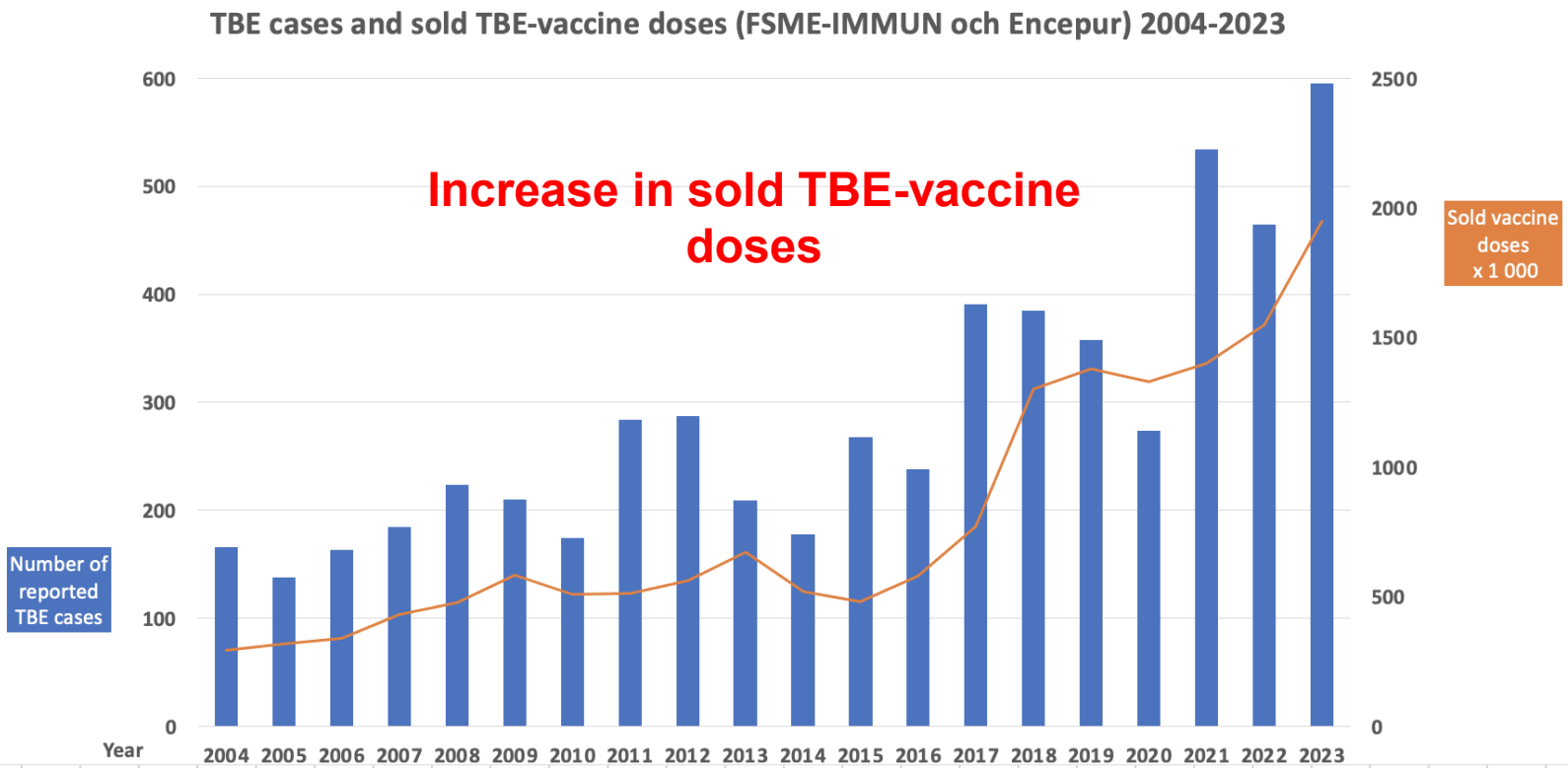
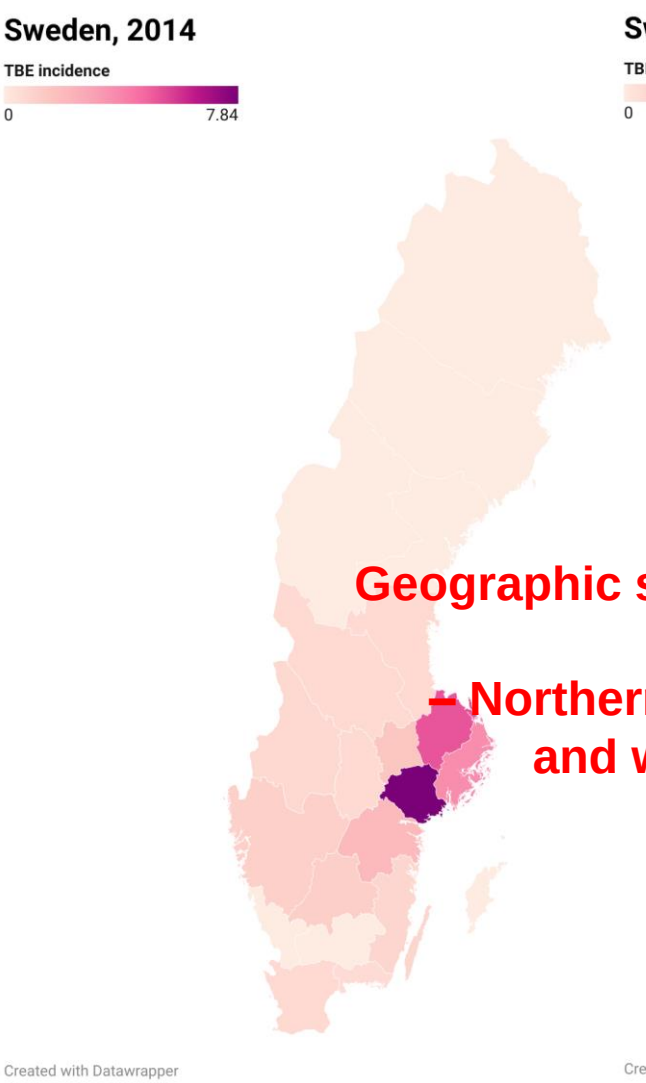


