TECHNICAL REPORT

Epidemiological situation of tick-borne encephalitis in the European Union and European Free Trade Association countries

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This report is based on work commissioned by the European Centre for Disease Prevention and Control (ECDC), (Ref: OJ/2010/01/08-PROC/2010/001) coordinated by Herve Zeller and Wim Van Bortel. The report was produced by Pawel Stefanoff, Natalia Parda, Aleksandra Polkowska, Fortunato D'Ancona, Pedro Anda, Annapaola Rizzoli, Rachel Escudero, Elena Kocianová, Oliver Donoso-Mantke, Maria Kazimirova, Emoke Ferenczi, Luisa P. Sánchez Serrano, Joanna Zajkowska and Sarah Randolph, with contributions from Tomasz Chmielewski, Horacio Gil, Wiebke Hellenbrand, Isabel Jado García, Ilona Mączka, Hana Orlikova, Justyna Rogalska, Stanislawa Tylewska-Wierzbanowska, Virginia Estevez and Bertrand Sudre.

We would like to acknowledge all country respondents for their provision of accurate and timely information on the national situation.

Suggested citation: European Centre for Disease Prevention and Control. Epidemiological situation of tick-borne encephalitis in the European Union and European Free Trade Association countries. Stockholm: ECDC; 2012.

Stockholm, September 2012

ISBN 978-92-9193-384-6

doi 10.2900/62311

Contents

Abbreviations

CSF	Cerebrospinal fluid
CNS	Central Nervous System
ECDC	European Centre for Disease Prevention and Control
EDEN	Emerging Diseases in a changing European eNvironment –collaborative research project funded by the European Commission 6th Framework Programme, 2005–2010
EFTA	European Free Trade Association
ELISA	Enzyme-linked immunosorbent assay
ENIVD	European Network for Diagnostics of 'Imported' Viral Diseases
EQA	External Quality Assurance
HI	Haemagglutination inhibition
IFA	Immunofluorescence assay
Med-Vet-Net	European Network of Excellence for Zoonoses research, funded by the European Commission 6th Framework Programme, 2004–2009
TBE	Tick-borne encephalitis
TESSy	The European Surveillance System
VENICE	Vaccine European New Integrated Collaboration Effort

Executive summary

Tick-borne encephalitis (TBE) is a viral tick-borne infectious disease that occurs in endemic areas across large regions of Europe and Asia. It requires the presence of competent reservoir hosts, tick vectors and the pathogen. TBE virus (family Flaviviridae) is the aetiological agent of the disease.

To obtain a better understanding of the current magnitude of TBE in the European Union (EU) and European Free Trade Association (EFTA) countries the current project aimed to summarise existing information on the occurrence of TBE. The specific objectives were to characterise the different reporting systems for TBE in EU/EFTA countries; to identify and assess the current epidemiological situation for TBE; identify key risk areas for the disease and provide ECDC with data into its study on burden of disease.

First, an online survey was distributed to nominated national surveillance experts requesting information on TBE surveillance systems. From countries which implement surveillance for TBE, surveillance data were requested for the period 2000–2010. Information on routinely collected surveillance data was supplemented with published and unpublished data on TBE from environmental, animal and human sources, covering the period 2000–2010.

Surveillance systems for TBE exist in 20 of the 30 EU/EFTA countries, with a surveillance case definition adopted in 10 out of the 20 countries. Although human surveillance systems for TBE were implemented in the majority of EU/EFTA countries, important differences existed in terms of case definitions used, clinical syndromes reported and variables collected at national level. Similarly, there were significant differences among countries in terms of access to laboratory diagnosis.

The main risk areas for TBE are in central and eastern Europe and the Baltic and Nordic countries. The area extends to the west of Europe as far as Switzerland and the French region of Alsace, and to the south of Europe as far as northern Italy and the Balkan countries. The highest risk for TBE was among males aged 40–60 years, indicating that persons working outdoors may be at increased risk of TBE. However, an accurate identification of high-risk populations would necessitate collection of more detailed surveillance data and epidemiological studies to assess the TBE risk factors at individual level.

This report was a first effort to collect existing data on TBE in EU/EFTA countries. The data, covering the period 2000–2010, were collected from different sources using different case definitions, time scales, and spatial units and do not reflect the complete picture and complexity of the epidemiology of this disease. Therefore a number of recommendations were made to improve the surveillance and to increase our understanding of TBE in EU/EFTA countries: to implement the standard EU case definition for TBE; to initiate routine collection of surveillance data from EU countries, to at least NUTS-3 geographical level, and to use data from tick and animal surveys in addition to human cases surveillance to define TBE endemic areas.

Background

Tick-borne encephalitis (TBE) is a viral tick-borne infectious disease that occurs in endemic areas across large regions of Europe and Asia. It requires the presence of competent reservoir hosts, tick vectors and the pathogen. The TBE virus (family Flaviviridae) is the aetiological agent of the disease and includes three subtypes: western subtype which is endemic in central, eastern and northern Europe; Siberian subtype, endemic in eastern Europe, Russia and northern Asia; and far eastern subtype, endemic in eastern Russia and some parts of China and Japan, see examples [1-4].

The main vectors of the TBE virus in Europe are ticks of the family Ixodidae, mainly *Ixodes ricinus* (central, northern and eastern Europe) and *Ixodes persulcatus* (parts of the Baltic States, Finland, Russia, Siberia). Competent reservoir hosts of the TBE virus are mainly small rodents (voles, mice), but also insectivores and carnivores. Hosts that support virus circulation indirectly by enabling tick reproduction are different species of wild and domestic mammals (foxes, bats, hares, deer, wild boar, sheep, cattle, goats, and dogs). Humans are incidental and dead-end hosts. In addition to being bitten by an infected tick, in endemic areas humans can also acquire TBE infection by consuming infected raw dairy products [1, 3].

Every year, the TBE virus causes thousands of cases of neuroinvasive illness in humans across Europe and Asia and is becoming a growing public health concern in Europe and other parts of the world. In recent decades, the number of human TBE cases in endemic regions of Europe has increased, endemic areas have spread northwards and to higher altitudes and new foci have emerged. TBE has also become an international public health problem due to increasing mobility and increased travel to endemic areas [4-6]. Possible reasons for the increasing reported incidence of TBE and its spread to new areas are global change, including climate and socio-economic change, modification to habitat structure and wildlife community composition resulting in an increasing abundance of deer, greater public awareness and improved reporting and diagnosis [4, 6–8].

Approximately two-thirds of human TBE virus infections are asymptomatic. In clinical cases, TBE often has a biphasic course. The first phase is associated with non-specific symptoms (such as fever, fatigue, headache, myalgia, or nausea). This phase is followed by an afebrile asymptomatic interval that precedes the second phase, when the central nervous system is affected (such as meningoencephalitis, myelitis or paralysis). The western European subtype is associated with milder disease, mortality rates of 0.5%–2%, and severe neurologic sequelae in up to 10% of patients. The far eastern subtype is associated with monophasic illness, with no asymptomatic interval preceding the onset of neurological disease, mortality rates of up to 20% and higher rates of severe neurologic sequelae [9]. There is no specific treatment for TBE, but an inactivated vaccine is available for prevention. Modern vaccines are safe and the rate of protection is over 95% [10].

TBE clinical cases do not have distinct symptoms and their diagnosis needs laboratory confirmation. TBE cases are routinely confirmed through detection of specific anti-TBE virus antibodies in serum or cerebrospinal fluid (CSF) through enzyme-linked immunosorbent assay (ELISA), immunofluorescence assay (IFA) or haemagglutination inhibition (HI) [11]. Methods based on detection of TBE virus genetic material have limited use in clinical practice due to the short duration of viraemia. The limitation of serological methods is the cross-reactivity with antibodies directed to other flaviviruses. Application of the method of choice for flavivirus differentiation, the virus neutralisation assay, is especially recommended in regions where co-circulation of other flaviviruses has been documented.

