

# Epidemiology of TBE

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### Key points

- TBE is a flavivirus infection of the central nervous system (CNS), transmitted by ticks and in some rare instances by ingestion of unpasteurized milk
- It is diagnosed in the Boreal and Temperate Forest Belt of Eurasia ranging from the UK, eastern France, The Netherlands and Norway down to Italy through central and Eastern Europe, Russia, Kazakhstan, and China to Japan.
- About 10,000 cases of TBE are reported annually, likely a significant underestimate as serological testing is more sporadic than complete and, in some countries, (like Japan) not even available.
- The European Centre for Disease Prevention and Control (ECDC) have put TBE on their list of notifiable diseases. Their case definition requires clinical symptoms of CNS infection plus virological or serological confirmation of the infection, usually by detection of specific immunoglobulins IgG and IgM.
- Vaccination against TBE is on the World Health Organization's List of Essential Medicines, the safest and most effective medicines needed in a health system.
- Surveillance of TBE and the TBEV is incomplete. Reported incidences do not reflect actual risk since this fluctuates annually as a result of changes in exposure, vaccine uptake, intensity of case finding and reporting, climate factors, reservoir animals and ticks - just to mention the most relevant factors.
- For largely unknown reasons (including human behavior, improved diagnostics, or climate change) TBEV appears to be spreading north (e.g. northern Scandinavia), west (e.g. United Kingdom, even south (e.g. Tunisia) and to higher altitudes (e.g. in the Alps) to areas that were previously believed to be free of the virus.
- The vectors for TBE virus are ticks like *Ixodes ricinus* and *Ixodes persulcatus*. Reservoir animals for TBE virus are mainly small rodents.

### Burden of disease and case definition

#### 1. Burden of disease and case definition

Since the first description of the clinical symptoms of TBE and the detection of TBEV in Far Eastern Russia nearly a century ago<sup>1</sup>, TBE has become the most important tick-borne viral disease across Eurasia. To date, tick-borne encephalitis virus (TBEV) foci have been identified in Europe, Russia, through to northern and eastern Asia up to Japan. Up to 12,000 human tick-borne encephalitis (TBE) cases are registered annually from countries where the disease is reportable. However, this number likely represents an underestimate due to under-diagnosis and/or underreporting. Case fatality rates between 0.2% to 20% are reported, depending on region and perhaps on viral subtype<sup>2</sup>. Severe long-term sequelae of TBE are well described both in children and in adults (see Chapters 8 and 9).

#### 1.1 TBE case definition

Because TBEV is present in reservoir animals in nature, eliminating or eradicating the disease is impossible. Thus TBE is an important concern for the potentially exposed individual who becomes infected, but it is also of public health relevance, as acknowledged by the World Health Organization (WHO) in all position reports from 1983 to date (2011)<sup>3-5</sup>. Moreover, TBE vaccination against TBE is on the World Health Organization's List of Essential Medicines, the safest and most effective medicines needed in a healthcare system<sup>6</sup>. In addition, in 2012 the European Center for Disease Prevention and Control (ECDC) decided to add TBE to the list of mandatory notifiable diseases and provided for the first time ever a uniform disease case definition<sup>7</sup> (Table 1).

As ECDC case definition and reporting have not been universally implemented around the globe or even throughout Europe, data on the burden of disease from

**Table 1: TBE case definition by the ECDC4 “NA”= Not applicable****TICK-BORNE ENCEPHALITIS****1. Clinical criteria**

Any person with symptoms of inflammation of the CNS (e.g. meningitis, meningoencephalitis, encephalomyelitis, encephaloradiculitis)

**2. Laboratory criteria****Laboratory criteria for case confirmation:\***

At least one of the following five:

- TBE specific IgM AND IgG antibodies in blood
- TBE specific IgM antibodies in CSF
- Sero-conversion or four-fold increase of TBE-specific antibodies in paired serum samples
- Detection of TBE viral nucleic acid in a clinical specimen,
- Isolation of TBE virus from clinical specimen

**Laboratory criteria for a probable case:**

- Detection of TBE-specific IgM-antibodies in a unique serum sample

**3. Epidemiological criteria**

Exposure to a common source (unpasteurized daily products)

**Case classification****A. Possible case NA****B. Probable case**

Any person meeting the clinical criteria and the laboratory criteria for a probable case

OR

Any person meeting the clinical criteria and with an epidemiological link

**C. Confirmed case**

Any person meeting the clinical and laboratory criteria for case confirmation

*\*Serological results should be interpreted according to the vaccination status and previous exposure to other flaviviral infections. Confirmed cases in such situations should be validated by serum neutralization assay or other equivalent assays.*

different countries are difficult to compare. Even if clear case definitions are provided and routinely implemented by local authorities, differences between countries exist regarding the classification of clinical diseases associated with TBEV infections. For example, Austria reports only “serologically proven hospitalized cases,” whereas the Czech Republic reports any case with “clinical and laboratory signs of aseptic meningitis / meningo-encephalitis, not necessarily associated with hospitalization and Germany reports all diagnosed (serology, virus detection) human infections, irrespective of their clinical manifestation.”<sup>8</sup>

In addition to the use of different case definitions and case classifications, there is a lack of implementation of routine diagnostics in any patients with CNS infection. This is exemplified by the Polish experience: between 2004 and 2008, only 39% of the country’s hospitals had access to TBEV-serology. Therefore, a pilot project of enhanced surveillance for TBE was implemented in 2009. Routinely testing for TBE in patients with signs of meningitis or encephalitis in the entire country doubled case numbers in 2009 compared to previous years, moreover, and additional 38 endemic districts were identified. Seven of the „new“ endemic districts were located far away from previously known endemic foci, most notably in the northwest of the country<sup>9</sup>.

Finally, vaccine uptake substantially modifies the number of cases in a TBE risk area, as exemplified again by Austria,

where in the last decade fewer than 100 cases are reported annually while this number, however, had been up to 700 cases annually before the introduction of a vaccination program. The 7-fold difference is easily explained by the about 84% vaccine uptake in Austria. Neighboring countries with lower vaccine uptake continue to have increasing TBE case numbers<sup>10</sup>.

It should be noted, that there are many “fever only” TBE virus infections without ZNS symptoms not being captured by the ECDC definition<sup>11</sup>.

## 1.2. Burden of disease. Incidence and trends

A characteristic feature of TBE is that the incidence of the disease in risk areas can vary significantly from year to year. However, in addition to short-term fluctuations, there are also longer-range undulations of incidence rates recognizable in many countries. (TBE cases by country and year see [table 2](#)).

In Estonia for example, a country with one of the highest overall TBE incidences in Europe case numbers in the years 2005 - 2017 fluctuated between 6.2 and 18.6 with a mean incidence between 5.2 and 52.8 (see Chapter 12b, Estonia).

These longer-range undulations are well recognized and in synchrony in a time interval of 12-15 years in countries like Germany, Czech Republic, Slovakia, Switzerland, Austria

(see [figure 1a](#)), and similarly in Poland and Slovenia. The long-term trend, however, shows an increase in Germany, Austria, Slovakia, Switzerland and Poland, a constant trend the last 22 years in the Czech Republic and decreasing in Slovenia.

Countries like Lithuania, Estonia, Latvia show a similar long-range undulation of about 12-15 years, time-wise incongruous to the central European countries. Trends in case numbers however are constant over time (Lithuania, Latvia) or even decreasing long term (Estonia) (see [figure 1b](#)).

Disease numbers in Sweden, Finland, Norway and even Italy have shown a substantial and continuous increase in the last couple of years (see [figure 1c](#)). In Sweden there is an increase reported from approximately 1.9/100,000 inhabitants in 2010 to 5.1/100,000 inhabitants in 2021<sup>12</sup>. However, those countries do not have the same long-range awareness and screening as the countries mentioned above. So this observed increase may at least in part be explained by an increasing awareness and surveillance in the respective country. (e.g. Sweden<sup>13</sup>)

But also new countries, until recently regarded TBE-virus free, have been identified in the last decade as areas where TBEV circulates.