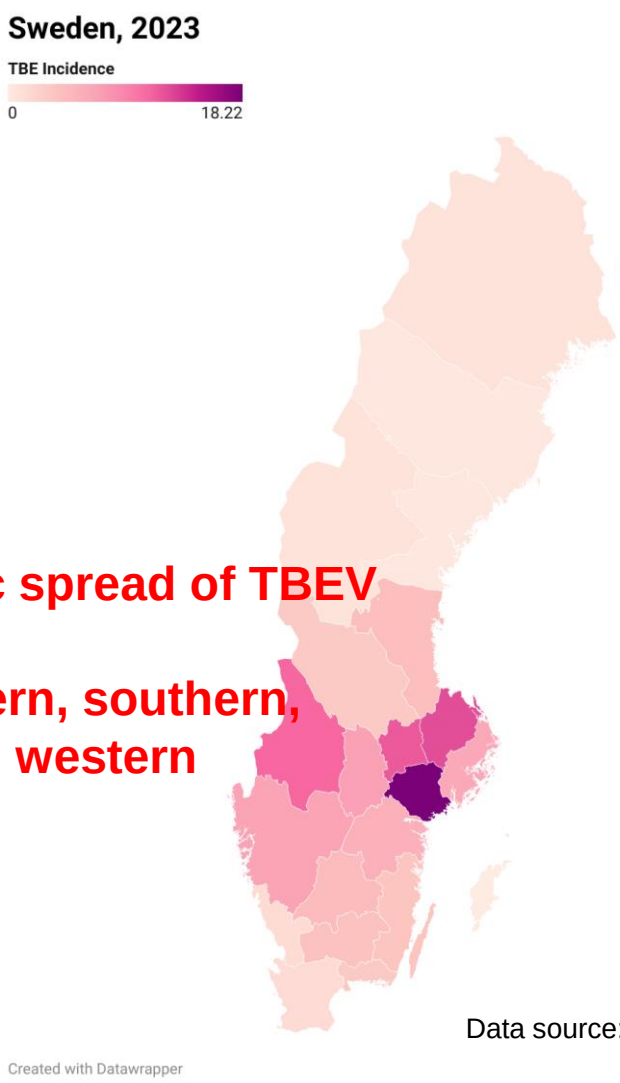
Figure 1. Mean altitude of reported cases of tick-borne encephal (TBE), Slovakia, 1980–2004. Black line, mean altitude; red li linear least-square fit; gray lines, 95% confidence intervals; a above sea level.