Despite increasing awareness of TBE, a greater understanding of the true magnitude of this disease in Europe is needed. Some initiatives have been already undertaken at European level. Recently a survey of vaccine recommendations was performed within the framework of the Vaccine European New Integrated Collaboration Effort (VENICE II) collaboration [12]. This survey addressed the availability of surveillance data and an ascertainment of endemic areas. The European Network for Diagnostics of Imported Viral Diseases (ENIVD) has collected data from EU countries on virological methods available to confirm TBE virus infection and availability of epidemiological data on TBE [13, 14]. Collection via diagnostic laboratories is a principal – probably under-reported – data source, complicated by varying criteria for serological diagnosis and patterns of test referrals. Other potential sources of data include physician surveys, hospital records, and national surveillance systems.

Environmental conditions linked to global changes that affect the spatial and temporal distribution and dynamics of TBE incidence in Europe have been identified and evaluated in a co-ordinated European approach under the EU FP6 EDEN (Emerging Diseases in a Changing European Environment) project (http://www.eden-fp6project.net/) (2004–2010). The aim of this project was to provide predictive emergence and spread models on a global and regional scale along with preventive early warning, surveillance and monitoring tools and scenarios.

In order to obtain a better understanding of the current magnitude of TBE in the EU and EFTA countries, the current project aimed to summarise existing information on the occurrence of TBE. The specific objectives were to characterise the different reporting systems for TBE in EU/EFTA countries; identify and assess the current epidemiological situation for TBE; identify key risk areas for the disease and provide ECDC with data for its study on burden of disease. First, an online survey was distributed to nominated national surveillance experts requesting

information on TBE surveillance systems. Surveillance data were requested for the period 2000–2010 from countries which implement TBE surveillance. Information on routinely collected surveillance data was supplemented with published and unpublished data on TBE from environmental, animal and human sources, covering the period 2000–2010.

Methods

The project was implemented using the following data collection methods (a detailed description of the project is presented in Annex 1:

- On-line survey (questionnaire) regarding surveillance of TBE, microbiological methods and other epidemiological data. The questionnaire was sent to all EU countries and three EFTA countries.
- A literature review of published data on TBE epidemiology in Europe.
- Collection of surveillance data from countries.

Survey on TBE data availability

The aim of the survey was to obtain an overview of TBE surveillance systems in the EU and EFTA countries. The specific objectives of the survey were:

- to characterise the type and number of existing TBE surveillance systems, the type of data collected (case-based/aggregated), the data availability on surveillance sensitivity and case definitions adopted in surveillance systems;
- to collect information on laboratory tests used to diagnose suspected TBE cases, number of samples processed each year for diagnosis of TBE cases, presence of reference laboratories and information about External Quality Assurance (EQA) in relation to TBE diagnosis;
- to summarise information on reports of human cases of TBE which are not available in Medline, collect information regarding special studies on TBE prevalence in animals or ticks which are not available in Medline.

A standardised online questionnaire was developed (Annex 2). The questionnaires were tested by consortium members and ECDC project coordinators. The pilot study was conducted in February 2011. After the pilot study, the questionnaires were reviewed and amended and the on-line survey was prepared with the assistance of EpiConcept in February 2011 and implemented on a VoozaNoo platform in March 2011.

The respondents from 27 EU Member States and three EFTA countries were identified through existing networks: EDEN-TBD, VENICE II, ENIVD, and Med-Vet-Net. The list of initially selected respondents was sent to ECDC for approval and the nominated person was able to delegate part of the work to relevant experts.

Collected data were analysed using Microsoft Excel and EpiInfo software to produce descriptive statistics.

Epidemiological TBE data collection

During the implementation of the TBE survey (described in detail above), respondents who indicated the implementation of at least one TBE surveillance system were contacted by the project coordinator, on behalf of ECDC, to ask whether they were willing to provide data collected through their surveillance system. Following the discussion of potential concerns and clarification of details, the respondents were asked to provide case-based or aggregated data covering the period 2000–2010. To assure possible future integration of the data with the European Surveillance System (TESSy), the TESSy metadata specification was used. During February and March 2011, the TESSy team was consulted over the data format. The specification for aggregated data was also used for the literature review – data extraction procedure.

Literature review on TBE data availability

The objective of the literature review was to identify and analyse published data on human cases of TBE occurring in Member States and EFTA countries, and to study those articles which provided important information for interpretation of disease risk in humans.

The literature search, covering the period 2000–2010, was performed using Medline, Embase, Global Health, Cochrane Database of Systematic Reviews, and CAB Abstracts linked databases, through the German Institute of Medical Documentation and Information (DIMDI, http://www.dimdi.de/static/en/index.html). The following search string was used to retrieve relevant papers: (tick-borne encephalitis OR TBE OR TBEV) AND (surveillance OR epidem$ OR inciden$ OR prevalen$ OR outbreak$ OR cluster$) (see Annex 1 for details).

Data from selected papers, including data on human cases, were retrieved using the TESSy-compatible aggregated format. All possible aggregation variables were retrieved, prioritising year of onset, region of residence, gender and age group.

In addition, supportive evidence on TBE epidemiology in EU countries, including papers describing or evaluating TBE surveillance systems, seroprevalence surveys of humans, animals and vector studies, were selected as a supplementary source of information. Full papers were also retrieved for all these studies.

Where no surveillance data were available from a particular country, the data captured from the literature search were used to assess the epidemiology of the disease. If surveillance data were available for a given country/region during the specified period, the literature cases were omitted.

A complementary literature search was conducted to identify publications relevant for estimating the risk of TBE in European countries that might have been omitted during the initial literature review. New articles were identified by reviewing the references of the previously identified publications, screening titles, year of publication and abstracts. The articles were recognised on the basis of prior established inclusion criteria. Additionally, countries were requested to provide references relating to their country. The identified publications were analysed thoroughly and a decision taken on inclusion/exclusion. Those included were assessed and categorised according to whether data could be extracted on human cases or whether they contained information to help analyse the risk of TBE.

Results

Survey on TBE data availability

Among the 30 participating countries, 20 (67%) had developed surveillance systems for TBE. Comprehensive surveillance exists in 18 countries (60%). In France, there is a special form of surveillance carried out by the National Reference Centre for Arboviruses. Meanwhile, in Belgium, a sentinel system has been developed with voluntary reporting of TBE cases.

In 18 countries (60%) surveillance is implemented at national level, in one country at sub-national level, and in Italy, the system operates at national level but in practice it is only implemented in those regions where the disease is endemic. There is mandatory reporting of TBE cases in 16 countries (53%), voluntary reporting in one country and undefined reporting in three countries (Figure 1, Table 1).