Since 2016, the Netherlands<sup>14,15</sup>, Belgium<sup>16</sup> and the United Kingdom<sup>17,18</sup> have reported autochthonous human cases. Recently, TBEV has even been detected in ticks collected in North Africa, in Tunisia (see country chapter). These findings illustrate that increased awareness and forced investigations to detect TBEV can lead to identification of new TBEV endemic areas and “artificially” increase cases numbers.

In recent years, new TBE foci have been reported from altitudes up to 2100 meters above sea level<sup>19-22</sup>. New endemic zones in previously unaffected alpine regions in western Austria<sup>23</sup> and in Switzerland were established, and a first report of TBEV being detected at locations in Norway up to more than 65°N latitude was published 2018<sup>24</sup>.

Various factors may explain all these findings, at least in part: social factors (socio-political changes with changes in human behavior, duration, and type of leisure-time activities), ecological factors (e.g., effects of climate changes on the tick population and change in availability of tick host species, new flight routes of migrating birds which may lead to importation of TBE virus infected ticks into areas which have so far been free of TBE virus), and/or technological factors (advanced diagnostics, increased medical awareness).

There is increasing research interest in habitat suitability modeling to define universal environmental characteristics of TBEV foci, to predict suitable conditions where potentially human TBEV infections may occur<sup>25-27</sup>.

Certainly, reporting of TBE cases has improved substantially over the years, and TBE is now a notifiable disease in the EU. In the end, all factors mentioned above play an “interactive role” resulting in complex interactions that may explain the observed changes in TBE epidemiology. But still, TBE surveillance in Europe is in many countries more sporadic than systematic, and TBE cases are likely underreported<sup>2,28</sup>.

## 2. TBE risk areas

### 2.1. Risk area definition

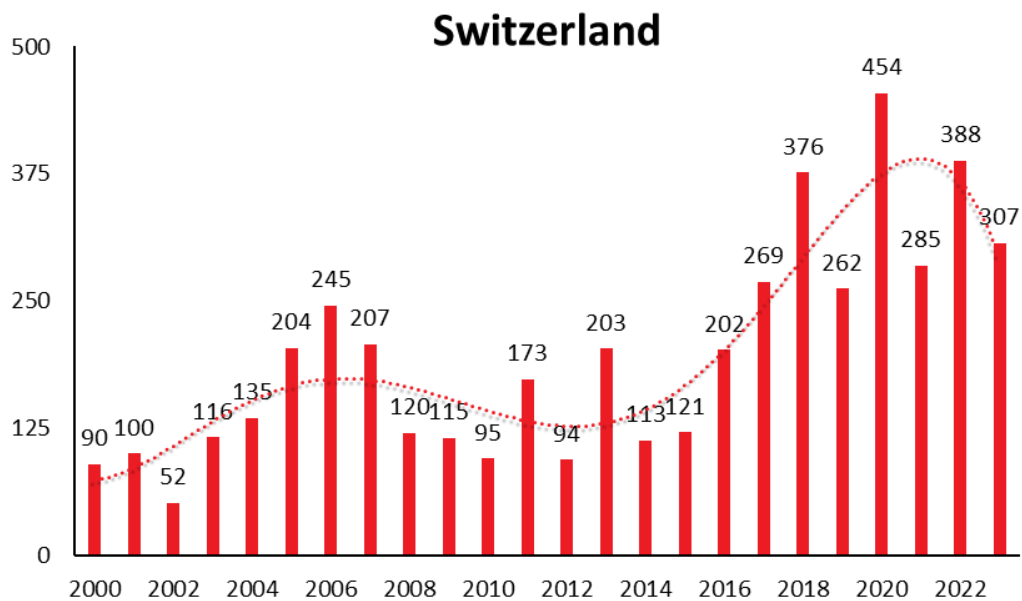
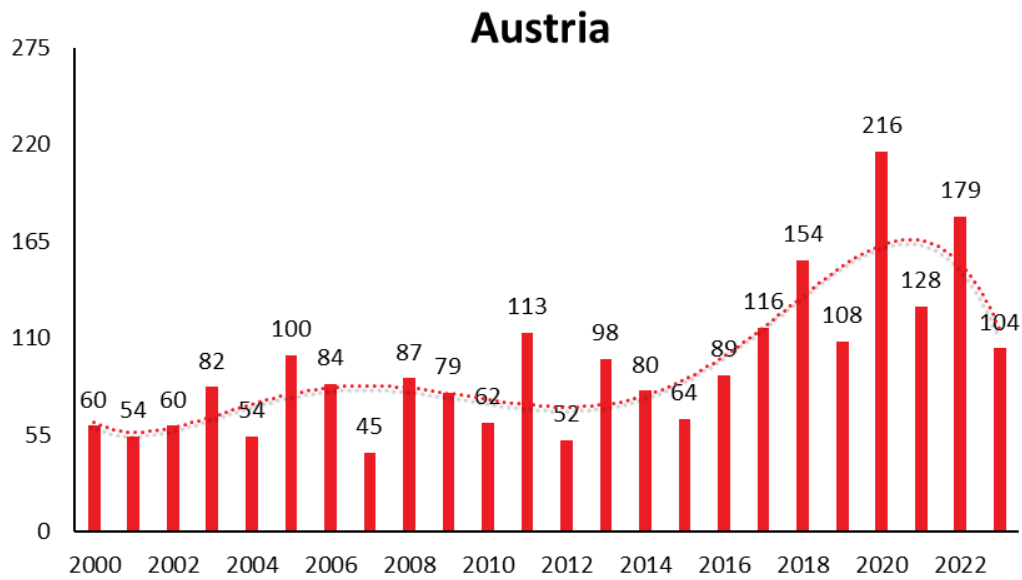
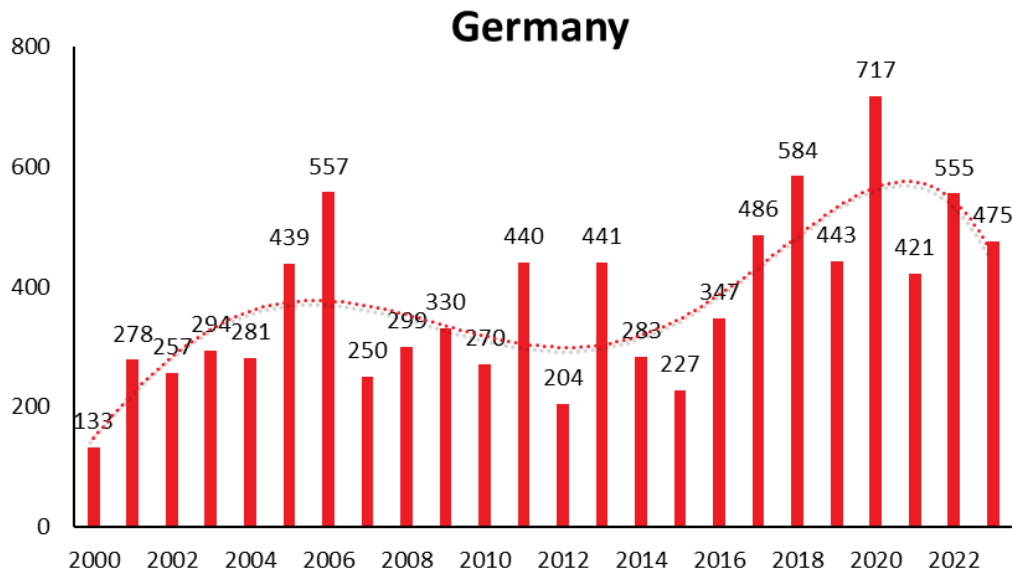
The TBE virus is restricted to specific endemic regions, and various procedures can be used to assess if and where TBE virus is circulating.

