NEMOCNICE
ČESKÉ BUDĚJOVICE, a.s.

ID teaching NW England
Liverpool, UK, 6 Dec 2023

Tick-Borne CNS infections

Ales Chrdle
Ceske Budejovice Hospital, Czech Republic
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Outline

Tick biology

Map exercise

Encephalitis/encephalopathy

Tick-borne encephalitis (TBE)

Lyme disease (neuroboreliosis)

Summary

Ticks and their biology

Hard ticks

Ixodes ricinus – central Europe

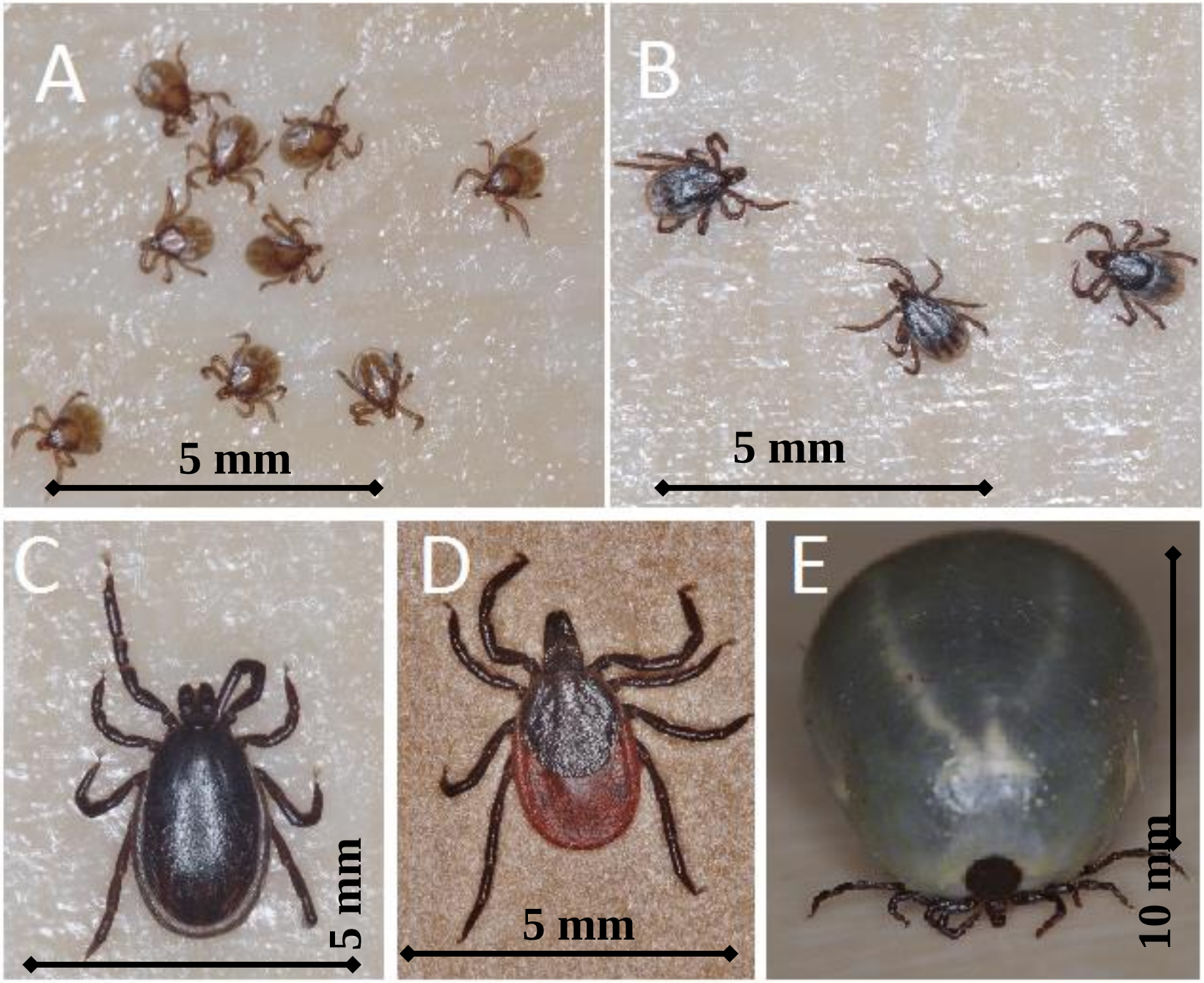
Ixodes persulcatus – Far East, Siberia

Rodents, small mammals

In Europe: 0.1 – 3% ticks infected

risk of infection after a tick bite 1:25 – 1:1,000

Danielová, V. Nova Science Publisher, New York. 2006; pp. 59 – 103. Bormane, A.Int. J. Med. Microbiol. 2004;293 Suppl 37:36-47. Süss, J. Vaccine 2003;21 Suppl 1:S19-35.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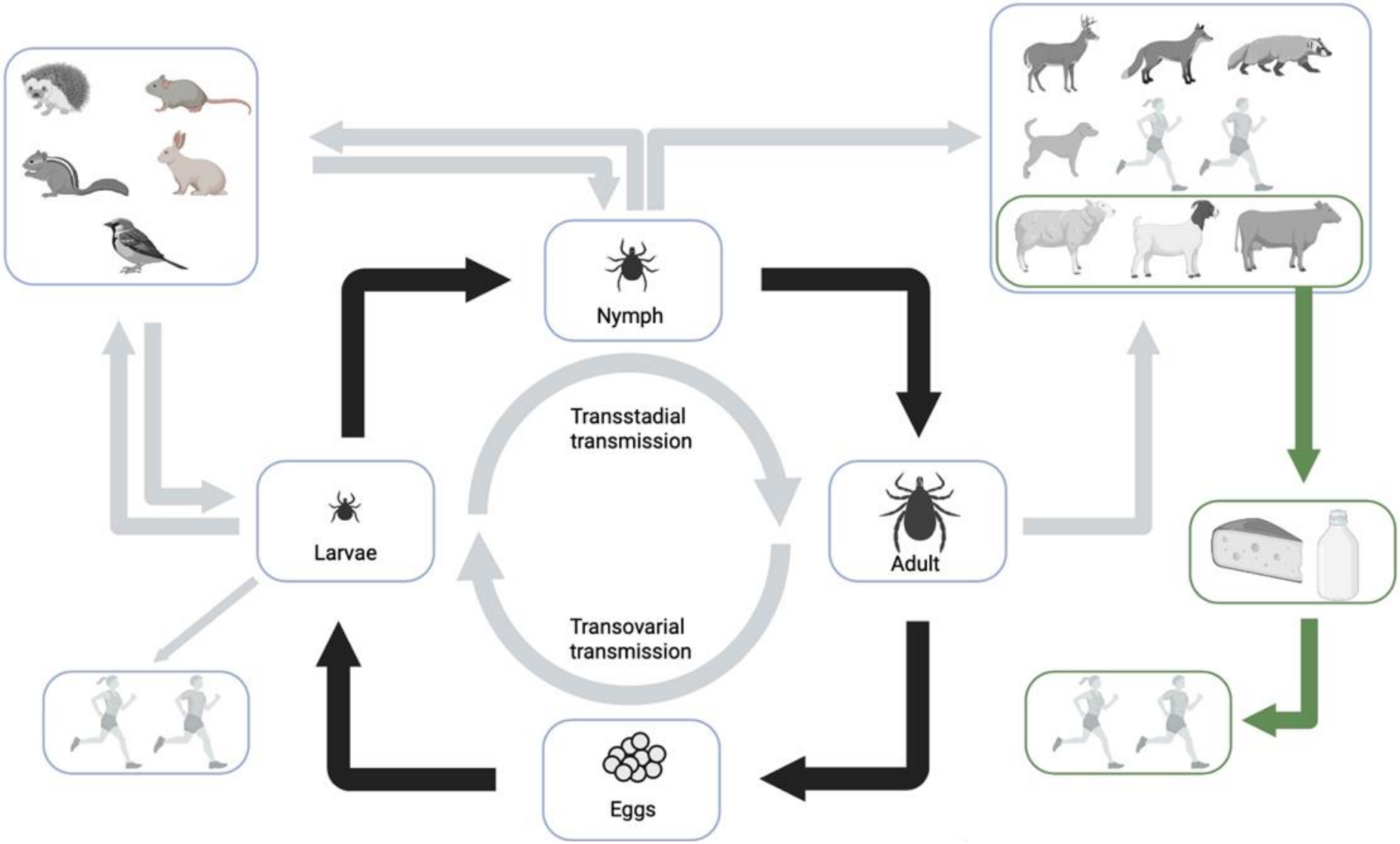
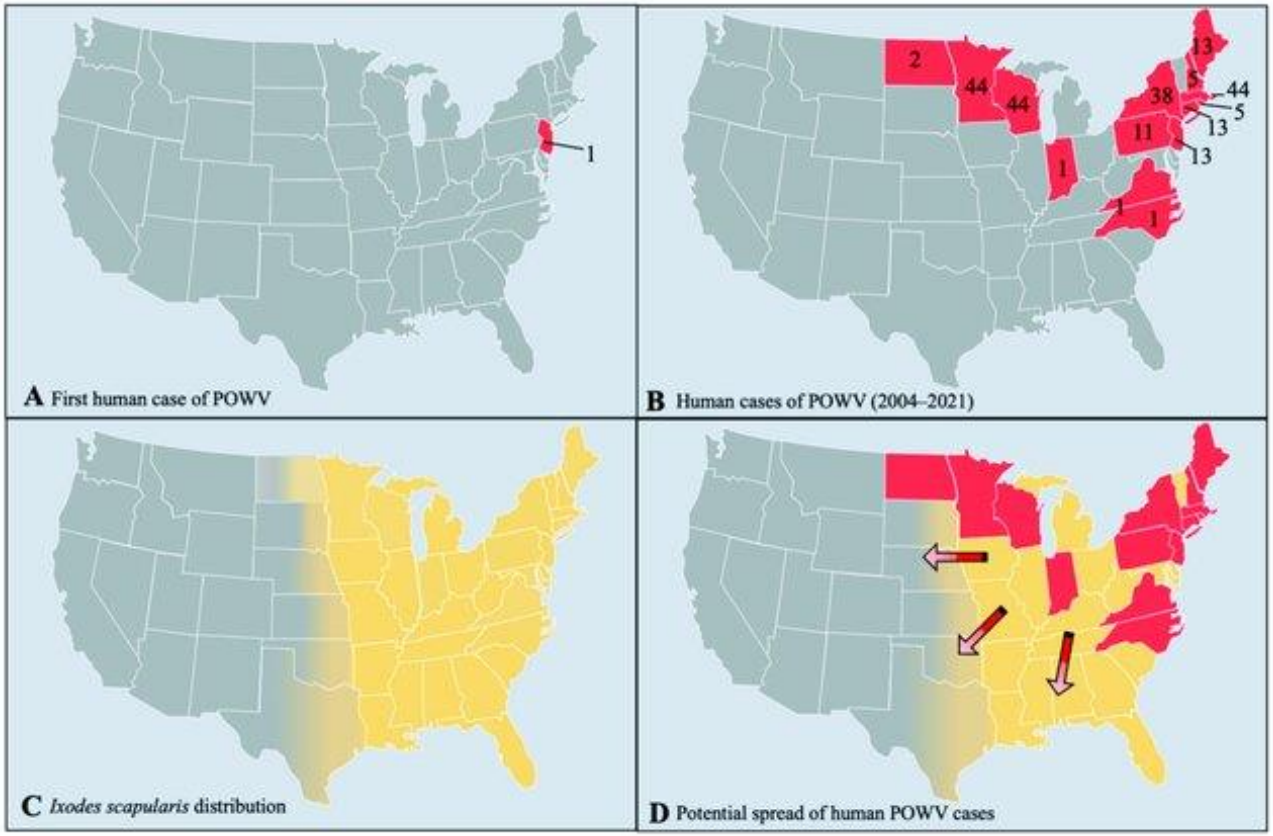


Chiffi G, Grandgirard D, Leib SL, Chrdle A, Růžek D. Tick-borne encephalitis: A comprehensive review of the epidemiology, virology, and clinical picture. *Rev Med Virol*. 2023;33(5):e2470. doi:10.1002/rmv.2470