Figure 1. Overview of TBE surveillance implemented in EU/EFTA countries

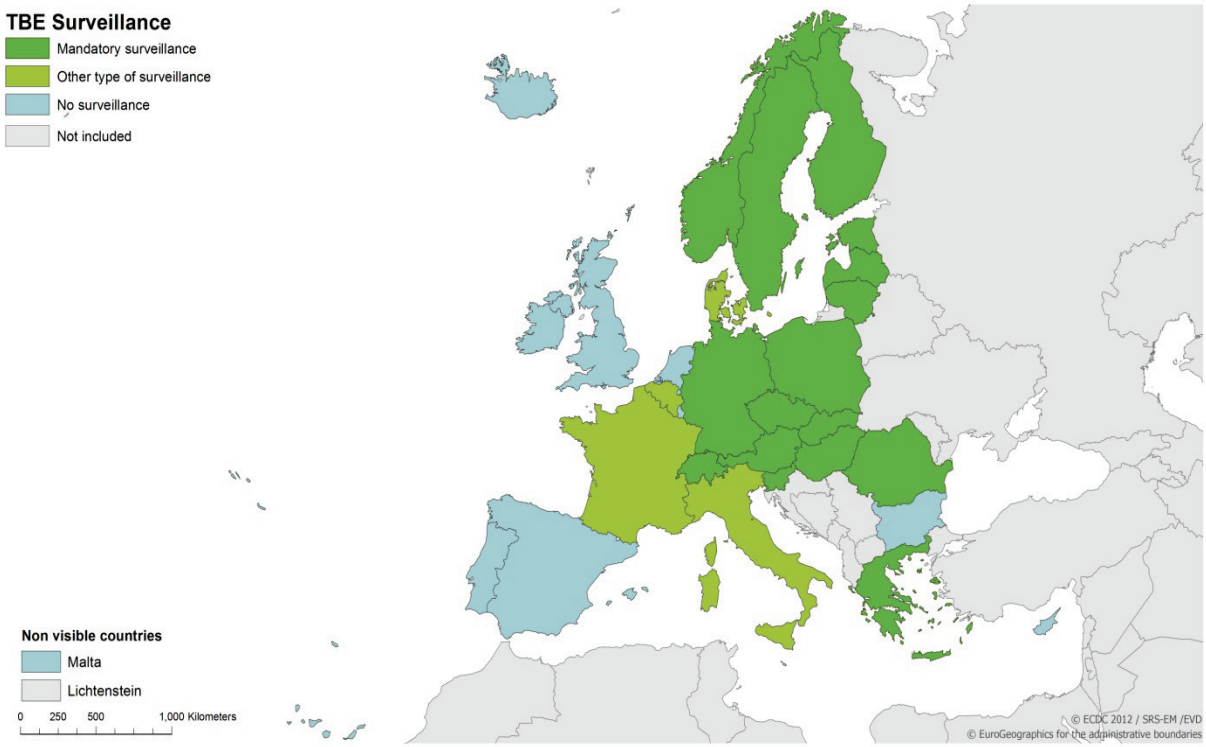


Table 1. Type of TBE surveillance in EU/EFTA countries

Country*	Type of surveillance	System operating	Type of reporting
Austria	Comprehensive	At national level	Mandatory
Belgium	Sentinel	At national level	Voluntary
Czech Republic	Comprehensive	At national level	Mandatory
Denmark	Comprehensive	At national level	Not well defined
Estonia	Comprehensive	At national level	Mandatory
Finland	Comprehensive	At national level	Mandatory
France	National Reference Centre for Arboviruses	At national level	Not well defined
Germany	Comprehensive	At national level	Mandatory
Greece	Comprehensive	At national level	Mandatory
Hungary	Comprehensive	At national level	Mandatory
Italy	Comprehensive	Other	Not well defined
Latvia	Comprehensive	At national level	Mandatory
Lithuania	Comprehensive	At national level	Mandatory
Norway	Comprehensive	At national level	Mandatory
Poland	Comprehensive	At national level	Mandatory
Romania	Comprehensive	At sub-national level	Mandatory
Slovakia	Comprehensive	At national level	Mandatory
Slovenia	Comprehensive	At national level	Mandatory
Sweden	Comprehensive	At national level	Mandatory
Switzerland	Comprehensive	At national level	Mandatory

*The following countries have not developed TBE surveillance systems: Bulgaria, Cyprus, Iceland, Ireland, Luxembourg, Malta, the Netherlands, Portugal, Spain and United Kingdom.

Data for surveillance purposes are derived from varied sources, mainly from hospital physicians, general practitioners and laboratory reports (Table 2).

Table 2. Sources of TBE surveillance data in EU/EFTA countries

	Source of data				
Country	Reporting by general practitioners	Reporting by hospital physicians	Reporting of deaths from infectious diseases	Laboratory reporting	Death register records
Austria	✓	✓	✓	✓	
Belgium				✓	
Czech Republic	✓	✓	✓		✓
Denmark	✓	✓		✓	
Estonia	✓	✓		✓	
Finland				✓	
France				✓	
Germany				✓	
Greece	✓	✓	✓		
Hungary	✓	✓	✓	✓	✓
Italy	✓	✓			
Latvia	✓	✓			
Lithuania	✓	✓	✓	✓	
Norway	✓	✓		✓	
Poland	✓	✓		✓	
Romania		✓			
Slovakia	✓	✓	✓	✓	
Slovenia	✓	✓	✓	✓	
Sweden	✓	✓		✓	
Switzerland	✓	✓		✓	
Number of countries	15	16	7	15	2

Eight countries report all clinical forms of TBE. All symptomatic cases (including tick-borne fever) are registered in three countries. In nine countries only cases with central nervous system involvement are registered. The clinical syndromes routinely reported to surveillance are summarised in Table 3.

Table 3. Type of TBE cases routinely reported in EU/EFTA countries with surveillance

Country	Types of cases routinely reported		
	All cases including asymptomatic infection	All symptomatic cases including tick-borne fever	Only cases with central nervous system involvement
Austria			✓
Belgium	✓		
Czech Republic			✓
Denmark	✓		
Estonia		✓	
Finland	✓		
France			✓
Germany	✓		
Greece			✓
Hungary			✓
Italy		✓	
Latvia	✓		
Lithuania	✓		
Norway	✓		
Poland			✓
Romania			✓
Slovakia	✓		
Slovenia			✓
Sweden			✓
Switzerland		✓	
Number of countries	8	3	9

A case definition of TBE is used for surveillance purpose in 10 countries (Table 4). Four countries use a possible, probable and confirmed case classification, while five countries only use a confirmed case classification.

Table 4. List of countries with case definition for TBE used in surveillance system with indication of the starting date and the case classification used. (Detailed description of the case definitions appears in Annex 3).

Country		Case classification		
	Year	Possible	Probable	Confirmed
Austria	2009			✓
Czech Republic	Unknown			✓
Estonia	2004		✓	✓
Finland	Unknown			✓
Germany	Unknown			✓
Norway	2008			✓
Poland	2005, revised in 2009	✓	✓	✓
Romania	2008, revised in 2011	✓	✓	✓
Sweden	2004	✓	✓	✓
Switzerland	1988, revised in 2007	✓	✓	✓

Case-based surveillance data are collected in twenty countries (67%). The type of data collected varies in particular countries and mostly contains information on demographic variables, notification source (general practitioner, hospital, laboratory, other), laboratory test details and date of notification (Table 5).

Table 5. Variables collected for TBE cases in EU/EFTA countries (n=20) indicating the number of countries using the variable (See Annex 4 for more details).

Type of case-based data	Number of countries
Notification source (general practitioner, hospital, laboratory, other)	19
Date of notification	19
Presumed date of infection	17
Case classification (according to the case definition)	7
Demographic variables (age, gender)	20
Geographical location of residence: Eurostat NUTS1 (usually country regions)	14
Geographical location of residence: Eurostat NUTS2 (usually country provinces)	10
Geographical location of residence: Eurostat NUTS3 (usually districts or counties)	17
Geographical location of presumed exposure: Eurostat NUTS1 (usually country regions)	10
Geographical location of presumed exposure: Eurostat NUTS2 (usually country provinces)	9
Geographical location of presumed exposure: Eurostat NUTS3 (usually districts or counties)	11
Exposure to tick-bite(s)	14
Occupational exposures	10
Information of presumed vehicle of infection (uncooked dairy products)	10
Hospitalisation	16
Laboratory test details	17
Clinical signs/symptoms	11
Clinical complications	8
Outcome (dead/alive/disabled)	15
Vaccination status	14
Imported case	16

In the survey the countries were asked to assess the sensitivity of their TBE surveillance and provide the specific methods used to measure this attribute (capture-recapture analysis, mathematical modelling and comparison of different sources). Of the 20 countries with TBE surveillance systems only Germany used capture-recapture analysis and in Poland the sensitivity of the surveillance system was assessed by comparing different sources. Representatives of twelve countries subjectively assessed their surveillance systems as national with fair sensitivity; two assessed their systems as national with important regional differences in sensitivity; one as national with overall low sensitivity; one as regional with very low sensitivity and one as regional with fair sensitivity (Table 6).

Table 6. Sensitivity of TBE surveillance in EU/EFTA countries assessed by the respondents of the questionnaire.