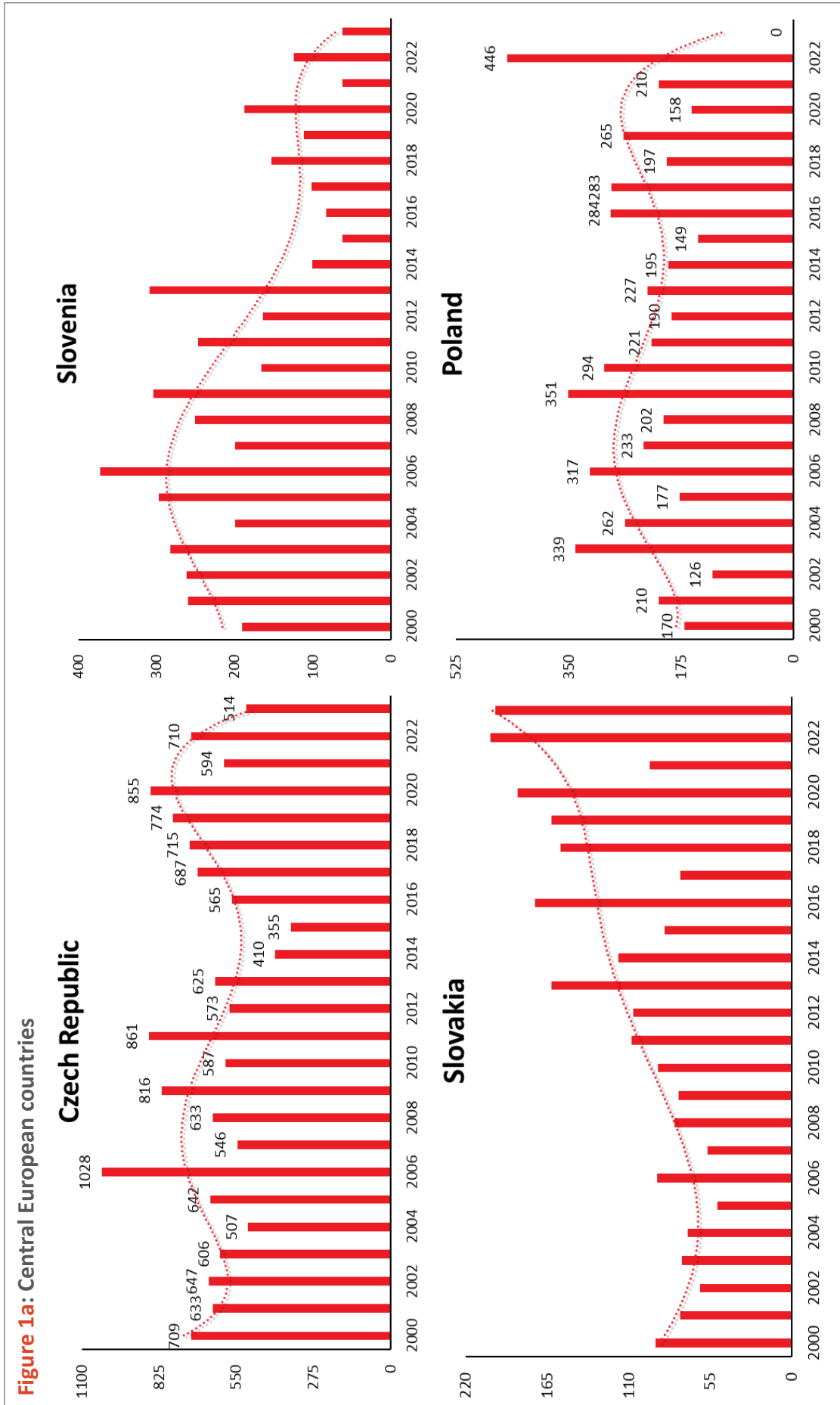
1. One of the most common methods used are antibody-prevalence studies in sera from humans or animals using ELISAs or indirect immunofluorescence tests which have the advantage that a high number of sera can be tested in relatively short time.
2. However, cross-reactivity with other flaviviruses can be misleading, and therefore, confirmation by neutralising tests are of utmost importance.
3. Another approach, but less often used, is the detection of TBEV-specific genomic sequences in ticks or in samples of milk from infected hosts like sheep, goats or cows.

For many countries in Eurasia, which are classified as TBE risk areas and are part of the TBE belt, this assessment is based on the sum of different documented evidence. Interpreting the results of such investigations and the definition of such risk areas is tricky and may be influenced by a number of factors:

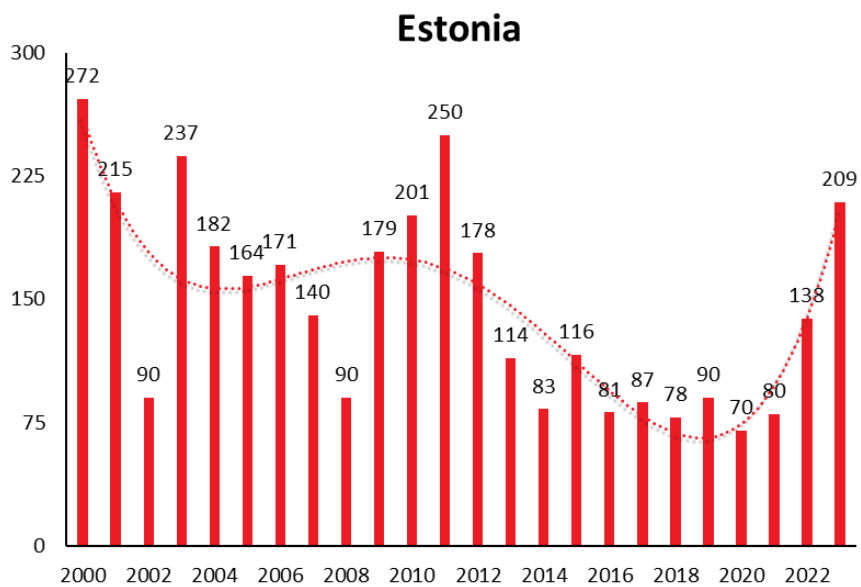
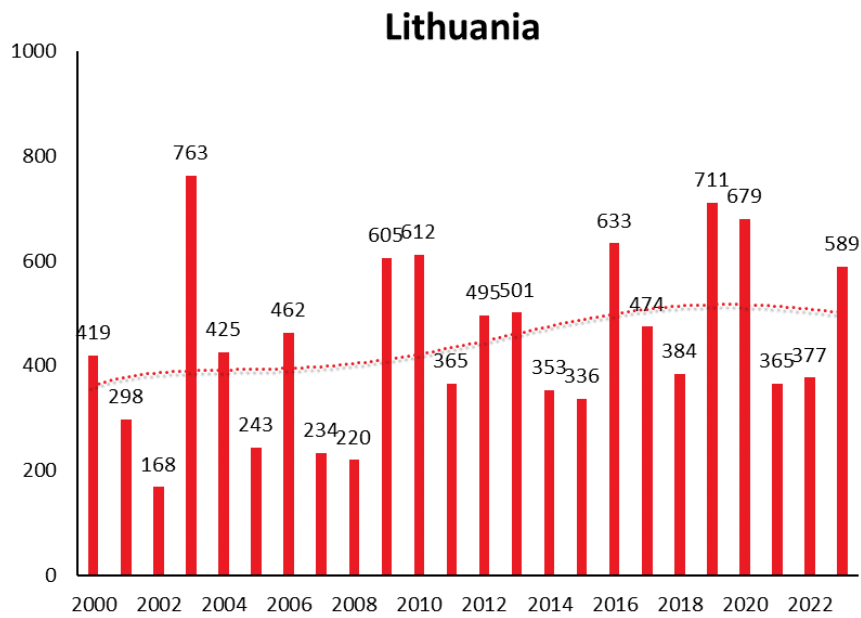
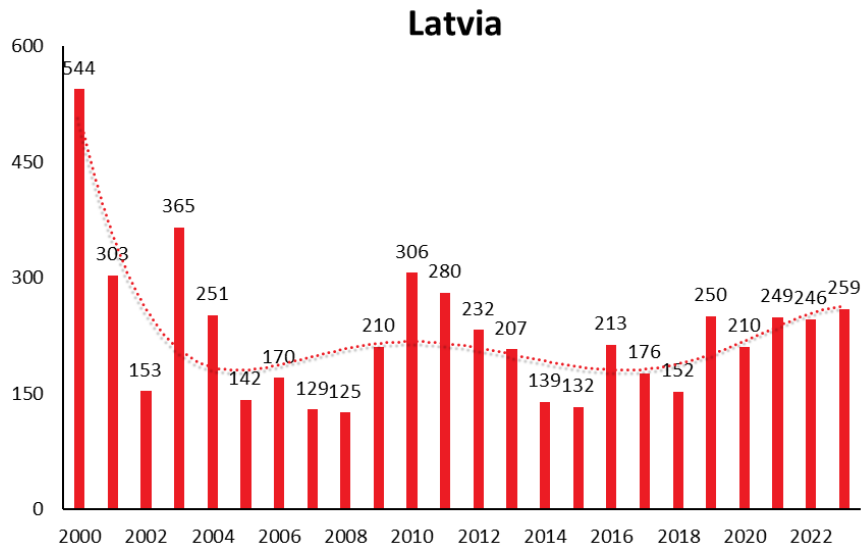
- Very often the exact place of human TBE infection cannot be determined with certainty
- Epidemiology of TBE is the result of a complex interaction between reservoir animals, birds, ticks, vegetation, climate, weather.
- Human case numbers are to be interpreted with care. Behavior may change from time to time, and population density may be different in different regions of the world (see following country chapters for details). Finland for example is the eighth-largest country in Europe and the most sparsely populated country in the European Union (Population density is 18 inhabitants per square kilometer. This is the third-lowest population density of any European country). The majority of the population lives in the central and southern parts of the country. However, according to monitoring data for 2015–2019, the calculated incidence of tick-borne encephalitis in 2019 is as high as 53 per 100,000 inhabitants in the municipality of Pargas, 42 in Simo, 20 in Kustavi, and it is 30 on the island of Åland. Recommendations per municipality are