Know your maps

- Powasan virus, 160 human cases, 10% fatal



Hassett EM, Thangamani S. Ecology of Powassan Virus in the United States. *Microorganisms*. 2021; 9(11):2317. https://doi.org/10.3390/microorganisms9112317

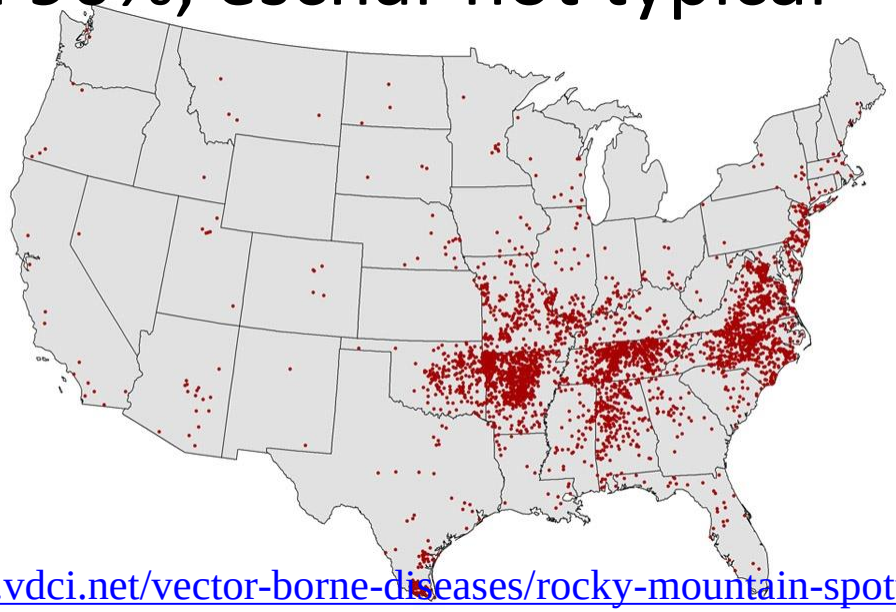
Know your maps

Rocky mountains spotted fever, *R. rickettsii*

2000 cases/yr, mortality 20-80% before doxy era

Rx within 5 days

rash 90%, eschar not typical

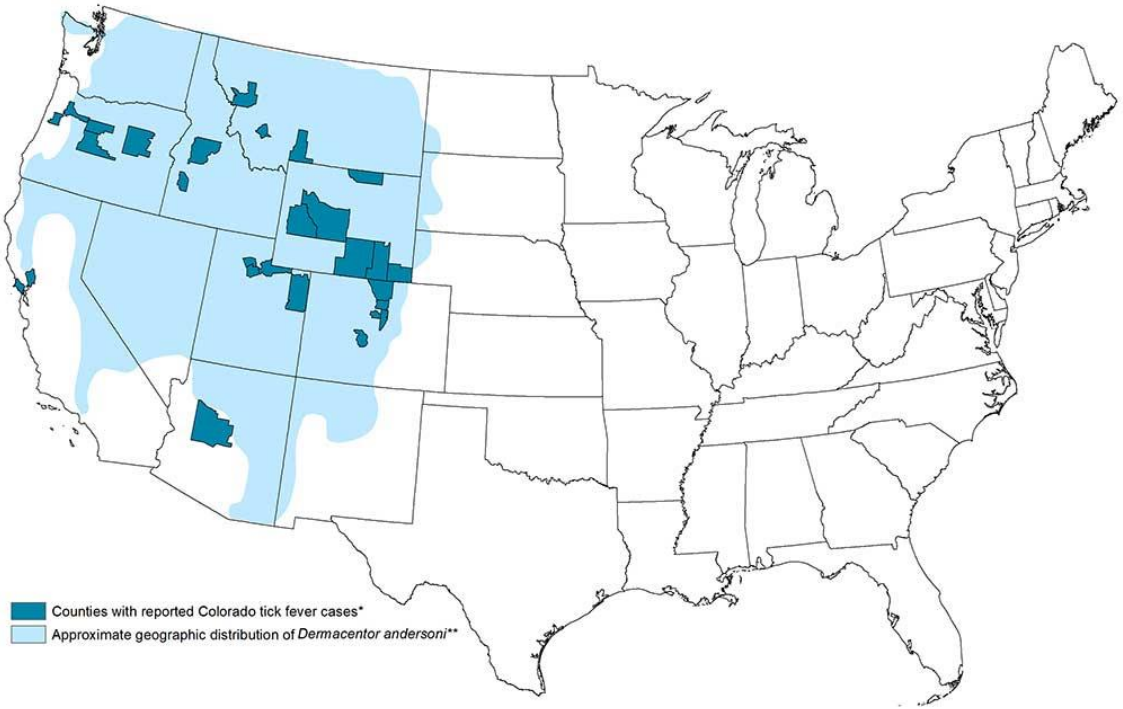


https://www.vdci.net/vector-borne-diseases/rocky-mountain-spotted-fever-education-and-tick-management-to-protect-public-health/

https://www.cdc.gov/ticks/tickbornediseases/rmsf.html

Know your maps

Colorado tick fever -~50% of patients biphasic illness, prolonged convalescence



Yendell SJ, Fischer M, Staples JE. Colorado tick fever in the United States, 2002-2012. *Vector Borne Zoonotic Dis* 2015;15:311–316.
https://www.cdc.gov/coloradotickfever/statistics.html