Country	Surveillance sensitivity
Austria	National, fair sensitivity
Belgium	Other
Czech Republic	National, fair sensitivity
Denmark	National, fair sensitivity
Estonia	National, fair sensitivity
Finland	National, fair sensitivity
France	Unknown
Germany	Unknown
Greece	National, fair sensitivity
Hungary	National, overall low sensitivity
Italy	Regional, very low sensitivity
Latvia	National, fair sensitivity
Lithuania	National, fair sensitivity
Norway	National, fair sensitivity
Poland	National, important regional differences in sensitivity
Romania	Regional, fair sensitivity
Slovakia	National, important regional differences in sensitivity
Slovenia	National, fair sensitivity
Sweden	National, fair sensitivity
Switzerland	National, fair sensitivity

Microbiological methods used for TBE diagnosis

Out of 30 participating countries 26 indicated that laboratory confirmation is used for TBE cases on their territory. In Malta, Portugal and Cyprus there is no possibility for laboratory confirmation of TBE cases.

Laboratory tests used to diagnose suspected TBE cases differ depending on the country. The most popular tests to confirm TBE are ELISA and RT-PCR. Detailed information on microbiological methods is presented in Table 7 below.

Table 7. Laboratory test used for diagnosis of TBE cases in EU/EFTA countries

Country*	Indirect detection**						Direct detection**		
	ELISA	IFA	HIA	CFT	WB	NT	RT-PCR	VI	SEQ
Austria	✓		✓			✓	✓	✓	✓
Belgium	✓						✓		
Bulgaria	✓			✓			✓	✓	✓
Czech Republic	✓	✓		✓		✓	✓	✓	
Denmark	✓						✓		
Estonia	✓								
Finland	✓		✓						
France	✓	✓				✓	✓	✓	✓
Germany	✓	✓	✓			✓	✓	✓	✓
Greece									
Hungary	✓	✓	✓			✓	✓	✓	✓
Ireland	✓								
Latvia	✓						✓		
Lithuania	✓	✓							
Netherlands	✓								
Norway	✓	✓					✓		✓
Poland	✓								
Romania	✓								
Slovakia	✓			✓		✓	✓		
Slovenia	✓			✓			✓	✓	
Spain	✓						✓		✓
Sweden	✓					✓	✓	✓	✓
Switzerland	✓	✓					✓		
United Kingdom	✓				✓		✓		
Total	23	7	4	4	1	7	16	8	8

** No information was available for Italy and Luxembourg, Greece did not provide information on the tests used.*

***ELISA: enzyme-linked immunosorbent assay; IFA: immunofluorescence assay; HIA: haemagglutination inhibition assay; CFT: complement fixation test; WB: Western blot; NT: neutralisation test; RT-PCR: reverse transcriptase polymerase chain reaction; VI: virus isolation; SEQ: sequencing.*

Accessibility to laboratories which can perform diagnostic tests for TBE varies among countries. Countries with high-risk areas (where TBE virus circulation is notably intensive) have the largest number of laboratories, e.g. Czech Republic, Poland and Estonia. In seven countries there is one laboratory which performs diagnostic tests for TBE cases, in eight countries there are 2–5 laboratories, and in eight countries more than five laboratories (Table 8). A total of 15 countries have reference laboratories for TBE. Eight of them are officially nominated by the respective ministries of health for reference diagnostics (Austria, Bulgaria, Germany, Hungary, Lithuania, Norway, Spain, and Switzerland).

The number of processed samples for diagnosis of TBE cases in the country laboratories ranges from fewer than 100 in seven countries to more than 1 000 in five countries. Microbiological testing results are reconciled (linked) with epidemiological case reports and available at the national level in 18 countries . Detailed information for each country is presented in Table 8 below.

Table 8. Number of laboratories and samples processed for TBE diagnosis in EU/EFTA countries.

Country	Number of laboratories	Number of reference laboratories	Number of processed samples	Microbiological testing results reconciled with epidemiological case reports
Austria	>5	One	>1000	Yes
Belgium	N/A	One	Unknown	No
Bulgaria	1	One	<100	Yes
Czech Republic	>5	One	750-<1000	Yes
Denmark	1	N/A	<100	No
Estonia	>5	N/A	250-<500	Yes
Finland	2-5	N/A	Unknown	Yes
France	2-5	N/A	100-<250	No
Germany	>5	One	>1000	Yes
Greece	N/A	N/A	Unknown	No
Hungary	1	One	>1000	Yes
Ireland	1	N/A	<100	Yes
Italy	>5	More than one	Unknown	No
Latvia	2-5	One	>1000	Yes
Lithuania	2-5	One	500-<750	Yes
Luxembourg	N/A	Unknown	Unknown	Unknown
Netherlands	2-5	N/A	<100	No
Norway	2-5	One	100-<250	Yes
Poland	2-5	One	750-<1000	Yes
Romania	2-5	N/A	<100	Yes
Slovakia	>5	One	250-<500	Yes
Slovenia	1	N/A	250-<500	No
Spain	1	One	<100	Yes
Sweden	>5	One	>1000	Yes
Switzerland	>5	One	Unknown	Yes
United Kingdom	1	N/A	<100	Yes

In nine countries, reference laboratories participated in an international External Quality Assurance (EQA) in relation to TBE diagnosis. Five of them had undergone two to four EQA within five years, two countries had participated in just one EQA and one country in five (Table 9).

Table 9. Participation of TBE reference laboratories in international External Quality Assurance

Country	EQA frequency over five years	Latest EQA
Austria	2-4	2010
France	1	More than two years ago
Hungary	2-4	2009
Italy	Unknown	Unknown
Lithuania	5	2010
Norway	2-4	2011
Slovakia	2-4	2010
Spain	1	More than two years ago
Sweden	2-4	2010

Literature review on TBE data availability

Of the 1 050 abstracts selected on TBE, 125 met the inclusion criteria, 913 were excluded and 12 full texts were not available. The most common reason for exclusion was that the abstracts discussed issues that were not concordant with the objectives of the study (Annex 5). During the complementary literature review a total of 15 publications were identified: data could be extracted from seven articles, two papers investigated TBE risk using seroprevalence in humans and six discussed the prevalence of the TBE virus in animals and ticks.

In total 86 publications provided data on human cases and data could be extracted from 73 articles. Information on animals and vectors was presented in 54 articles and 13 articles were devoted to serological surveys of humans (Table 10).

Table 10. Abstracts on TBE fulfilling inclusion criteria by study type and subject

Study type	Abstract fulfilled inclusion criteria	Subject of the study	
		TBE in humans	TBE in animals, vector
Case report	16	16	
Case series	29	29	
Cross-sectional			
Cohort			
Case-control	1	1	
Serological survey	16	13	3
Outbreak report	2	2	
Other or unknown	76	25	51
Total	140	86	54

During the 10-year period evaluated, 72% of the articles on TBE risk came from 20% (6) of the countries with high endemic TBE virus circulation: Czech Republic, Germany, Lithuania, Slovenia, Sweden and Switzerland. The majority of articles referred to the risk of TBE in Germany (Annex 5).

Overview of TBE epidemiology in EU/EFTA countries

To obtain an overview of TBE epidemiology in Europe, surveillance data sent by countries were used (13 countries, n = 12 344), along with summary data provided by several countries for the purpose of this report (four countries, n = 17 741) (Table 11).