**Figure 1: TBE disease cases (as of table 2) from 2000-2023, polynomial trendlines added**





**Figure 1b: Baltic countries**



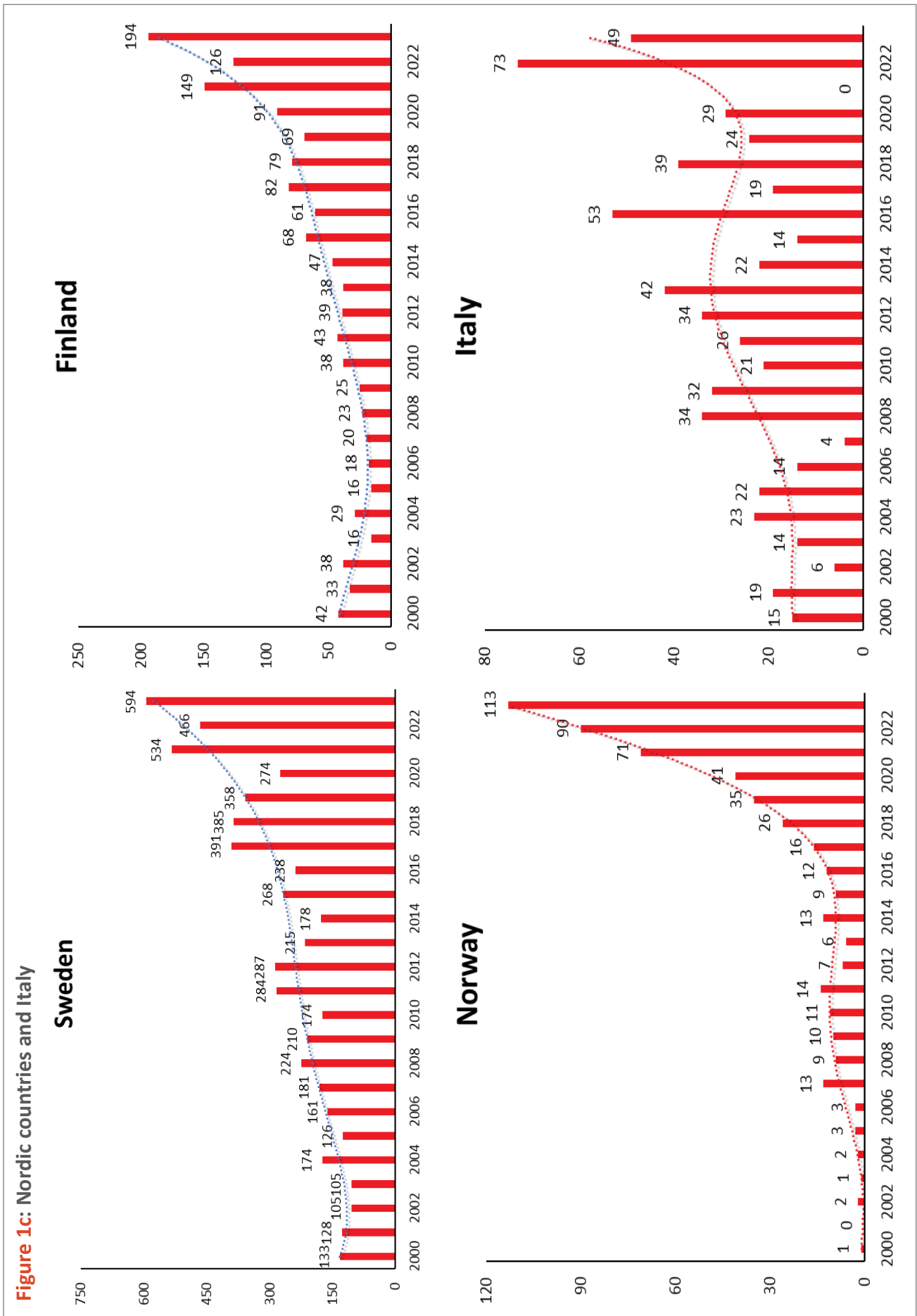


Figure 1c: Nordic countries and Italy

Table 2: TBE cases by year and country (source: data provided by the authors of Chapter 13, among others available upon request)

Country	1999	1992	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022	2023	
Austria	128	84	102	178	109	128	99	62	41	60	54	60	82	54	100	84	45	87	79	62	113	52	98	80	64	89	116	154	108	216	128	179	104	
Belarus										23	61	18	53	44	46	108	82	66	88	91	108	122	109	119	77	141	142	135	171	108	102		n.a.	
Belgium																							2	3	1	1	3	2	0	3	2	2	2	2
Bosnia and Herzegovina										1										2				5						0	n.a.	n.a.	n.a.	
Bulgaria																			2	0	0	1	0	0	2	0	1	0	1	2	1	0	0	0
China																																n.a.	n.a.	
Croatia	60	27	76	87	59	57	25	24	26	18	27	30	36	38	28	20	12	20	44	36	26	45	44	42	25	6	10	24	14	15	3	23	9	
Czech Republic	356	337	618	619	727	571	412	422	490	709	633	647	606	507	642	1028	546	633	816	589	861	573	625	410	355	565	687	715	774	855	594	710	514	
Denmark				2			2	3	4	3	3	1	4	8	2	2	1	2	2	4	1	1	3	1	1	1	0	4	5	5	7	5	12	
Estonia	68	163	166	177	175	177	404	387	185	272	215	90	237	182	164	171	140	90	179	201	250	178	113	84	116	81	87	85	83	70	80	138	209	
Finland		14	25	16	23	8	19	16	12	42	33	38	16	29	16	18	20	23	25	38	43	39	38	47	68	61	82	79	69	91	149	126	194	
France	1	1	4	3	4	1	2	2	5	5	8	4	3	8	4	10	6	6	2	3	8	4	4	10	11	29	18	24		35	n.a.			
Germany	44	142	118	306	226	114	211	148	115	133	255	239	277	274	432	544	239	289	313	260	424	195	420	264	221	353	485	582	443	717	421	555	475	
Hungary	299	190	339	264	234	246	102	74	69	54	55	80	114	89	54	57	63	55	70	50	43	44	53	31	24	19	16	32	18	6	29	24		
Italy	0	2	2	8	6	8	8	11	5	15	19	6	14	23	22	14	4	34	32	21	26	34	42	22	14	53	19	39	24	29	19	73	49	
Japan																										1	2	1	0	0	0	0	0	

\*Autochthonous cases only. For travel-related cases, see country chapter.