Encephalitis/encepalopathy

Tickborne Relapsing Fever (TBRF)

Borrelia hermsii, B. turicatae

Hard Tick Relapsing Fever

Borrelia miyamotoi

Anaplasmosis (Human Granulocytic Ehrlichiosis)

Anaplasma phagocytophilum

Ehrlichiosis

Ehrlichia chaffeensis, Ehrlichia ewingii, Ehrlichia muris eauclairensis

Lyme Disease and Other Nonsyphilitic Spirochetal Infections. In: Jameson J, Fauci AS, Kasper DL, Hauser SL, Longo DL, Loscalzo J. eds. Harrison's Manual of Medicine, 20e. McGraw Hill; 2020.

https://www.cdc.gov/ticks/tickbornediseases

Doxycycline responsive disease

Tickborne Relapsing Fever (TBRF)

Borrelia hermsii, B. turicatae

Hard Tick Relapsing Fever

CONFIRMATION OF THE DIAGNOSIS IS BASED ON LABORATORY TESTING, BUT ANTIBIOTIC THERAPY SHOULD NOT BE DELAYED IN A PATIENT WITH A SUGGESTIVE CLINICAL PRESENTATION.

Anaplasma phagocytophilum

Ehrlichiosis

Ehrlichia chaffeensis, Ehrlichia ewingii, Ehrlichia muris eauclairensis

Lyme Disease and Other Nonsyphilitic Spirochetal Infections. In: Jameson J, Fauci AS, Kasper DL, Hauser SL, Longo DL, Loscalzo J. eds. Harrison's Manual of Medicine, 20e. McGraw Hill; 2020.

https://www.cdc.gov/ticks/tickbornediseases

Other tick-borne encephalopaties

Crimean-Congo hemorrhagic fever *CCHF virus*	Asia, Africa, and Europe. Also acquired by contact with infected blood or saliva or inhalation of infected aerosols.
Omsk hemorrhagic fever *Omsk hemorrhagic fever virus*	Southwestern Russia. May be acquired by direct contact with infected muskrats.
Kyasanur Forest disease	Southern India, Saudi Arabia (aka Alkhurma disease in Saudi). Exposure while harvesting forest products.

https://www.cdc.gov/ticks/tickbornediseases/abroad.html

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Original article

Tick-borne encephalitis virus vaccination breakthrough infections in Germany: a retrospective analysis from 2001 to 2018

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[3] Bavarian Health and Food Safety Authority, Department of Infectious Disease Epidemiology & Taskforce Infectiology/Airport, Oberschleissheim, Germany
[4] Robert Koch Institute, Department of Infectious Disease Epidemiology, Immunization Unit, Berlin, Germany
[5] Division of Infectious Diseases, Department of Medicine II, University of Freiburg Medical Centre and Faculty of Medicine, Freiburg, Germany
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ABSTRACT

Objectives: There are few data available regarding the clinical course of tick-borne encephalitis virus (TBEV) vaccination breakthrough infections. The published studies suggest that vaccination breakthrough infections may have a more severe course than native TBEV infection in unvaccinated individuals—potentially due to antibody-dependent enhancement. Here we report a large analysis of vaccination breakthrough infections.

Methods: This retrospective analysis was based on a national surveillance dataset spanning the years 2001–2018. Variables reflecting disease severity, such as 'CNS symptoms', 'myelitis', 'fatal outcome' and 'hospitalization' were analysed as well as general epidemiological variables. Cases were categorized as 'unvaccinated' or 'ever vaccinated', the latter category including cases with at least one dose of a TBEV vaccine.

Results: A total of 6073 notified TBEV infection cases were included in our analysis. Sufficient data on vaccination status were available for 95.1% of patients (5777/6073); of these, 5298 presented with a native infection. A total of (334/5777) cases developed an infection despite having been vaccinated at least once. Comparing unvaccinated patients with those with at least one vaccination, we find an odds ratio (OR) 2.73, (95% confidence interval (CI) 0.79–9.50) regarding the variable fatal outcome that did not reach statistical significance. Analysing the clinical variables 'CNS symptoms' and 'myelitis', there is no difference between these groups (OR 0.86, 95% CI 0.68–1.08; and OR 1.30, 95% CI 0.74–2.27 respectively). Patients who were vaccinated and had an assumed protection at symptom onset ($n = 100$) had a higher risk for the development of myelitic symptoms (OR 2.21, 95% CI 1.01–4.86]) than unvaccinated patients.

Conclusion: Our findings could neither verify that vaccination breakthrough infections might cause a more severe disease than native infections nor prove a clear antibody-dependent enhancement phenomenon. It remains unclear whether the increased myelitis risk in a subgroup of vaccinated patients is a true effect or confounded. **G. Dobler, Clin Microbiol Infect 2020;26:1090.e7–1090.e13**

Diagnosing TBE in vaccinated

Increase of TBEV IgM and IgG in serum (during acute stage and 2-4 weeks later)

Presence of TBEV IgM and IgG in CSF

Virus neutralization antibody testing in serum (during acute stage and 2-4 weeks later)

TBEV IgG avidity testing

Case study 1

45M, store manager, previously fit and well,

been fishing in the Czech Republic in May

Early June – sore throat, temp. 37.5, some headache and myalgia

WBC 2.8, Plt 110

CRP 20 (0-5)

ALT 80 (0-40), GTT 45 (0-40)

After 5 days back to normal

Case study 1

Mid June – spiking temps T 38-39 for a few days, severe headache, photophobia, nausea/vomiting, tremor upper limbs and eyelids

Exam: mild neck stiffness, intention tremor, poor finger-to-nose coordination/dysmetria

Recalls a tick bite end May
Not vaccinated against tick borne encephalitis (TBE)

Case study 1

Admission – WBC 10.2, Plt 250

ALT 40 (0-40), CRP 10 (0-5)

TBE serology negative IgM, IgG

Management plan?