- Climate
- Human behavior
- Wildlife
- Most complex – different factors in different geographical areas


TBE cases and sold TBE-vaccine doses (FSME-IMMUN och Encepur) 2004-2023
Increase in sold TBE-vaccine doses
Number of reported TBE cases
Sold vaccine doses x 1 000
Year
600
500
400
300
200
100
0
2500
2000
1500
1000
500
0
2004 2005 2006 2007 2008 2009 2010 2011 2012 2013 2014 2015 2016 2017 2018 2019 2020 2021 2022 2023





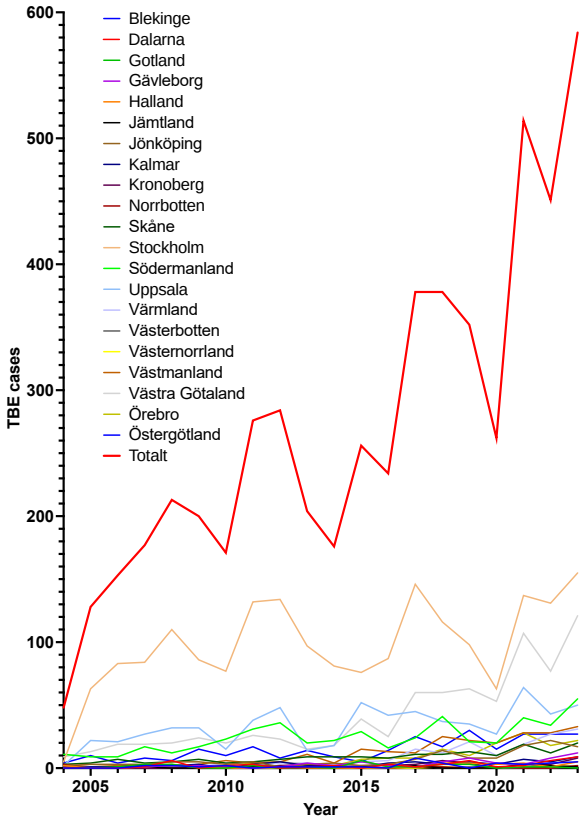


Geographic spread of TBEV