**Table 2: TBE cases by year and country (source: data provided by the authors of Chapter 13, among others available upon request)**

Country	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022	2023		
Kazakhstan	20	19	12	17	22	30	43	38	60	44	35	55	30	50	49	33	32	34	49	30	40	33	27	28	49	48	34	46	35	31	24	32	24		
Kyrgyzstan																																			
Latvia	227	287	791	1366	1341	736	874	1029	350	544	303	153	365	251	142	170	129	125	210	306	280	232	207	139	132	213	176	152	250	210	249	246	259		
Lithuania	14	17	198	284	427	310	645	548	171	419	298	168	763	425	243	462	234	220	605	612	365	495	501	353	336	633	474	384	711	679	365	377	589		
Moldova																																			
Mongolia															5	6	52	12	8	9	13	6	15	7	40	52	62	32	19	20	5	8	34		
Netherlands																	0	0	0	0	0	0	0	0	0	0	2	1	2	2	5	2	2	5	
Norway								1	1	1	0	2	1	4	4	5	13	11	10	11	14	7	6	13	9	12	16	26	35	41	71	90	113		
Poland	4	8	241	181	267	259	201	208	208	170	210	126	339	262	177	317	233	202	351	294	221	190	227	195	149	284	283	197	265	158	210	445	659		
Romania																		8	4	3	3	3	1												
Russia	5194	6239	7571	5640	5933	1037	6804	7531	1001	6010	6569	5231	4773	4178	4593	3433	3142	3140	3141	3094	3533	2716	2236	1978	2304	2035	1934	1727	1775	967	1015	1969	n.a.		
Serbia														1	6	1						4			4	1	1	5	13				1	1	
Slovakia	24	16	51	60	89	82	76	54	63	92	75	62	74	70	50	91	57	79	76	90	108	107	162	117	88	174	75	156	161	185	96	203	200		
Slovenia	118	80	197	531	157	406	274	137	150	196	260	262	282	199	297	372	199	251	304	166	247	164	309	100	62	83	102	153	111	187	62	124	62		
South Korea																																			
Sweden	68	84	48	116	68	45	74	65	53	133	128	104	101	174	126	161	181	224	210	174	284	287	209	178	268	238	391	385	358	274	534	466	594		
Switzerland	37	66	44	97	60	62	123	68	112	89	96	52	114	131	204	238	105	119	112	96	170	96	202	108	122	202	269	376	262	454	285	388	307		
Tunisia																																			
Ukraine												12	28	4	8	7	4	7	8	3	10	3	3	6	3	6	6	4	5	2	2	n.a.			
UK																																1	1	0	2

\*Autochthonous cases only. For travel-related cases, see country chapter.

based on human incidence numbers exclusively and do not consider those many municipalities where there are only few people living.

- Environmental variables change annually resulting in great annual differences in case numbers, demonstrated in the country chapters as well as in [Table 2](#). For instance, in some highly endemic areas, TBEV prevalence in ticks reaches 20–40%, but in other areas it can be as low as 0.1–0.5% (see Chapter 11)
- A high local vaccine uptake may result in a low disease incidence, whereas the incidence in the unvaccinated (e.g., a traveler) may be much higher than the reported risk in the local population indicates. This is relevant information for travelers.
- TBEV-infected ticks are typically found in microfoci, i.e. the virus is often detectable in small areas only, whereas the surrounding areas are TBEV-free.

To date there is no commonly accepted definition to characterize “TBE risk areas”. Most definitions and consequently vaccination recommendations (even from the WHO) so far are based on the human TBE incidence numbers in a given area.

A more holistic proposal was presented by the ECDC for assessing the risk for arbovirus infections in general<sup>29</sup>.

- The key point from this is that “... any area where the chances of transmission of an arthropod-borne disease to humans are higher than nil is a risk area.” This definition is compelling as it refrains from requiring any specific level of risk (which can be small or large), like incidence data, which vary from year to year even for the same region.
- The authors then graded risk areas as follows<sup>29</sup>:
  - A predisposed area is a risk area where existing conditions might enable the transmission of an arthropod-borne disease to humans, but the respective pathogen has not been detected. This may result from the fact that now surveillance for the TBEV had been accomplished to date.
  - An imperiled area is a risk area with no human cases detected, but where the pathogen has been detected in vectors, or transmission of the pathogen to animals or humans has been detected indirectly (by serology, e.g. if routine testing is not available).
  - An affected area is a risk area, where human TBE disease cases have occurred either sporadically or in a timewise restricted matter.
  - An endemic area is a risk area where recurrent transmission of TBE to humans is taking place over several seasonal cycles.

In order to assign an arbovirus-risk based on the ECDC definition<sup>29</sup> an area must be accurately determined geographically and by biological and epidemiological

findings (surveillance of human and animal cases, field investigation etc.) in order to avoid misunderstandings and imprecision.

This however is NOT the case with TBE, as the quality of surveillance and reporting is significantly different among countries and data cannot be simply compared. Therefore, the ECDC classification is a way to grade available evidence by the time of evaluation. However, as noted above, the epidemiology of TBE is a “moving target”, the process of unequivocal classification of a country as TBE risk area and the decision on vaccination recommendation is a stepwise process and can take many years. Countries with reasonable evidence for risk area assessment (see [fig 2](#)) are discussed in the respective country chapters (see below). For some countries, preliminary data are available regarding the prevalence of TBE virus which do not yet allow a risk area assessment. (see below paragraph 2.3.)

## 2.2. TBEV subtype and vector distribution

Three main TBEV subtypes have been described based on their distribution pattern and sequence similarity (see [fig 3](#)): the European subtype virus (previously CEE virus, Central European encephalitis virus; TBEV-EU), the Far Eastern subtype (previously RSSE virus; TBEV-FE), and the Siberian subtype (previously west Siberian virus; TBEV-Sib). In addition to the 3 primary TBEV subtypes, there is a fourth accepted subtype, designated as (Baikalian subtype (TBEV-BKL) with the prototype strain “886-84”. Recently, two additional lineages have been described as possible TBEV subtypes, namely the “strain 178-79”, and the Himalayan subtype (TBEV-HIM)<sup>30</sup> (details see chapter 11). So far, it is unclear whether the recently detected strain “Sallandse” from The Netherlands forms its own subtype or belongs to the European subtype.