Table 11. TBE surveillance data availability in EU/EFTA for the period 2000–2010

Country	Period for which TBE data are available			Number of cases provided by countries for the purpose of the report		
	Aggregated	Case-based		Aggregated[d]	Case-based[d]	Overview report
Austria	2000–2001	2002–2010		113	656	
Belgium[a]		2000–2010				
Bulgaria[b]						
Cyprus[b]						
Czech Republic		2000–2010				7371
Denmark		2001–2010			44	
Estonia	2000–2007	2008–2010		1471	470	
Finland		2000–2010			304	
France[c]		2000–2010				
Germany		2001–2010				3126
Greece[a]						
Hungary		2000–2010		686		
Iceland[b]						
Ireland[b]						
Italy		2001–2010		159		
Latvia	2000–2006	2007–2010		1928	1177	
Lithuania	2000–2009	2010			612	4449
Luxembourg[b]						
Malta[b]						
Netherlands[b]						
Norway		2000–2010		62		
Poland		2000–2010			2680	
Portugal[b]						
Romania		2008–2010			14	
Slovakia	2000	2001–2010		184	698	
Slovenia		2000–2010				2795
Spain[b]						
Sweden		2005–2010			1086	
Switzerland[c]		2000–2010				
United Kingdom[b]						
Total number	-	-		4603	7741	17741

[a]No cases; [b]No TBE surveillance; [c]No data provided; [d]Data provided in the format of the project. This format is based on TESSy metadata specifications.

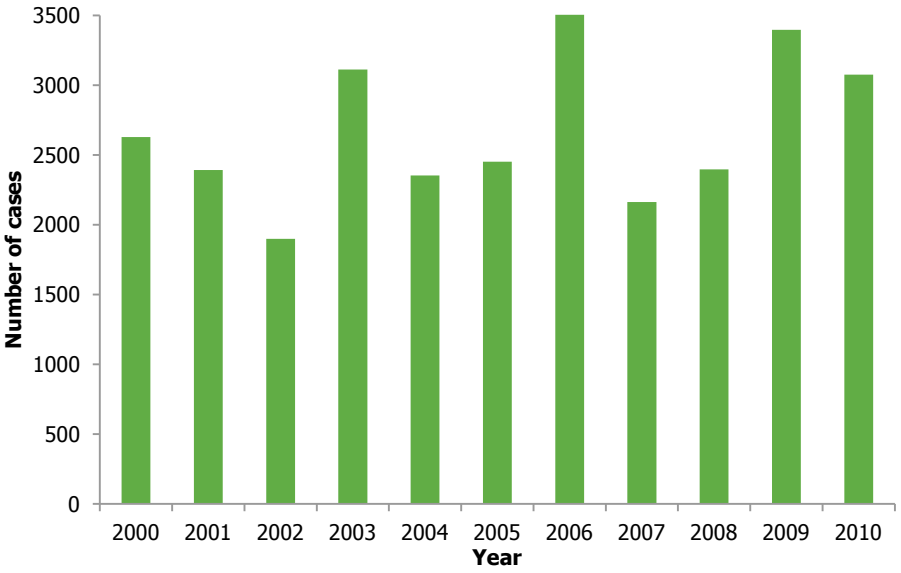
During the 2000–2010 period, the overall number of reported TBE cases (all case definitions combined) stayed relatively stable, with notable increases in 2003, 2006 and 2009–2010 (Figure 2). The Czech Republic reported 25% of all reported cases, Lithuania 15%, Latvia and Germany 11% each and Slovenia 10%. In Europe, TBE cases occurred more commonly among men than women and the number of reported cases increased with age (Figure 3). The majority of cases reported during 2000–2010 showed disease onset between July and October (Figure 4). However, seasonal data are missing for the countries that reported the most cases.

Figure 5 presents an overview of the TBE situation in Europe. The level of spatial precision and the time window of the reported data differed according to the country. The incidence is based on the place of residence of the patient – which might be different to the place of infection – because information on place of infection was not systematically available. Areas with very low incidence might be artefacts. The map shows that the key risk areas for TBE are located in central and eastern Europe (notably the Baltic states) and the Nordic countries, extending to Switzerland in the west of Europe and to northern Italy and the Balkan countries in the south. Data retrieved from

the literature for France revealed 29 cases between 2000 and 2006 and identified Alsace as the main risk area (data not displayed on the map, Annex 5).

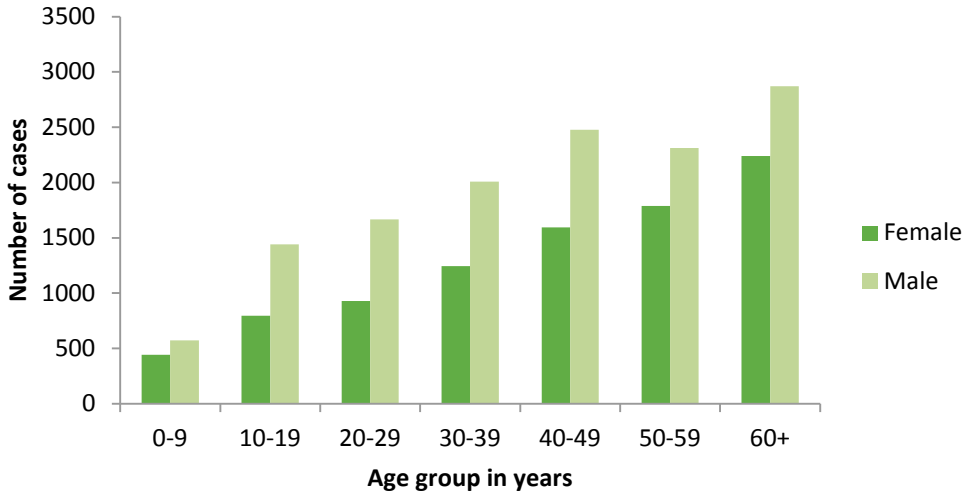
Summarised information for each country that implemented TBE surveillance is presented in the *Country profiles* section. The country profiles have not been prepared for countries where no surveillance was implemented during the period 2000–2010, and consequently no systematically recorded information on TBE risk could be presented. These countries are: Bulgaria, Cyprus, Iceland, Ireland, Luxembourg, Malta, the Netherlands, Portugal, Spain, and United Kingdom. The figures for each country reflect the level of detail available on the basis of the information provided. Additional information is provided by country based on the literature search. During the literature review three publications were identified that could help to estimate the risk of TBE in countries where no surveillance system exists [15-17]. These articles provide information for Luxembourg, Netherlands and Spain.

Figure 2. Number of TBE cases, regardless of the applied case definition, by year reported in 16 EU/EFTA countries, 2000–2010 (n= 29 381).



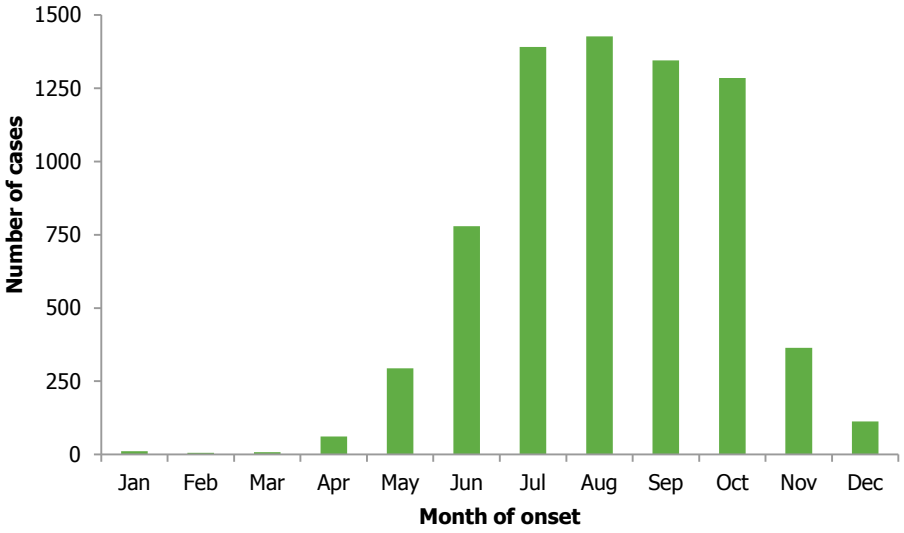
NOTE: The figure is based on data provided by Austria, Czech Republic, Denmark (no data for 2000), Estonia, Finland, Germany (no data for 2000), Hungary, Italy (no data for 2000), Latvia, Lithuania, Norway, Poland, Romania (data covering 2008–2010), Slovakia, Slovenia, and Sweden (data covering 2005–2010).