– Northern, southern, and western

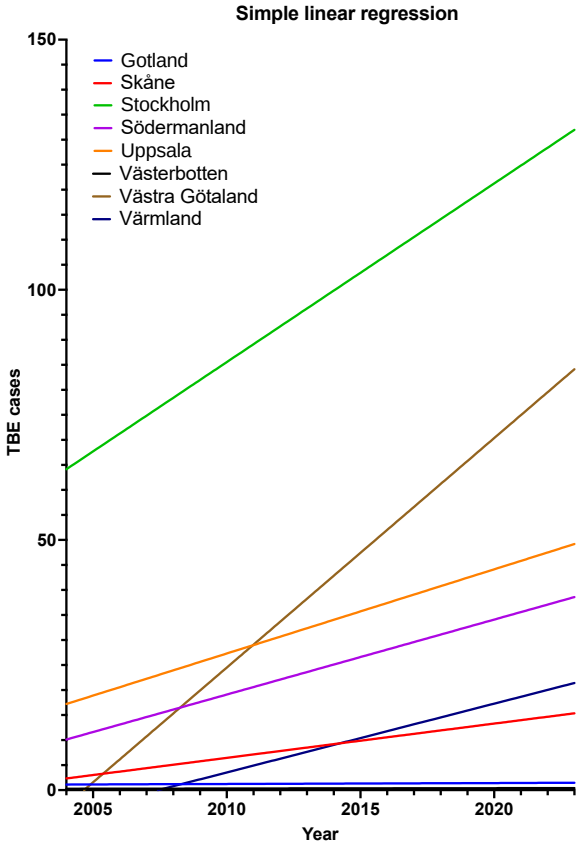
Data source: FC

TBE cases, 2004–2023



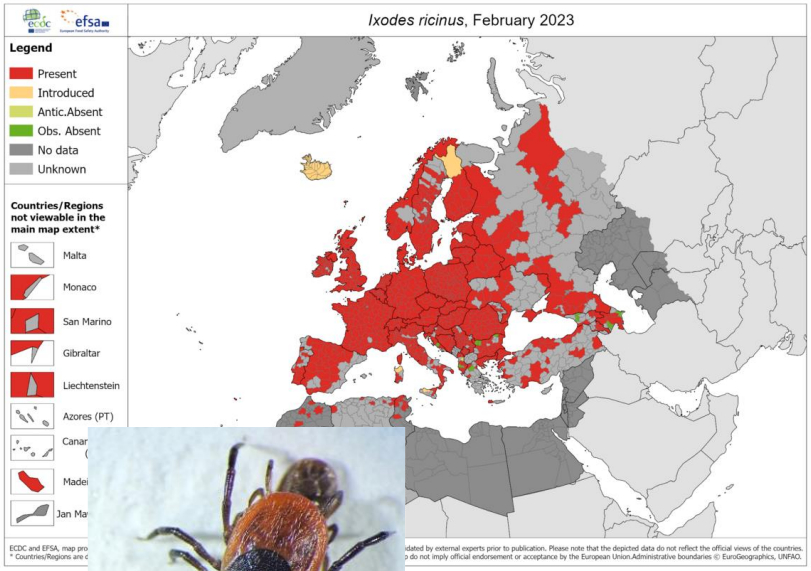
Increase in TBE cases over time

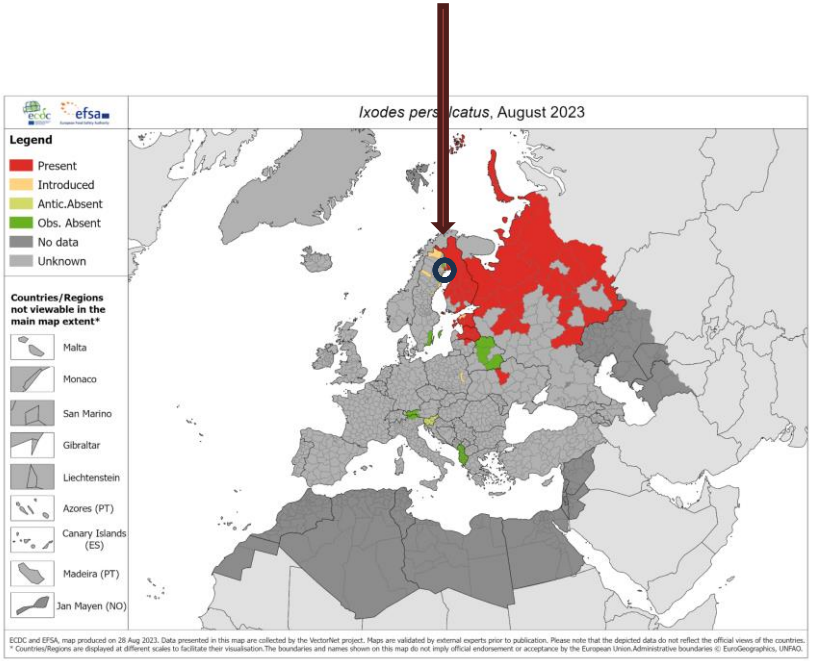
Yearly variations



Data source: FOHM

Ixodes ricinus and Ixodes persulcatus

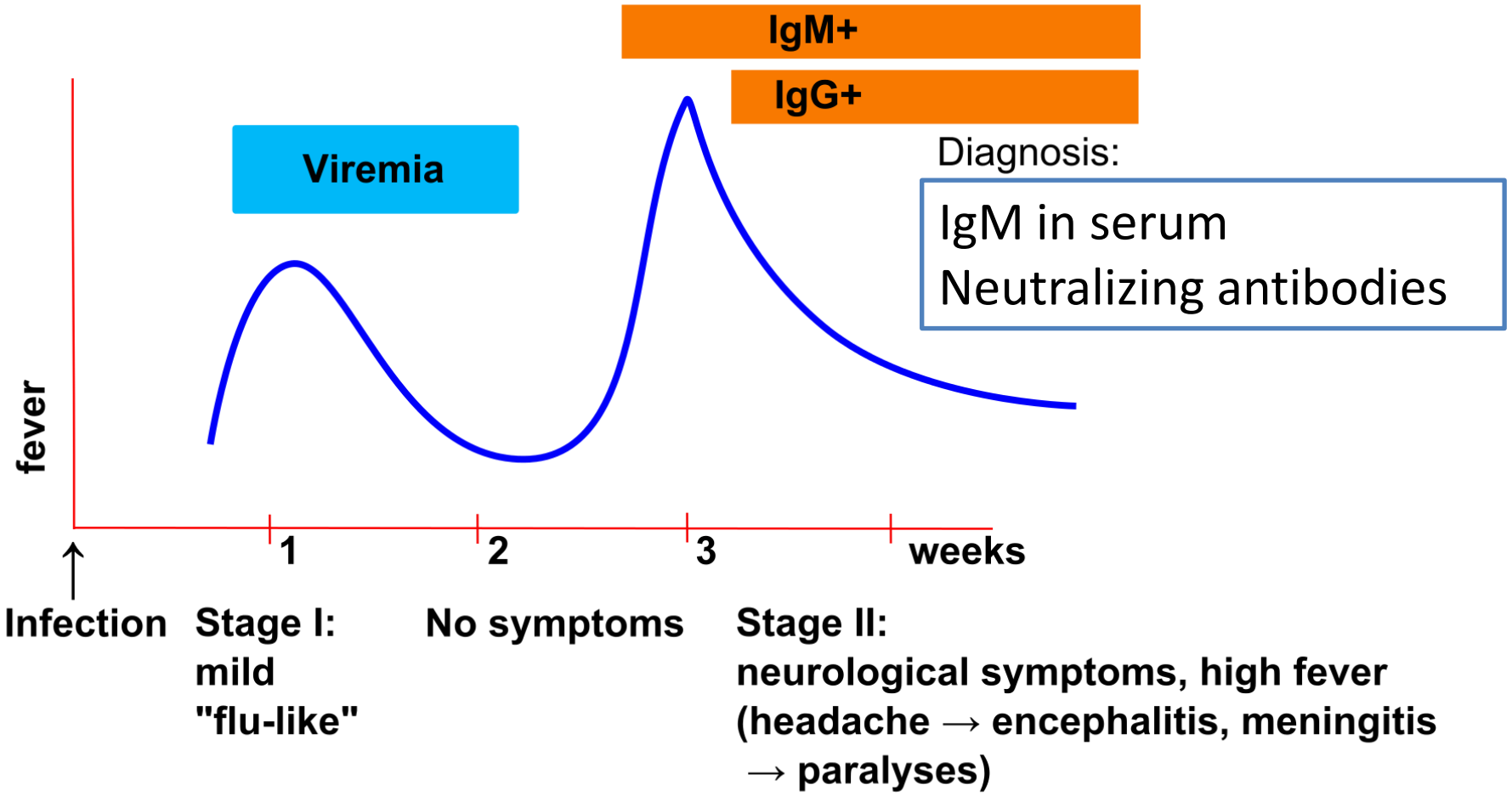




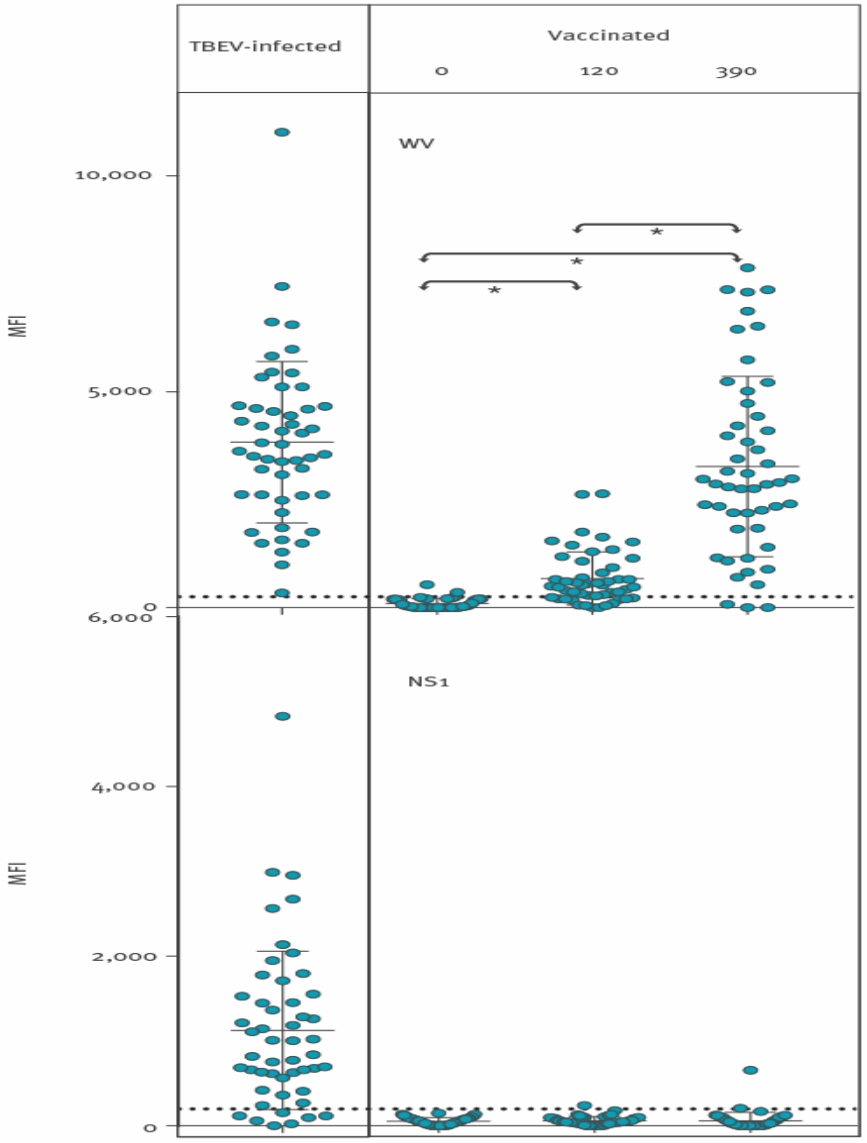


Geographical spread of TBEV vectors in Sweden

TBEV pathogenensis and clinical course