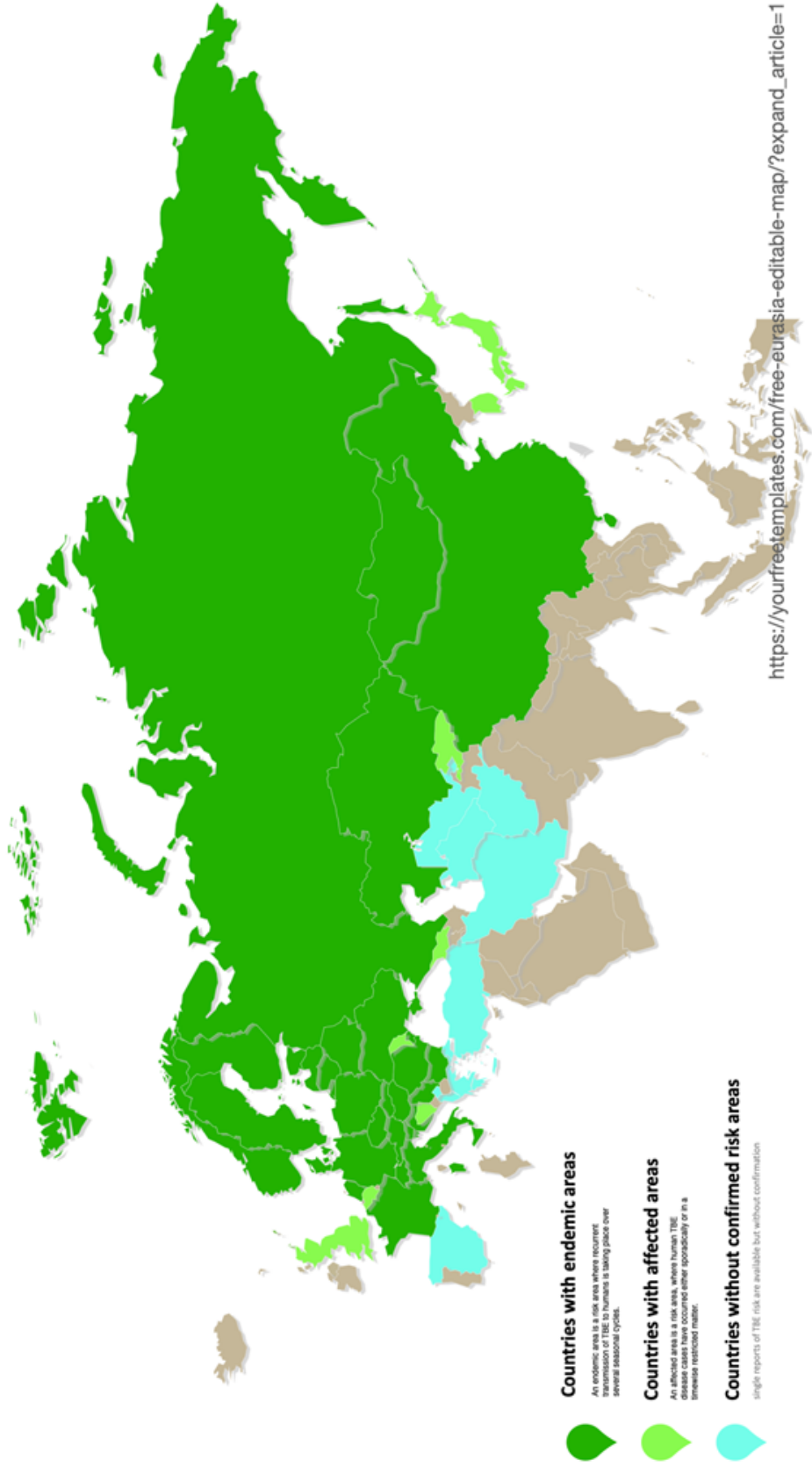
TBEV-FE prevails in the regions of far-east Russia, in China, Mongolia and in Japan. TBEV-SIB prevails in eastern and western Siberia, in the Ural and European part of Russian territories. TBEV-EU is predominant in Eastern European countries including Ukraine and in central, western, and northern Europe. However, there is a big overlap in the distribution pattern of the three main subtypes as outlined in [fig 3](#).

TBEV-BLK was found in East Siberia near Lake Baikal and in Northern Mongolia, and TBEV-HIM was recently isolated in wild rodents (*Marmota himalayana*) in the Qinghai-Tibet Plateau in China<sup>30</sup>.

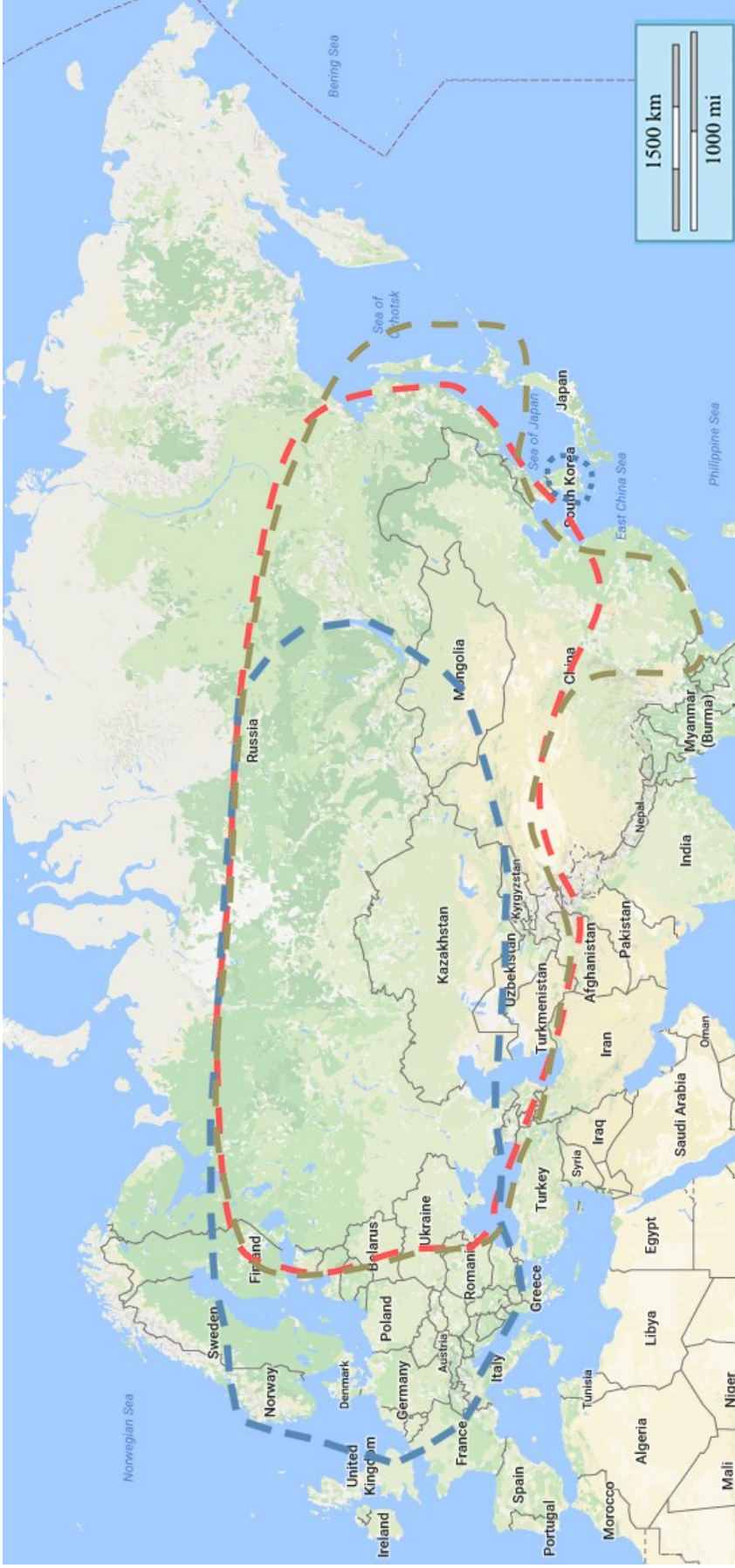
The principal vector as well as the reservoir for the TBEV-EU subtype is the tick *I. ricinus*, whereas TBEV-FE and TBEV-SIB subtypes are transmitted predominantly by *I. persulcatus*. The ranges of the 2 tick species as well as the TBEV subtypes overlap in Estonia, parts of Latvia, Finland, northern Sweden, and the European part of Russia. Interestingly in Finland *I. ricinus* infected with TBEV-Sib and *I. persulcatus* infected with TBEV-Eu have both been detected<sup>31,32</sup>.

**Figure 2:** Countries with TBE risk areas (as discussed in the respective country chapters and their status - endemic - affected - without confirmed risk area)

# COUNTRIES WITH TBE RISK AREAS



**Figure 3** : Distribution of TBEV subtypes by country



**Distribution of TBEV subtypes:**

**TBEV-Eu**

dotted blue line: prevails Europe, virus isolates in Siberia also, most eastern virus isolation Lake Baikal

**TBEV-Sib**

dotted red line: prevails Siberia and Ural region, most western virus isolation Baltics and Moldavia, most eastern virus isolation far eastern region of Russia

**TBEV-Fe**

dotted brown line: prevails far eastern region of Russia, most western virus isolation Baltics and Moldavia, most eastern virus isolation Hokkaido, Japan

Islands of unusual TBEV subtype distribution are reported in South Korea (TBEV-EU)



All 3 main TBEV subtypes have been found in Estonia and Latvia<sup>33,34</sup>. From the limited virus isolates available from the Ukraine so far, there is evidence that all TBEV subtypes are present on the Crimean peninsula, too<sup>35,36</sup>. The TBEV-SIB has been detected in Bosnia as well<sup>36</sup>.