Figure 3. Number of TBE cases, regardless of the applied case definition, by age group and gender reported in 16 EU/EFTA countries, 2000–2010 (n= 22 378).



NOTE: Figure is based on data provided by Austria, Czech Republic, Denmark (no data for 2000), Estonia, Finland, Germany (no data for 2000), Hungary, Italy (no data for 2000), Latvia, Lithuania, Norway, Poland, Romania (data covering 2008–2010), Slovakia, Slovenia, and Sweden (data covering 2005–2010).

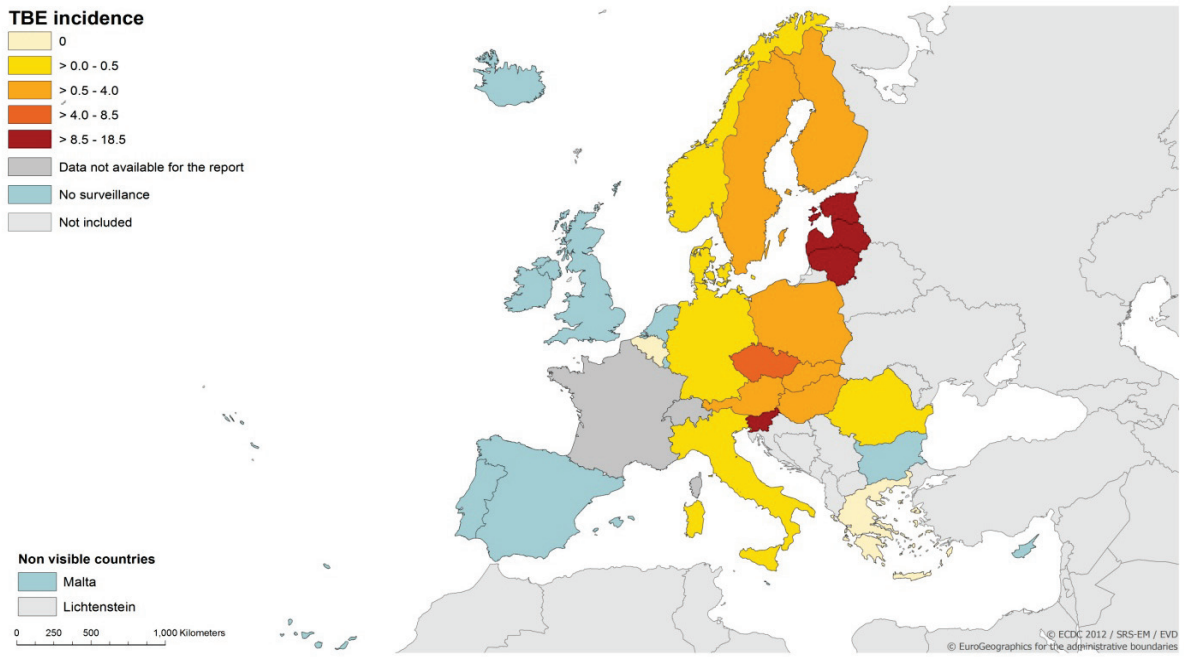
Figure 4. Number of TBE cases, regardless of the applied case definition, by month of onset reported in nine EU/EFTA countries, 2000–2010 (n= 7 083).



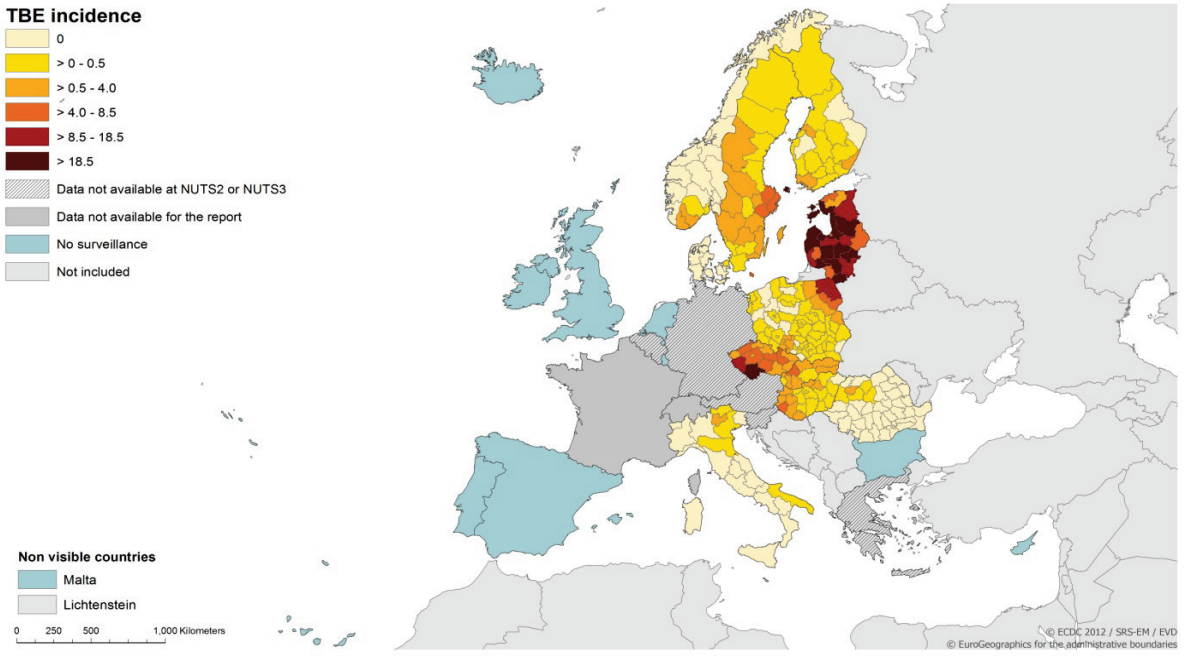
NOTE: Figure is based on data from Denmark (no data for 2000), Estonia, Finland, Latvia, Lithuania, Poland, Romania (data covering 2008–2010), Slovakia, and Sweden (data covering 2005–2010).

Figure 5. TBE average annual incidence rate per 100 000 inhabitants in the EU/EFTA. (A) At country level, (B) at lower administrative level NUTS 2 (Italy) or NUTS 3.

A



B



Note: The maps are based on the following data:

1. *Surveillance data submitted by the following countries: Austria (2000–2010, n=769), Denmark (2001–2010, n=28), Estonia (2008–2010, n=469), Finland (2000–2010, n=304), Hungary (2000–2010, n=686), Italy (2001–2010, n=159), Latvia (2007–2010, n=1 177), Lithuania (2010, n=612), Norway (2000–2010, n=53), Poland (2000–2010, n=2 680), Romania (2008–2010, n=14), Slovakia (2000–2010, n=790), Sweden (2005–2010, n=1 086). Additionally the map contains surveillance figures provided for the report by Czech Republic (2000–2010, n=6 583), Germany (2000–2010, n=3 126) and Slovenia (2000–2010, n=2 795). The administrative level to which the data referred was dependent on the accuracy of the country data.*
2. *Population data were retrieved from Eurostat (http://epp.eurostat.ec.europa.eu/portal/page/portal/eurostat/home/). The missing value of NUTS2 and NUTS3 population were computed. Over the study period a linear regression was applied for each spatial unit using STATA 10. Both graphical and statistical cross–checks were made to control potential outliers after extrapolation.*

Country profiles

Austria

The information below is based on the TBE surveillance survey (Table 12) and aggregated surveillance data provided by the country (n=769). TBE is endemic in all of Austria's federal states. In the pre-vaccination era, before 1980 [18], the numbers of hospitalised TBE cases recorded annually ranged from 300 to 700. Today, vaccination coverage is at about 85% of the total population in Austria which – because of the effectiveness of the vaccine [10] – has led to a dramatic decline in the disease in Austria, with the numbers of annual cases ranging from 50 to 100 in the last decade (Figure 6). A majority of the cases reported are males and the number of cases increase with age (Figure 7).