Luminex-based suspension multiplex immunoassay (TBE-SMIA) IgG reactivity with TBE whole virus (WV) and non-structural protein 1 (NS1) antigens in infected (n = 50) and vaccinated individuals (n = 50) at 0, 120 and 390 days after first vaccination, Sweden, 2017



Distinction between serological responses following tick-borne encephalitis virus (TBEV) infection vs vaccination, Sweden 2017.

Albinsson B, Vene S, Rombo L, Blomberg J, Lundkvist Å, Rönnberg B.

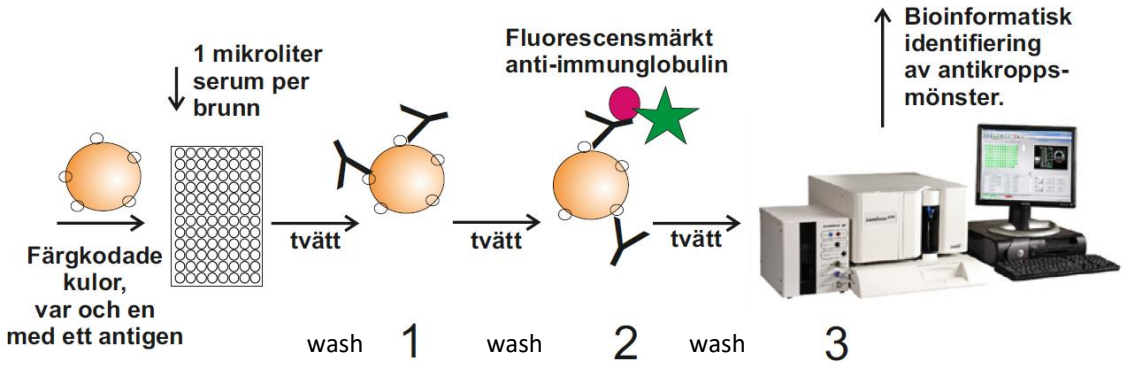
Euro Surveill. 2018 Jan;23(3). doi: 10.2807/1560-7917.ES.2018.23.3.17-00838

Vaccine failures/Vaccine breakthrough

Prevalence studies

Routine assay at Akademiska sjukhuset, Uppsala

Antibody detection by Suspension Multiplex Immunoassay - TBEV SMIA



- Detects antibodies against **TBEV** NS1-antigen (**NS1**) och Whole Virus antigen (**WV**) in the same well.
- **Infected** individuals develop **antibodies against TBEV NS1 and WV**.
- **Vaccinated** individuals **only** develop **antibodies against WV**.