TBEV-EU foci have been reported from South Korea, approximately 7000 km away from the European range of the TBEV-EU subtype circulation<sup>37</sup>. TBEV strains related to the TBEV-EU subtype were isolated in rodents and humans in eastern and western Siberia as well as in the Ural territory<sup>36,38</sup>. TBEV-FE foci have not only been reported from Crimea, about 3000 km away from the known TBEV-FE circulation area<sup>39</sup> but also from the Republic of Moldova between 2010 and 2011<sup>40</sup>.

Geographical circulation of the TBEV subtypes, unusual TBEV subtype foci, and various carrier vectors are well described in more detail in Chapter 2.

### 2.3. Areas without confirmed TBE risk assessment

As mentioned TBE-virus risk area assessment is a stepwise process and one should consider some core assumptions.

- i) Can tick species which are known as vectors for TBEV be found in the region to be analysed?
- ii) Is the climate of the region and the landscape suitable for these tick vectors?
- iii) How specific are the tests used to detect TBEV? What about cross-reactivity with other flaviviruses especially with those to be expected in the region?

A variety of flaviviruses genetically related to TBEV has been described (without being complete):

- Louping ill virus
- Spanish goat encephalitis virus
- Spanish sheep encephalitis virus
- Greek goat encephalitis virus
- Turkish sheep encephalitis virus
- Powassan virus
- Omsk haemorrhagic fever virus
- Alkhurma haemorrhagic fever virus
- Kyasanur forest disease virus
- Langat virus
- Negishi Virus
- West Nile fever virus
- Yellow fever virus
- Dengue virus
- Zika virus

- Japanese Encephalitis virus
- West Nile virus

Depending on the region where serological studies are carried out, at least one of these flaviviruses may interact with the test and may lead to cross-reactive false-positive results. The detection of a TBE positive serum (either in humans or animals and by ELISA or IFA) in an area so far not known as TBE endemic can only be a first sign and has to be followed by additional tests to confirm seropositivity. The golden standard for confirmation is the neutralisation test, and even this test has some minor cross reactivity.

When sera from animals are tested as sentinel, one has to take into consideration that samples from post mortem wild animals may lead to false-positive ELISA results and some samples may be toxic to cell cultures in the neutralization assay (e.g. from horses and foxes). When planning a seroprevalence study in animals, it should also be kept in mind that some animal species may be unsuitable as sentinels due to the fact that they do not seem to seroconvert, e.g. cats<sup>41</sup>.

When animal or human sera have been found to definitely be TBE sero-positive in a given region, the next step to demonstrate that TBEV is circulating in this area is the detection of TBEV in ticks. While ticks may be found in a wide range of different landscapes and places in that region, TBE foci, that means ticks infected by TBEV, may be small, sometimes smaller than a soccer field, and the prevalence of infected ticks may be low (mostly less than 1%). Consequently, it may be very useful, to contact individuals who had TBE and/or are TBE antibody-positive and can remember where they had been bitten by a tick about one to three weeks before onset of disease. The localization of potential TBE foci can help to increase the chance to detect TBEV genome in ticks collected by flagging. This approach to identify TBE foci is much more effective than just collecting ticks in the landscape.

Investigations on TBEV or TBE in areas outside of the Eurasian continent have been successful during the last decade. TBE foci and/or TBE virus could be identified on the British Islands - now the most western part of the TBE belt - and in Japan – now the most eastern part of the TBE belt. Surprisingly, TBE virus could also be detected in Tunisia, which today is the most southern TBE virus endemic region and so far the only one on the African continent. It is assumed that migrating birds are responsible for the extension of the TBE belt by transporting ticks over wide distances. This assumption is supported by genomic sequence analyses of strains isolated from new foci and which show a close genomic relationship to strains from other regions of the TBE belt.

For the following countries preliminary data are available regarding the prevalence of TBE virus which do not yet allow a risk area assessment.

## Countries close to the well-known TBE belt

### Spain

The first systematic studies to investigate the probable occurrence of TBEV in Spain were carried out from 2006 to 2008. A total of more than 1800 *Ixodes ricinus* nymphs and 630 adult ticks collected in northern Spain were analysed by real-time reverse transcriptase PCR. All test results were negative, and the authors concluded that TBEV prevalence in northern Spain was either very low or absent in the investigated regions of northern Spain<sup>42</sup>.

A sero-epidemiological study of West Nile virus, Usutu virus and TBEV in dogs has been carried out in Spain. Flavivirus antibodies were detected in 39/815 dogs using a commercial blocking ELISA. This test system detects antibodies targeting epitopes on domain III of the envelope protein common to antigenically related flaviviruses and thus, ELISA-positive results indicate the presence of antibodies against flaviviruses. TBE positivity was confirmed using a neutralisation test in 14 dog blood samples collected in southern (Andalusia) and southwestern (Extremadura) Spain<sup>43</sup>.

A sero-epidemiological study in breeding and sport horses resident in nine autonomous communities across Spain was carried out between 2011 and 2016. A total of 14/458 (3.1%) sera were positive in a TBE serum neutralisation test<sup>44</sup>. The authors discussed that the neutralization test used would not enable differentiation between TBEV and LIV, both members of the TBE sero-complex.

In 2011/12, a sero-epidemiological study was carried out in horses in order to assess seropositivity for various flaviviruses (Usutu virus, West Nile virus, TBEV), and 291 blood samples were taken from 172 horses<sup>45</sup>. The IgG seroprevalence for TBE was 0.6%. Seroprevalence for WNV was 6.4% and for USV was 1.2%. The authors concluded that zoonotic arboviruses circulate in Mallorca.

### Greece

In a sero-epidemiological study across Greece, 1.7% TBE positive samples were identified in apparently healthy persons by immunofluorescence testing. It is worth mentioning that the highest seroprevalence rate was found in a region where no *Ixodes ricinus* ticks have been shown to be prevalent<sup>46</sup>.

In a sero-epidemiological study, 921 sera and cerebrospinal fluid from individuals with infections of the central nervous system and living in northern Greece were analysed for IgM and IgG TBE antibodies. In two percent of the general population, TBE antibodies were found (0%-5.8% in different prefectures), but TBE could not be confirmed by laboratory analyses, and the authors concluded that a flavivirus of the TBE sero-complex is circulating in the investigated region<sup>47,48</sup>.

A dog with a history of tick infection and which displayed neurological symptoms was analysed for TBE by using a

commercial IgM and IgG TBE ELISA. The dog was tested positive for both IgM and IgG, and the authors concluded that diagnosis of TBE infection was confirmed by combining the clinical symptoms with this seropositivity<sup>49</sup>. The authors stated that one limitation of the study was that no confirmation test by serum neutralisation assay was carried out.

In a review article about tick-borne pathogens and diseases in Greece<sup>50</sup>, the authors concluded from the above cited publications that a flavivirus of the TBE sero-complex is circulating in Greece.

### Turkey

In 2007, a seroprevalence study was carried out for WNV and TBE analyzing sera from 181 samples collected at two state medical hospitals in the southeastern part of Turkey. Using a commercial TBE IgG ELISA, 10.5% were positive and 23% of the IgG positive sera were also positive in a TBE IgM ELISA. In an immunofluorescence test, 16% of the sera were positive for WNV, of which four sera were also positive for TBE. The authors concluded the possible presence of TBEV in southeastern Turkey<sup>51</sup>.

Some years later, a total of 2450 sera from healthy blood donors in central and northern Anatolia were analyzed by a commercial TBE IgG ELISA, and 47 donor samples (1.9%) were tested positive. One sample from the Black Sea region was positive in a plaque reduction neutralisation test. The authors discussed that the blood donors have had exposure to TBE virus or an antigenically similar tick-borne flavivirus<sup>52</sup>.

When 110 sera from Turkish children with fever and/or arthritis were analyzed by TBE IgM, five samples were tested positive. No sample was TBE IgG positive. Two samples were positive for WNV IgM and six sera were tested positive for WNV IgG. The authors concluded that children in Turkey were exposed to TBEV and WNV<sup>53</sup>.

In the Samsun province, a total of 419 human sera from healthy individuals were analyzed by TBE IgM and IgG ELISA. Four samples were positive for IgG and one sample tested positive for IgM. However, none of these sera were confirmed positive in a neutralization assay<sup>54</sup>.