The incidence of TBE in the unvaccinated population is similar to that in the pre-vaccination era (approximately five per 100 000 inhabitants) indicating that – despite the lower numbers of human cases – virus circulation in nature has not waned.

Austria has more than five laboratories offering TBE diagnosis and they process over 1 000 samples annually.

Data on human cases were extracted from seven articles [13, 19–24]. Two papers investigated TBE risk using alternative methods to human surveillance during the period 2000–2010. One article investigated the diagnostic and epidemiological aspects of viral encephalitis in dogs [25]. The analysis of CSF was performed on 112 out of 119 subjects involved in the study. TBE infection was confirmed in eight dogs. The other study aimed at determining the prevalence of TBE virus in a tick population in the district of Burgenland [26]. Overall, 306 ticks were examined for the presence of TBE virus. None of them was positive for the TBE virus.

Table 12. Overview of TBE surveillance in Austria

Indicator	Description
Type of surveillance	Comprehensive
Type of reporting	Mandatory
Type of data recorded	Case-based
Cases routinely reported	Cases with CNS infection
Case definition	Yes
Provision of surveillance data	Aggregated (2000–2001), case-based (2002–2010)
Estimated sensitivity of surveillance	National, fair sensitivity
Reference laboratory	Institute of Virology, Medical University of Vienna http://www.virologie.meduniwien.ac.at

Figure 6. Number of TBE cases (bars) and incidence per 100 000 inhabitants (line) by year, Austria (n=769)

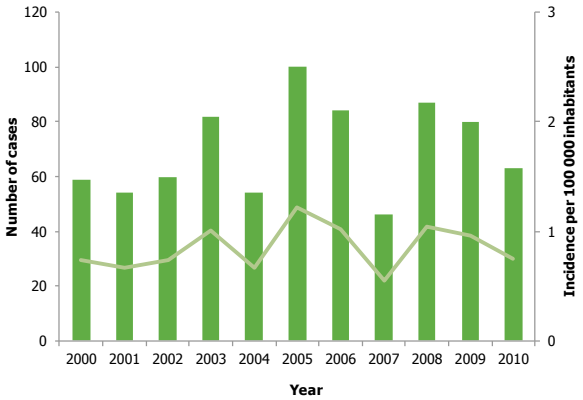
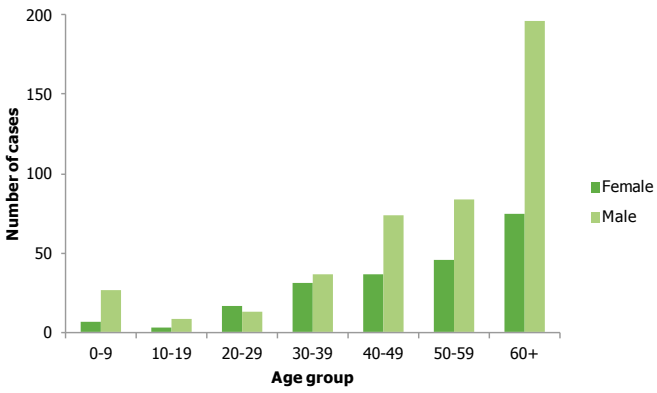


Figure 7. Number of TBE cases by gender and age, Austria (n=656, data from 2000–2010 pooled)



Belgium

The information below is based on the TBE surveillance survey (Table 13). During 2000–2010, there were no TBE cases reported. TBE is not known to be endemic in Belgium. Despite having climatic and environmental conditions that are conducive to the circulation of the TBE virus, no autochthonous cases of TBE have ever been reported in Belgium.

There is one reference laboratory, located within the National Reference Laboratory for Vector-borne Diseases in Brussels.

During the period 2000–2010, there was one paper which investigated TBE risk in humans. The objective of the study was to identify the TBE cases among patients with a viral CNS infection of unknown etiology [27]. Overall, 233 sera and/or CSF samples from eight centres in Belgium, France, the Netherlands and Sweden were examined for the presence of the TBE virus. None of the four patients from Belgium were confirmed as a TBE case.

Table 13. Overview of TBE surveillance in Belgium

Indicator	Description
Type of surveillance	Sentinel
Type of reporting	Voluntary
Type of data recorded	Case-based
Cases routinely reported	All cases
Case definition	N/A
Provision of surveillance data	N/A
Estimated sensitivity of surveillance	N/A
Reference laboratory	National Reference Laboratory for Vector-borne Diseases, Queen Astrid Military Hospital, Brussels

Czech Republic

The information below (Table 14) is based on the TBE surveillance survey and summary figures provided by the country. TBE is endemic in the Czech Republic and 500–1 000 cases are reported annually (Figure 8 and Figure 9). The Czech Republic is one of the countries with the highest incidence of TBE in Europe. TBE affects the whole country but the risk is significantly higher in the South Bohemian region (Figure 10).

There are more than five laboratories offering TBE diagnosis and they process between 750 and 1 000 samples annually.

Data were extracted on human cases from nine articles [13, 22–24, 28–32]. During the period 2000–2010, there were six papers investigating the risk of TBE using alternative methods to human surveillance. One of them focused on the epidemiological monitoring of seroprevalence in humans residing in Rimov [33]. A total of 280 subjects were examined. Seropositivity to the TBE virus was estimated at 16%. The findings resulted in increased vaccination coverage (from 15% to 65%) in the given community. The remaining five articles examined the relationship between geographical factors and the distribution of ticks [34–38]. Overall, 11 541 ticks were tested for the presence of the TBE virus. The sampling was conducted in the South Bohemian region and the northern Moravian, Šumava and Krkonoše mountains. The studies confirmed the shift of *Ixodes ricinus* to higher altitudes, which may lead to the expansion of the TBE risk area.

Table 14. Overview of TBE surveillance in the Czech Republic

Indicator	Description
Type of surveillance	Comprehensive
Type of reporting	Mandatory
Type of data recorded	Case-based
Cases routinely reported	Cases with CNS infection
Case definition	Yes
Provision of surveillance data	No, summary figures for this report
Estimated sensitivity of surveillance	National, fair sensitivity
Reference laboratory	National Reference Laboratory for Arboviruses, Institute of Public Health, Ostrava

Figure 8. Number of TBE cases (bars) and incidence per 100 000 inhabitants (line) by year, Czech Republic (n=7 371)

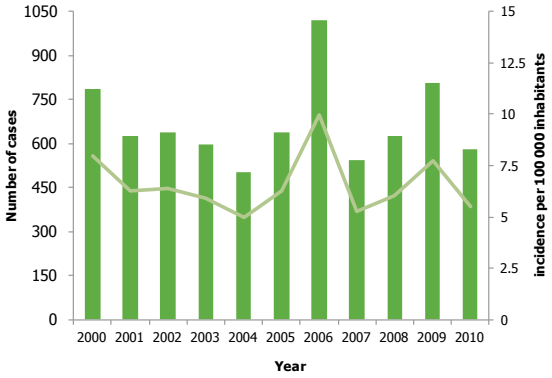


Figure 9. Number of TBE cases by gender and age, Czech Republic (n=7 371, data from 2000–2010 pooled)