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Research

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Seroprevalence of tick-borne encephalitis virus and vaccination coverage of tick-borne encephalitis, Sweden, 2018 to 2019

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Bo Albinsson[1,2,*], Tove Hoffman[1,*], Linda Kolstad[1], Tomas Bergström[4], Gordana Bogdanovic[5], Anna Heydecke[6], Mirja Hägg[5], Torbjörn Kjerstadius[7], Ylva Lindroth[8], Annika Petersson[9], Marie Stenberg[10], Sirkka Vene[1], Patrik Ellström[2,3], Bengt Rönnberg[1,2], Åke Lundkvist[1]

Hide Affiliations

Affiliations:

[1] Zoonosis Science Center, Department of Medical Biochemistry and Microbiology, Uppsala University, Uppsala, Sweden

[2] Laboratory of Clinical Microbiology, Uppsala University Hospital, Uppsala, Sweden

[3] Zoonosis Science Center, Department of Medical Sciences, Uppsala University, Uppsala, Sweden

[4] Department of Infectious Diseases, Institute of Biomedicine, University of Gothenburg, Gothenburg, Sweden

[5] Department of Clinical Microbiology, Karolinska University Hospital, Stockholm, Sweden

[6] Centre for Research and Development, Uppsala University, Region Gävleborg, Gävle, Sweden

[7] Laboratory Medicine, Clinical Microbiology, Central Hospital, Karlstad, Sweden

[8] Department of Laboratory Medicine, Medical Microbiology, Lund University, Skåne Laboratory Medicine, Lund, Sweden

[9] Department of Clinical Chemistry and Transfusion Medicine, Växjö Central Hospital, Växjö, Sweden

[10] Laboratory Medical Center Gotland, Visby hospital, Visby, Sweden

* These authors contributed equally to the work and share the first authorship.