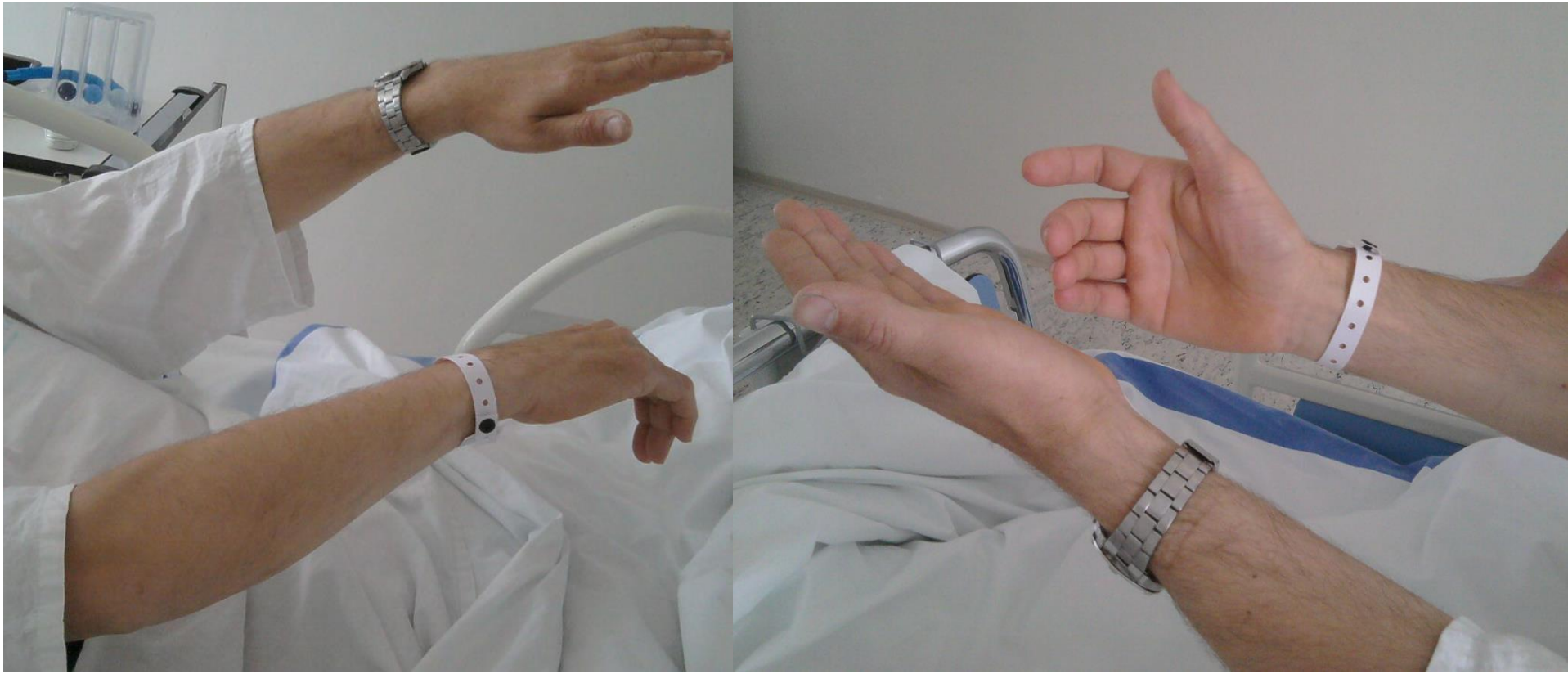
Case 1

Case 1

CT head negative

LP: protein 0.85 (0-0.45), glu 5.6, lactate 2.1

leukocytes 152 (0-3), 60% lymphocytes,

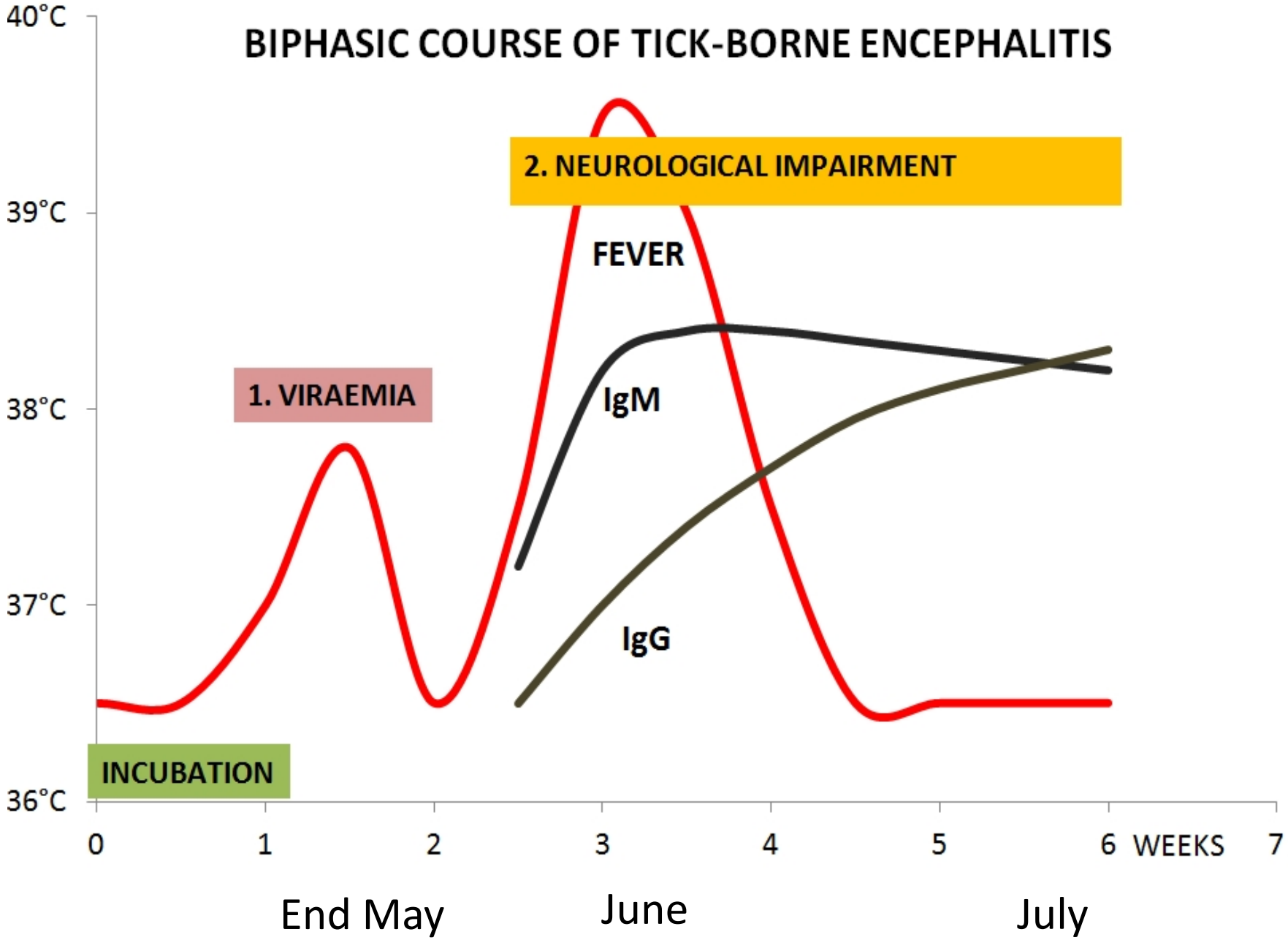


Case study 1

End June: no more fever, persisting headaches, better coordination, poor concentration

F/U serology TBE: positive IgG, positive IgM

End December: difficult to concentrate at work despite phased return, frequent headaches, sensitive to noise and light, mild tremor, erectile dysfunction



Chrdle A. In: Solomon T et al. Eds. Case Studies in Neurological Infections of Adults and Children. Cambridge University Press. 2018. ISBN: 9781107634916. DOI: 10.1017/9781139628839

Case study 1

End December: fatigue, difficult to concentrate at work, regular headaches, sensitive to noise and light, irritability, mild tremor, erectile dysfunction

1 miserable year of life

Post-encephalitic syndrome

Disease burden: DALY 3.1 years per case

2% acute illness, 5% mortality, 93% disability

Bogovič, P., Ticks and Tick-borne Diseases (2017), https://doi.org/10.1016/j.ttbdis.2017.12.001

Šmit R, Postma MJ, 2015, PlosONE 10(12):e0144988

Confirmed TBE cases in České Budějovice Hospital

C Bud ID unit (regional pop. 450k)

2016: 62

2017: 79

2018: 76

Austria (national pop. 8.7M)