A TBE seroprevalence study has been carried out among domestic animals in northern Turkey, and ticks were collected from animals (cattle, goat, sheep) and were analyzed for TBEV. No TBEV-specific genomic sequences were detected in a total of 2625 ticks. Screening of serum samples by a commercial TBE IgG ELISA revealed positive results in cattle (61/198, 30.8%), in goats (7/115, 6.1%) and sheep (15/147, 10.2%). The authors concluded that their study supports previous findings which indicates that TBEV is distributed in Turkey<sup>55</sup>.

### Albania and Bosnia and Hercegovina

Sero-epidemiological studies in humans and animals were carried out in the 1990s to analyse the distribution of

arboviruses in Albania, and TBE positive sera were detected<sup>56</sup>. However, the tests used in these investigations were based on indirect immunofluorescence techniques, and results may have been false-positive due to cross-reactivity with other flaviviruses. During the 2<sup>nd</sup> International Symposium on Tick-Borne Encephalitis in June 1991, Eltari reported about TBE cases in Albania<sup>57</sup>. Later, Sherifi et al. (2018) admitted that no accurate data were available on TBE in Albania, and their attempts to detect TBEV-specific genome in ticks collected by flagging had been negative<sup>58</sup>.

There is only one report from Bosnia mentioning human TBE cases (Burger, 2017).

However, Zlobin et al. (2006) isolated three Siberian TBEV subtype strains - Bosnian lineage, two strains from one male and one female *Dermacentor marginatus* and 1 strain isolated from *Ixodes ricinus* nymph<sup>59,60</sup>

In total, the southwestern Balkans (Albania, Bosnia and Herzegovina, Macedonia, Montenegro) have only a few or no studies about TBE and TBE related reports.

#### North Macedonia

In a study to assess the prevalence of antibodies to *Borrelia burgdorferi* and TBEV in North Macedonia and Serbia, one serum sample from a female in North Macedonia was positive for neutralising TBE antibodies. This result suggests the potential existence of TBE foci in North Macedonia, however, there is still the alternative explanation that this person was exposed to TBEV during a short stay in Austria<sup>61</sup>.

#### Afghanistan

In a serological study dealing with the seroprevalence of various flaviviruses, a commercial IgG and IgM ELISA was used to assess seropositivity among individuals in Afghanistan. A total of 30.8% of the sera were IgG-positive for TBE, and 20.6% were co-reactive in a WNV-ELISA. 2.2% of the sera were TBE-IgM positive. The authors concluded that TBEV may circulate in Afghanistan<sup>62</sup>. However, these high prevalence rates may be due to another circulating flavivirus of the tick-borne mammalian group, Royal Farm virus, which was isolated in Afghanistan in 1968 from soft ticks. With no NT testing available the situation remains unclear.

#### Georgia

In Georgia, 7% of acute febrile patients showed TBEV seropositivity<sup>63</sup>. Non-published data show that TBEV-EU may circulate in Georgia. The interpretation of the data is unclear.

#### Iran

Raw milk samples collected from local dairy markets around Qazvin, a city in northern Iran, have been analysed by using nested and multiplex PCR methods for the presence for various foodborne and zoonotic viruses. TBEV genomic sequences were detected in 42/492 (18.91%) of the analysed samples<sup>64</sup>. The authors concluded that the

presence of TBEV in raw milk may pose an immediate health risk for milk and dairy consumers, even without any reported TBE cases in the Qazvin area.

In a conference report<sup>65</sup>, data on the presence of TBEV in raw milk samples from sheep (4.4%), goat (4.4%) and cows (0%) in northwest Iran were presented, and TBE antibodies evaluated by ELISA were found in the milk of sheep (4.4%), goats (2.2%) and cows (1.1%). However, we did not find these data anywhere in a peer-reviewed journal.

A cross-sectional sero-epidemiological study has been carried out in rural areas in northern Iran in order to analyse the prevalence of TBE antibodies among the general population using a commercial TBEV ELISA IgG kit. A total of 16/448 serum samples tested positive. The authors discuss that there are uncertainties about the accuracy of positive results on serological tests, such a ELISA, owing to the antigenic cross-reactivity among flaviviruses, and they concluded that confirmation is needed by neutralisation test and that the results should be interpreted with caution<sup>66</sup>.

#### Central Asian countries

Within the Central Asian countries there are reports of TBE in Kazakhstan and Kirgizstan (see country chapters), the only other single report without any further details is from Turkmenistan<sup>67</sup>.

### **Countries remote from the TBE belt**

#### Comores

A cross-sectional survey of arboviral infections in humans was conducted on three islands of the Union of Comores in 2011. Using a commercial TBE IgG ELISA, 3/400 sera were positive in the TBE ELISA, but no neutralisation/confirmation tests were carried out<sup>68</sup>.

#### Kenya

A seroprevalence study was carried out in Kenya in 2000 to 2004 to evaluate the prevalence of arboviral infections. A high seroprevalence of TBE IgG (16% in older persons, 6% in children) was found using a commercial indirect immunofluorescent test, and the authors concluded that this was a result of cross-reactions amongst related flaviviruses<sup>69</sup>.

#### Djibouti

In a sero-epidemiological study carried out in Djibouti to assess the burden of a variety of arboviral diseases, antibodies to Dengue were the most frequent (21.8). In 2/1045 sera, TBE antibodies were detected using a commercial ELISA. While the first serum sample was negative in a TBE specific neutralisation assay and negative also for Alkhurma virus, the second serum was slightly positive for both viruses. The authors discussed that these two TBE seropositive individuals may have been migrants with a specific exposure to tick bites in a rural environment<sup>70</sup>.

### Vietnam

TBE sero-epidemiological analyses using an indirect immunofluorescence antibody test (IFAT) of sera from humans and rats gave positivity rates of 47.3% and 5.4%, respectively. The authors concluded that the TBE reactivity in both humans and rodents detected by the IFAT most likely reflected cross-reactivity with other flaviviruses, especially with Dengue virus and Japanese encephalitis virus<sup>71</sup>.

### Malaysia

Among farms workers, a TBE seropositivity of 36.5% was found using a commercial TBE IgG ELISA. However, when testing these sera against three antigenically related flaviviruses (DEN, WN, JEV), only 4.2% of the sera did not show cross-reactivity. The authors discussed that the remaining TBE seropositivity may be due to cross-reactivity to Langat virus and they concluded that even a virus neutralisation test could still lead to false TBE seropositivity results<sup>72</sup>.

### Summary

In this book, we did all possible to identify predisposed, imperiled, affected and endemic areas. For the countries mentioned in the end, surveillance data using TBEV-NT would be most simple to confirm TBEV circulation – which would be relevant for travelers. In endemic countries reporting should be enhanced and commercial tests for TBE should be easily accessible. Clearly, the country-specific information on TBE – epidemiology is still scarce and results in relevant underdiagnosis.

The following country reports in Chapter 13 provide standardized information, as available on:

- The risk area assessment based on the ECDC definition (see above)
- The history of TBE in the respective country as well as various specific aspects
- Virus, vector, transmission of TBE
- TBE-reporting and prevention by vaccination
- TBE case numbers over time
- Local demographics of TBE
- TBEV-isolation and TBE cases – risk area distribution

The risk map in chapter 13 shows the extent of TBEV based on documented TBE cases, TBEV infection, as well as on the detection of TBEV-circulation in nature (i.e., imperiled, affected and endemic areas). The map does not reflect the incidence of the disease or the universal prevalence of the virus in a given area. As the quality, intensity and completeness of epidemiological surveillance varies between different countries, the map presented here must be incomplete, and very likely TBEV infections and thus TBE may occur in additional (“new”) areas.

The risk map distribution is based on the second and third level of the Nomenclature of territorial units for statistics (NUTS) used for subnational analysis, depending on availability (Eurostat, the statistical office of the European Union. Nomenclature of Territorial Units for Statistics. Luxembourg: Eurostat. [Accessed: 7 Mar 2023]. Available from: <http://ec.europa.eu/eurostat/web/nuts/overview> )

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