Correspondence: Bo Albinsson

TBEV seroprevalence in Sweden, 2018–2019

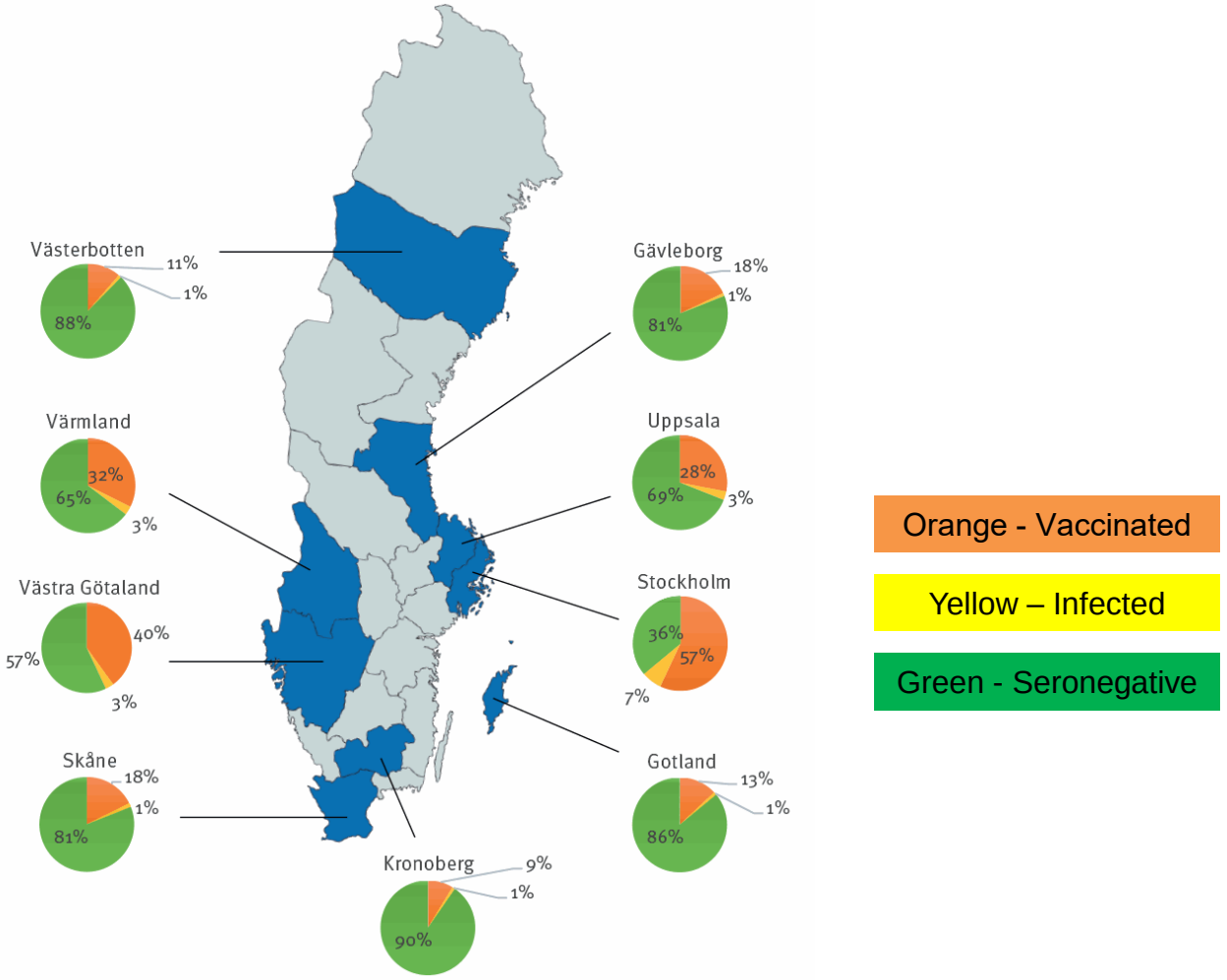


Figure. Estimated proportion of tick-borne encephalitis vaccinated, tick-borne encephalitis virus infected and seronegative blood donors, per region, Sweden, 2018–2019 (n = 2,700)

Calculated manifestation indices of TBE, Sweden

TBE cases in Sminet ⇩ **Based on our results** ⇩ **Percentages of reported cases of all infections** ⇩

Table 3

Calculated manifestation indices of tick-borne encephalitis, per region, Sweden, 2004–2019

Region	Notified TBE case incidence[a]	TBEV infection incidence[b]	TBE MI (%)
Gotland	4.0	50.0	8.0
Gävleborg	1.1	50.0	2.2
Kronoberg	1.2	50.0	2.3
Skåne	0.8	66.7	1.3
Stockholm	6.6	350.0	1.9
Uppsala	13.1	150.0	8.7
Värmland	2.4	150.0	1.6
Västerbotten	0.2	50.0	0.4
Västra Götaland	2.4	150.0	1.6
Mean	3.5	118.5	3.1

MI: manifestation index; NS1: non-structural protein 1; TBE: tick-borne encephalitis; TBEV: tick-borne encephalitis virus; WV: whole virus.

[a] Annual notifications per 100,000 inhabitants 2004–2018. Data source: Public Health Agency of Sweden.

[b] Infected (WV positive and NS1positive)per 100,000 inhabitants and year; estimated duration of TBEV NS1IgG: 20 years.

Knowledge gaps

- Lack of TBE vaccine registry → limited knowledge about TBE vaccination coverage
- Difficult to follow the TBE vaccination schedule, due to booster doses → lower immunity against TBE- virus in the population
  - Automated notifications about booster doses would be great
- Lack of serological methods that can distinguish antibodies against TBE-virus subtypes → difficult to perform TBEV surveillance
- Lower vaccination coverage in new risk areas?
- Vaccine breakthroughs?
- More ticks → more TBE-virus? → increased risk?

TBE research at ZSC

- Higher tick abundance → more TBEV?
- Effect of climate change on TBEV
- Increase of severe TBE?
- Continued development of novel assays
- TBE vaccine break-throughs

Thank you!

- **Many thanks to John Pettersson, Olli Vapalahti, Tove Hoffman and Bo Albinsson for slides and pictures**







It never rains in Southern California,
but certainly in Southern Uppsala