2014: 81

2015: 79

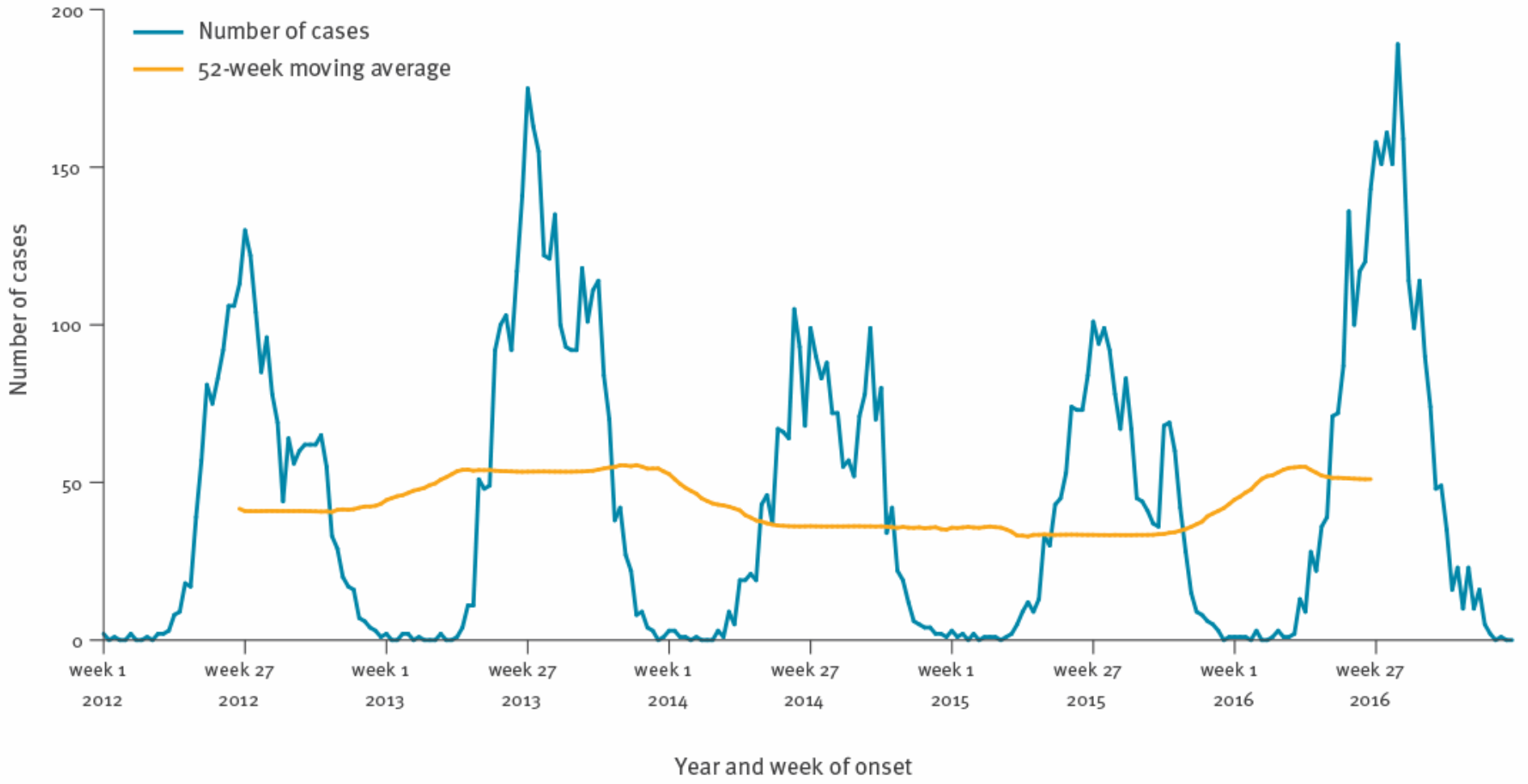
2016: 95

Europe (ECDC) notifiable disease

2500 cases/year

Total 7-10,000 cases/year

Seasonal incidence of TBE

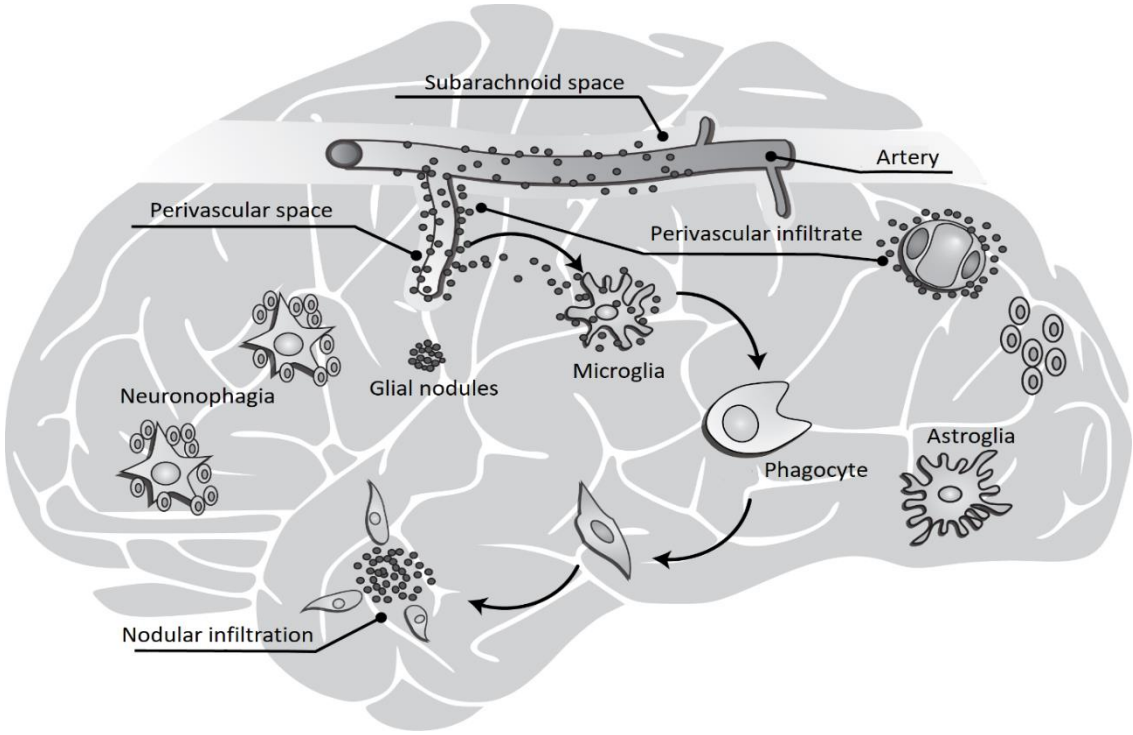


Beauté Julien. Euro Surveill. 2018;23(45):pii=1800201. https://doi.org/10.2807/1560-7917.ES.2018.23.45.1800201

Brain inflammation

Astrocytes and microglia - production of TNF-a, IFN-a, IL-1b, IL-6, IL-8, IL-12, IFN-g, IP-10

Neuronophagia
Endothelial activation
Perivascular infiltrates
Activated microglia
Histiocyte nodules
Cytotoxic T cell infiltration



Breakdown of blood brain barrier due to inflammation

Růžek D, Antiviral Research 164 (2019) 23–51

Case 2

66 years old farmer

Presented in September 2017

3 days fever, headache

1 day slightly confused and generally weak

HDU – weakness of upper limbs and slurred speech

Next day unable to cough and swallow

Case 2

66 years old farmer

Day 2 of admission intubated, ventilated, early tracheostomy, off sedation

Weaning of ventilator in 8 days

Unable to swallow, poor coughing

Left diaphragm palsy

Proximal biplegia of upper limbs

Weakness of lower limbs

Case 2

66 years old farmer

October – March 2018 – intensive care tracheostomy, parenteral nutrition, PEG feed

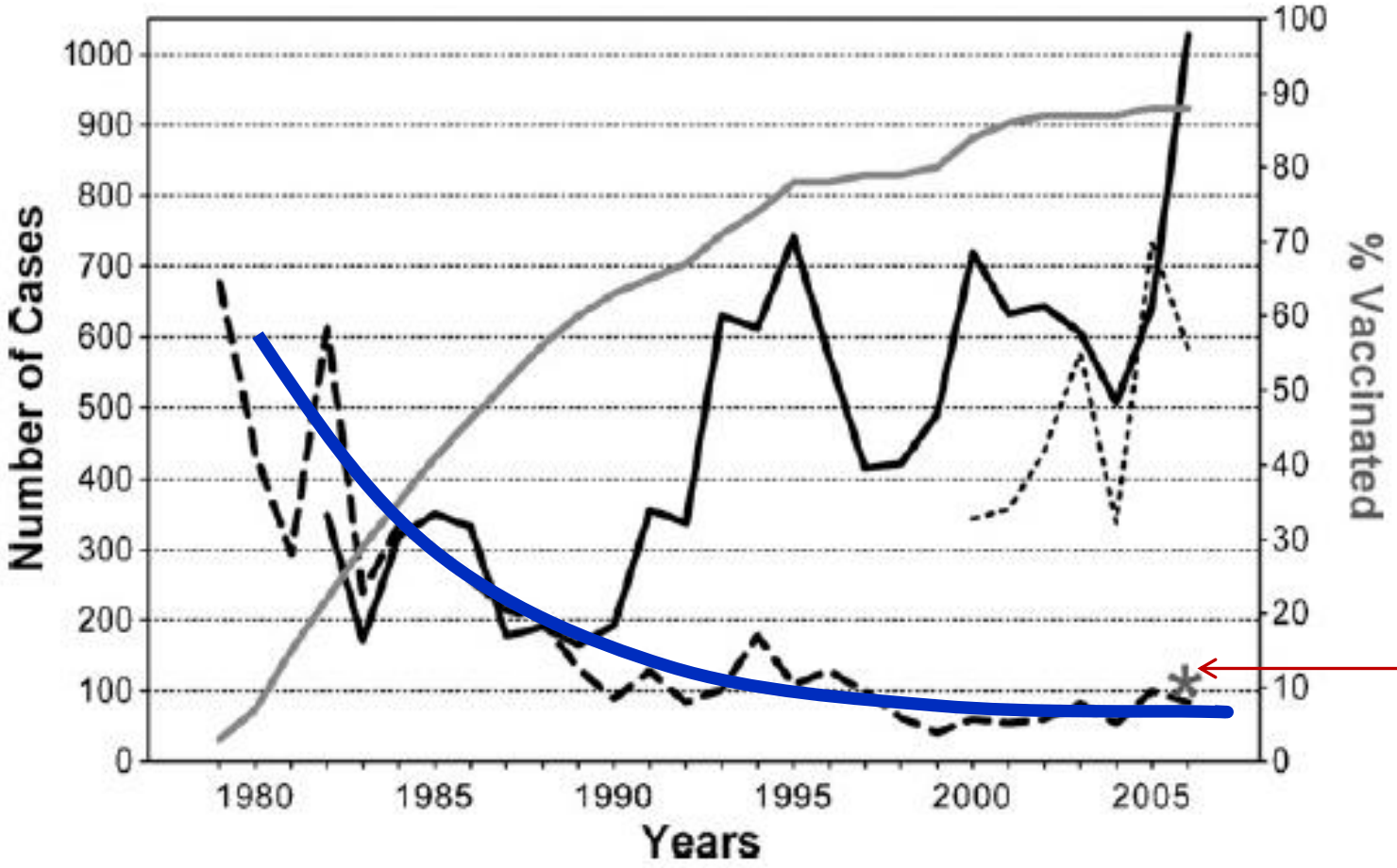
Repeat chest infections – bronchoscopic lavage of the left bronchi

General wasting

Fully alert throughout

Died of progressive respiratory failure 6 months after admission

Vaccination



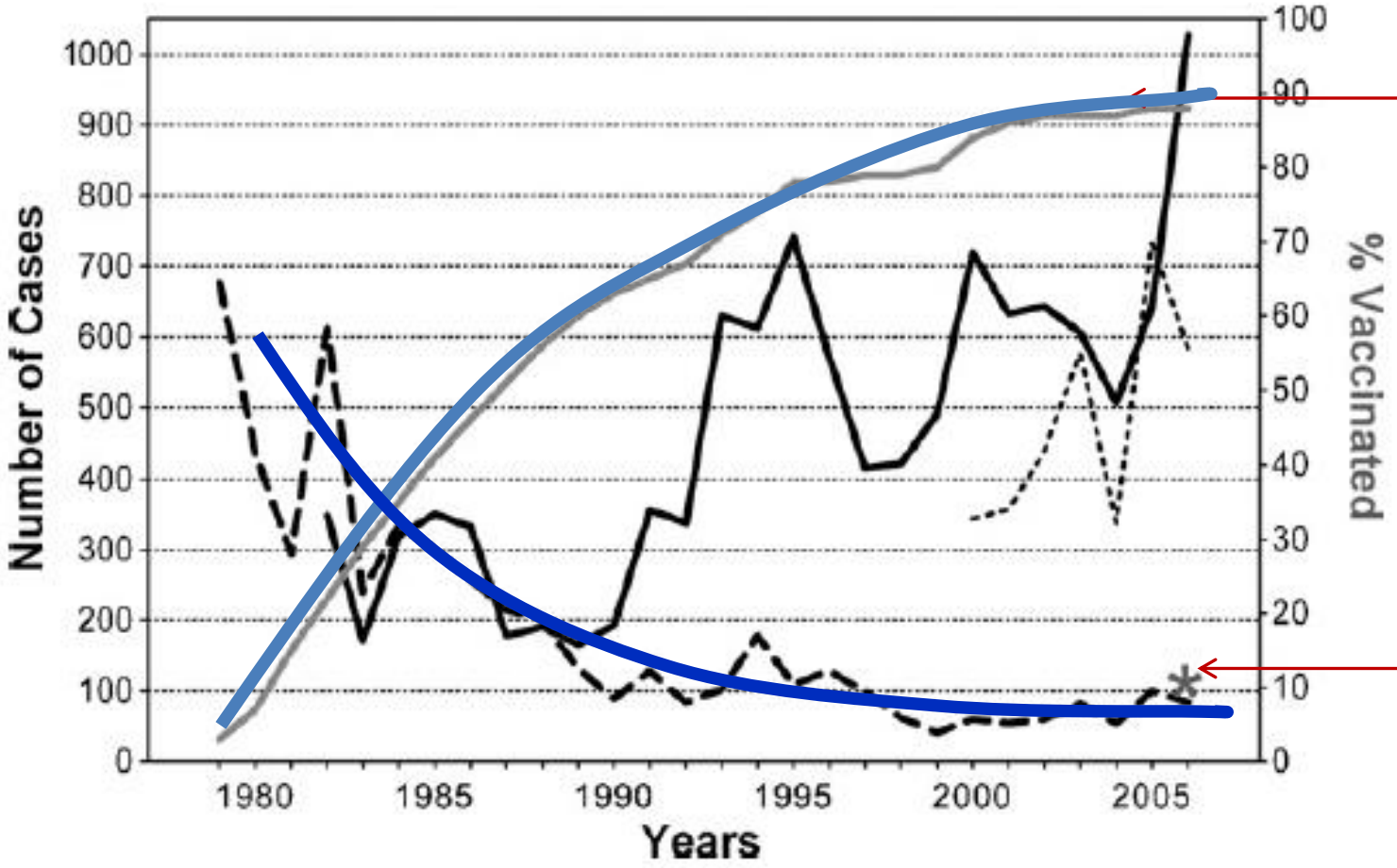
Vaccination uptake in Austria (1 shot, complete course 53%)

TBE incidence rate in CZ (where vaccination cover <15%)

TBE incidence rate in Austria

Heinz FX, Field effectiveness of vaccination against tick-borne encephalitis Vaccine. 2007 Oct 23;25(43):7559-67

Vaccination



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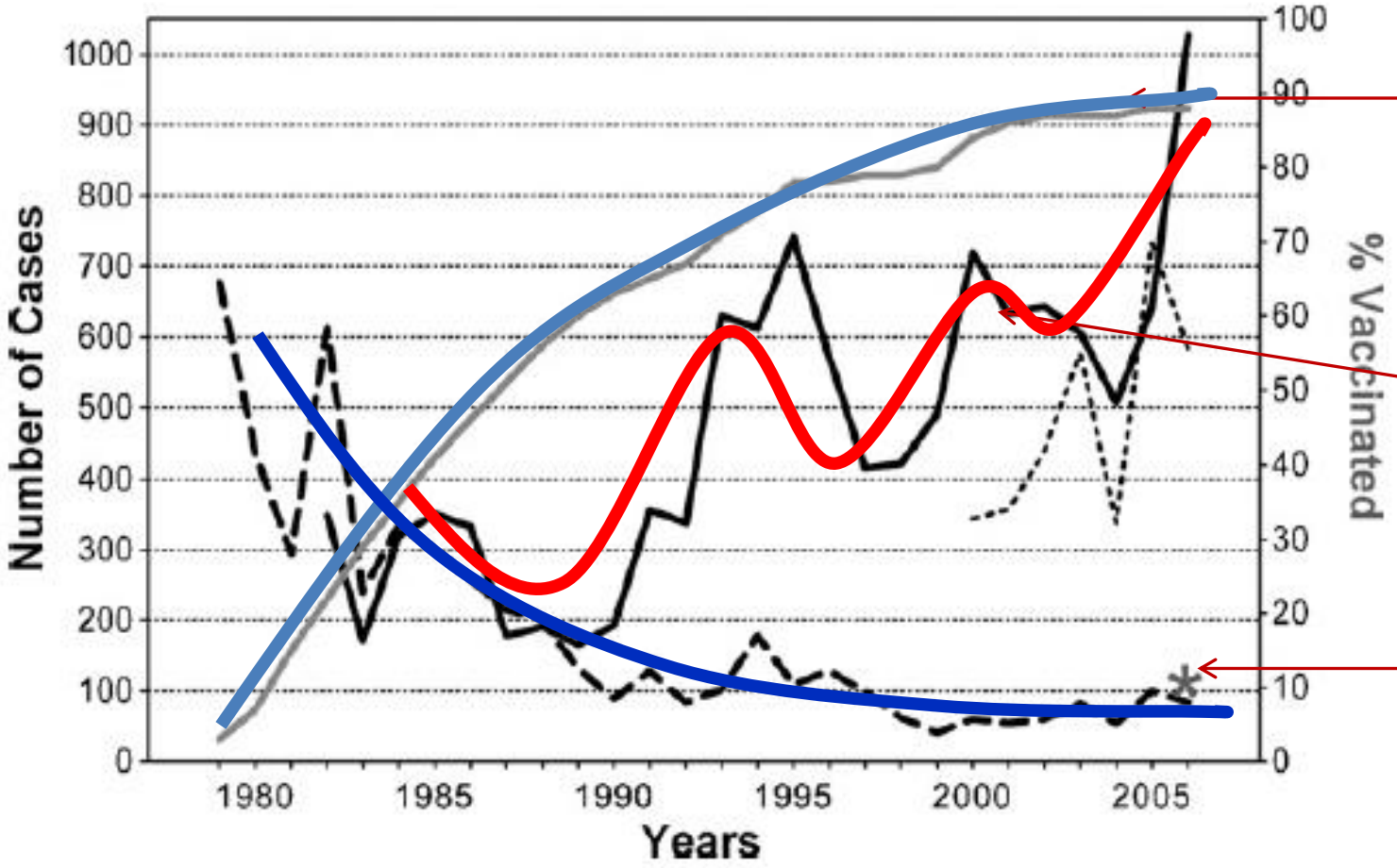

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Heinz FX, Field effectiveness of vaccination against tick-borne encephalitis Vaccine. 2007 Oct 23;25(43):7559-67

Vaccine

Highly purified inactivated whole virus vaccines (Germany, Austria, Russia x2), paediatric version

Scheme month 0/1/12, boosters every 3-5 yrs
Accelerated scheme day 0/14/150 or 0/7/21 d

Effective protection (>90%) 1 week after 2nd dose
Efficacy after three doses 99%
Antibodies protective up to 10 years in >90%

Ilaria Galgani, (2017) Expert Review of Vaccines, 16:9, 919-932, DOI: 10.1080/14760584.2017.1358620
Beran J et al. Vaccine. 2018 Feb 1. pii: S0264-410X(18)30022-7. doi: 10.1016/j.vaccine.2017.12.081.

Risk assessment

Factors of the environment

Region, country and region

Season (high risk from April to November);

Lower altitude (<1500 m above the sea level)

Factors of the individual

Outdoor aktivity - extent

Duration of stay

Higher age/comorbidities

Chrdle A. *Hum Vaccin Immunother*. 2016;12(10):2694-2699.

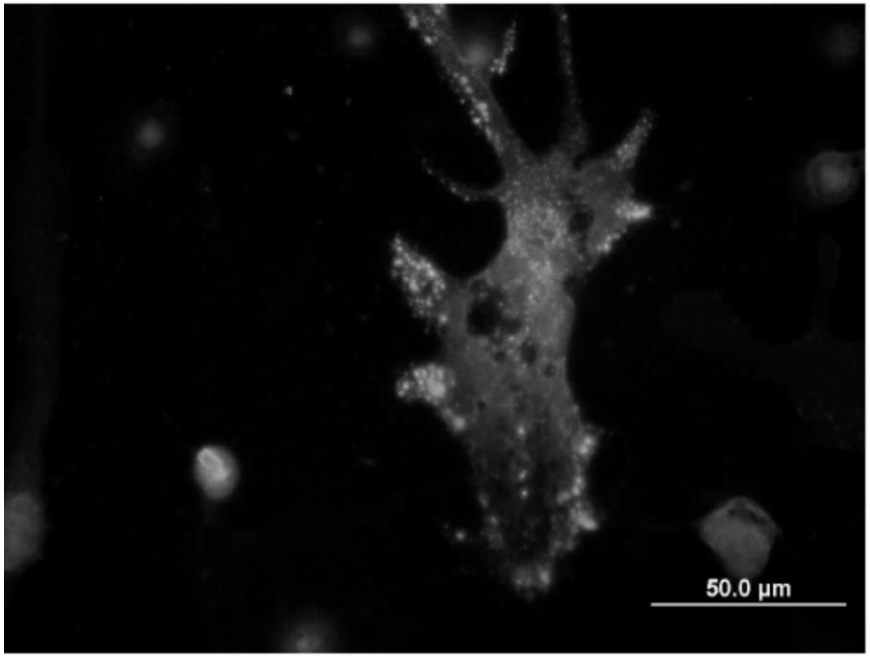
What we would like to know in diagnostics?

Urinary PCR in the viraemic/neurological phase

Functional MRI

Cytokine assay to predict possible disability

Host genomics to predict disease severity



Human neuron infected with TBEV, indirect immunofluorescence, D. Růžek, Tick Borne Encephalitis, Grada Publishing, Prague, 2015

Veje, M., et al. Detection of tick-borne encephalitis virus RNA in urine. J Clin Microbiol. 2014;52(11):4111-2

What we know in therapy?

Treatment and prophylaxis

No specific treatment for tick-borne encephalitis exists.

Studahl et al. Drugs. 2013,

There is no curative therapy for TBE, so supportive

Lindquist, Lancet 2008

7.3 Therapy and Prophylaxis

The treatment for TBE is currently symptomatic since no

Mansfield et al. Journal of General Virology 2009

What we would like to know in therapy?

In Austria/Germany/Baltic states: no corticosteroids

Mickiene, A. Clin. Inf. Dis. 2002;35:650-8

Czech practice: selected cases with refractory headache/hyperpyrexia, paresis, somnolence, or other signs of raised intracranial pressure

Ethical dilemma about RCT

In supportive Rx despite diagnosis: corticosteroids have antiedematous, antiemetic, and antipyretic effect. Effective in refractory hiccups.

Duniewicz, M. et al. Corticoids in the Therapy of TBE and Other Viral Encephalitides. Cas Lek Cesk 1974;9,113(32):984-7.

What we would like to know in F/U post discharge?

Bedrest vs. Early neurorehabilitation

Cognitive training
Goal setting
Coping strategies
Patient support groups
EEG – Biofeedback

Mild learing disability - in children

Steffen R. Ticks and Tick-borne Diseases, Volume 10, 1, January 2019, Pages 100-110
Krbkova L. 2015. Eur. J. Pediatr. 174 (4), 449–458.

What is the risk for short-stay travellers?

Imported cases:
the Netherlands, UK (5 notified cases since 2010),
Canada, USA, Australia, Israel

Estim. ~60 TBE cases/year exported from Austria

Risk similar to typhoid or *P. vivax* malaria in travellers to India (1:3,000-1:25,000 travellers)

Kunze, U. Is there a need for a travel vaccination against tick-borne encephalitis? Travel Med. Infect. Dis. 2008;6(6):380-383.
Rendi-Wagner P. Risk and Prevention of Tick-borne Encephalitis in Travelers. J Travel Med 2004; **11**:307–312

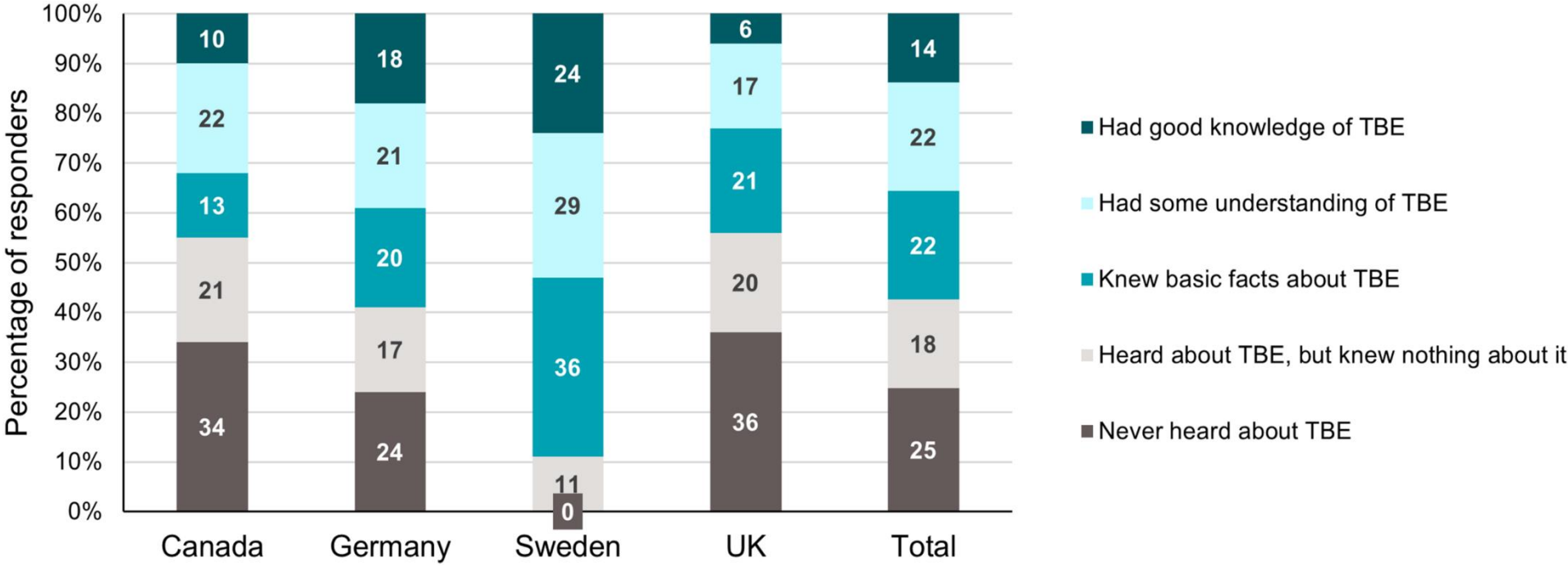
What is the risk for short-stay travellers?

2006–2014, 4 TBE cases among Israeli travelers. calculated TBE incidence at 321.0, 45.0, 13.2, and 7.5 cases/100,000 travelers/year of travel to Sweden, Switzerland, Austria, and Germany

Risk of JE 1.2 cases/100,000 travelers/year of travel, only 1 case of JE over 20 years in Israel
In 2012–2014, 46,773 JE vs. 960 TBE vaccine doses

Meltzer E, Paran Y, Lustig Y, Stienlauf S, Weinberger M, Schwartz E. Travel-Related Tick-Borne Encephalitis, Israel, 2006-2014. *Emerg Infect Dis*. 2017;23(1):119-121.

Perceptions of TBE among UK travellers



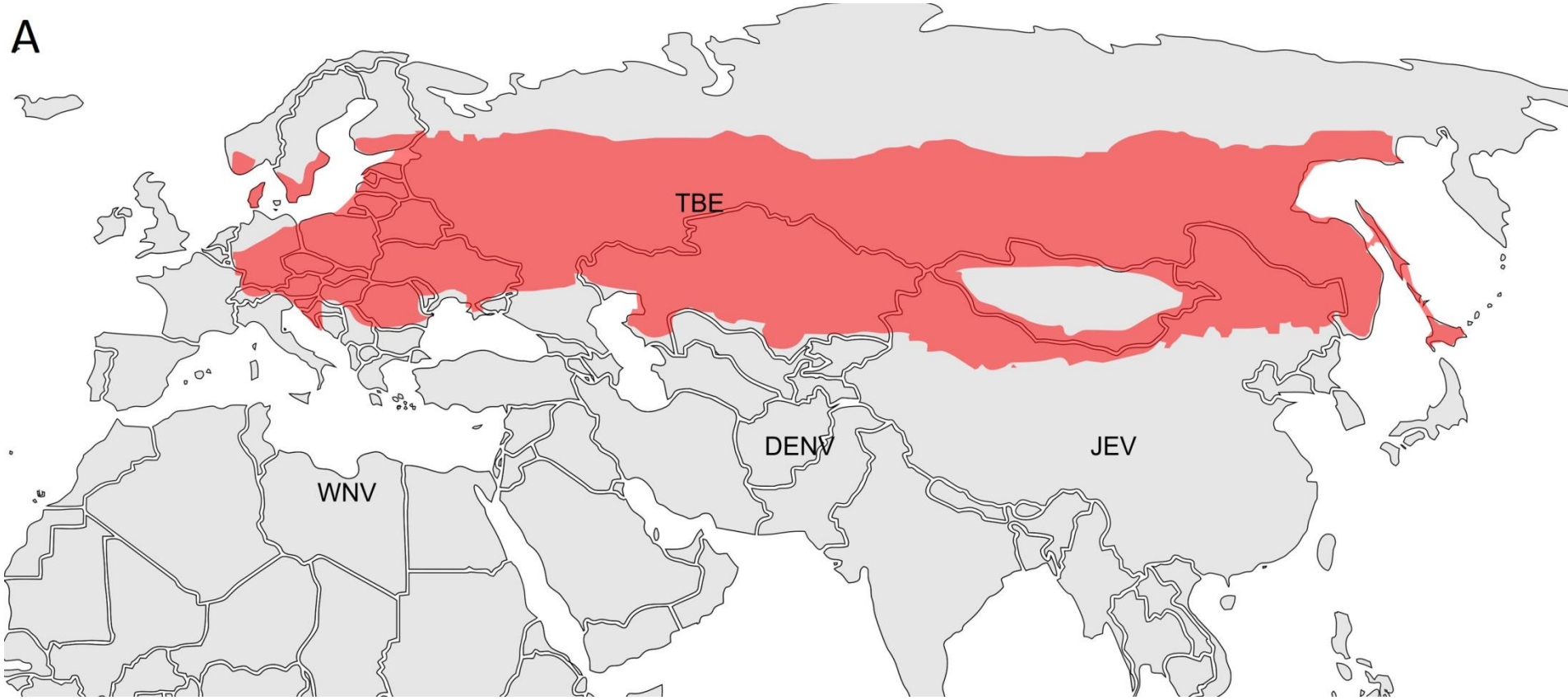
Marano C et al. Perceptions of tick-borne encephalitis risk: a survey of travellers and travel clinics from Canada, Germany, Sweden and the UK. J Travel Med. 2018 Nov 22. doi: 10.1093/jtm/tay063. [Epub ahead of print]

Perceptions of TBE among UK travellers

Measure	% of respondents: Aware of the measure	Taking the measure
Correct		
Wearing long trousers	66	49
Avoiding long grass/sticking to cleared paths	62	Not answered
Tucking trousers into socks	53	28
Being vaccinated against TBE	42	23
Using insect repellent	40	38
Avoiding contact with livestock	27	31
Travelling to risk areas in periods of lower risk	26	24

Marano C et al. Perceptions of tick-borne encephalitis risk: a survey of travellers and travel clinics from Canada, Germany, Sweden and the UK. J Travel Med. 2018 Nov 22. doi: 10.1093/jtm/tay063. [Epub ahead of print]

Tick borne encephalitis



Spreading to new regions and higher altitudes
(France, Germany, Switzerland, Italy, the Netherlands)

Vaccination of the immunosupressed?

Sweden
66 patients rheumatoid arthritis (TNFi and/or MTX)
56 matched healthy controls.
Median age was 58.5 years.

Seroprotective levels
after the last TBE-vaccine dose (one year after the first)
39% of the patients
79% of the healthy controls

Hertzell KB. Vaccine. 2016 Jan 27;34(5):650-655. doi: 10.1016/j.vaccine.2015.12.029. Epub 2015 Dec 22.