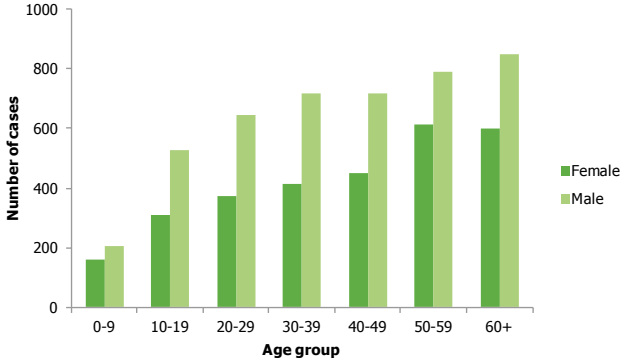
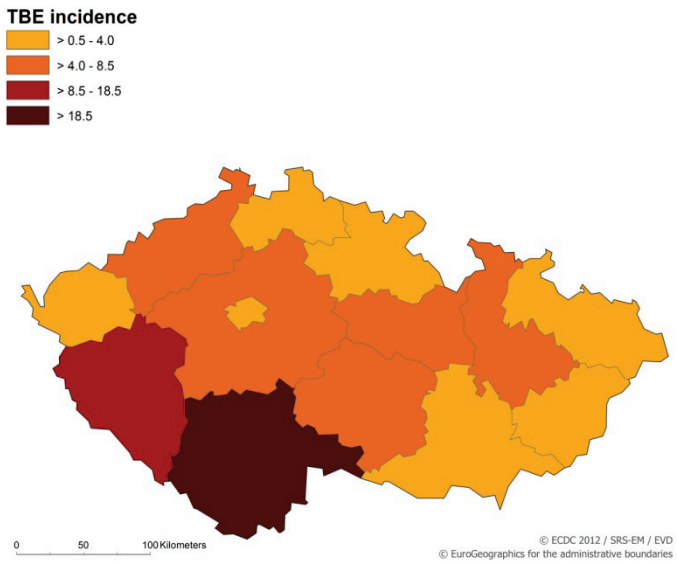


Figure 10. TBE average annual incidence rate per 100 000 inhabitants by NUTS3, Czech Republic (n=6 583, period 2000–2010)



Denmark

The information in Table 15 below is based on the TBE surveillance survey and case-based surveillance data provided by the country (n=44). In Denmark, TBE occurs sporadically, with 5–10 cases reported annually (Figure 11 and Figure 12). The island of Bornholm in the Baltic Sea is recognised as an area where TBE is endemic (Figure 13). TBE is not a notifiable disease in Denmark. The occurrence of TBE cases is monitored by the Department of Virology at the National Institute for Health Data and Disease Control (Statens Serum Institut). This is the only laboratory in Denmark performing diagnostics of TBE infections and it processes less than 100 samples annually.

Data on human cases were extracted from three articles [23, 24, 39]. During the period 2000–2010, three papers investigated TBE risk using alternative methods to human surveillance. Two of them examined the prevalence of TBE virus antibodies in animals [40, 41]. A total of 354 blood samples were collected from different regions of Denmark. The seroprevalence was 8.7% in roe deer and 30.4% in dogs. The third study attempted to determine the prevalence of TBE virus in ticks [42]. Overall, 810 ticks were collected and tested for TBE virus on Bornholm and 20 of them were found positive.

Table 15. Overview of TBE surveillance in Denmark

Indicator	Description
Type of surveillance	Comprehensive
Type of reporting	Not well-defined
Type of data recorded	Case-based
Cases routinely reported	All cases
Case definition	No
Provision of surveillance data	Case-based (2001-2010)
Estimated sensitivity of surveillance	National, fair sensitivity
Reference laboratory	No

Figure 11. Number of TBE cases (bars) and incidence per 100 000 inhabitants (line) by year, Denmark (n=44)

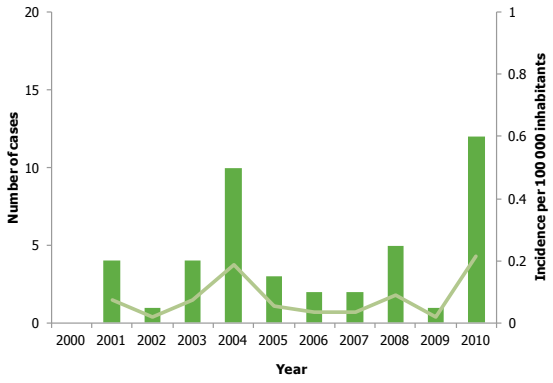


Figure 12. Number of TBE cases by gender and age, Denmark (n=44, data from 2001–2010 pooled)

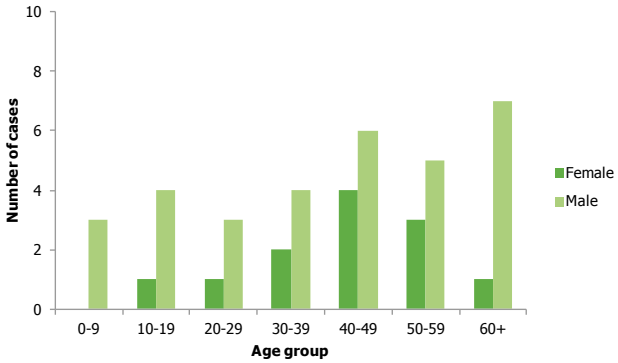
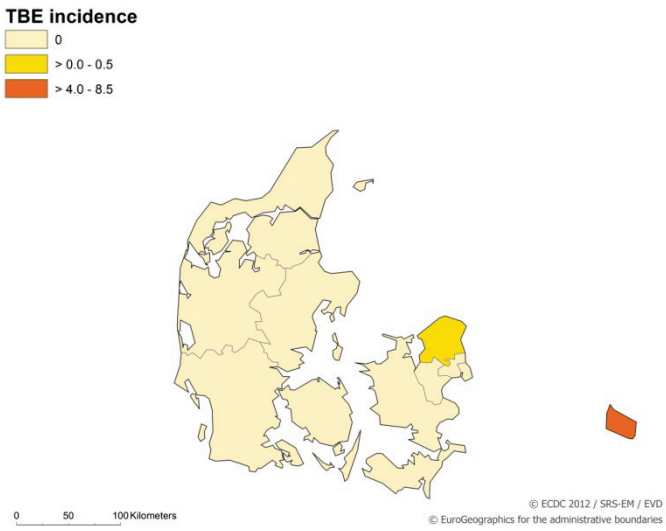


Figure 13. TBE average annual incidence rate per 100 000 inhabitants by place of exposure (NUTS3), Denmark (n=28, period 2001–2010)



Estonia

The information in Table 16 below is based on the TBE surveillance survey and case-based and aggregated surveillance data provided by the country (n=1 941). In Estonia TBE is endemic and 150–250 cases are reported annually (Figures 14 and 15). Estonia ranks among the countries with the highest incidence of TBE in Europe. The majority of TBE cases occurred in the western part of the country (Figure 16). A surveillance case definition has been in use since 2004.

Estonia has more than five laboratories offering TBE diagnosis, processing between 250 and 500 samples annually.

Data were extracted on human cases from five articles [13, 23, 24, 43, 44]. During the period 2000–2010, two papers investigated TBE risk using alternative methods to human surveillance. Both of them discussed the genetic analysis of TBE virus strains [45, 46]. The results confirmed the co-circulation of the three known TBE virus subtypes in Estonia: European, Far-Eastern and Siberian.

Table 16. Overview of TBE surveillance in Estonia

Indicator	Description
Type of surveillance	Comprehensive
Type of reporting	Mandatory
Type of data recorded	Case-based
Cases routinely reported	All symptomatic cases (including tick-borne fever)
Case definition	Yes (since 2004)
Provision of surveillance data	Aggregated (2000–2007), case-based (2008–-2010)
Estimated sensitivity of surveillance	National, fair sensitivity
Reference laboratory	No

Figure 14. Number of TBE cases (bars) and incidence per 100 000 inhabitants (line) by year, Estonia (n=1 941)

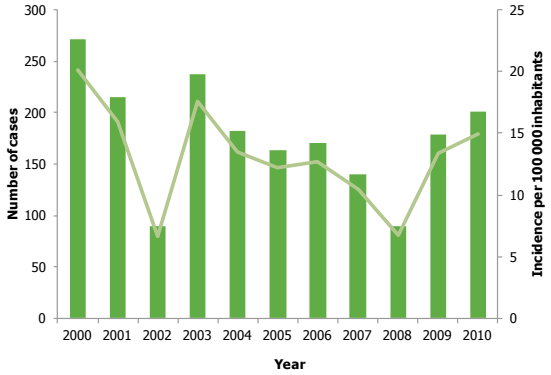


Figure 15. Number of TBE cases by gender and age, Estonia (n=1 941, data from 2000–2010 pooled)

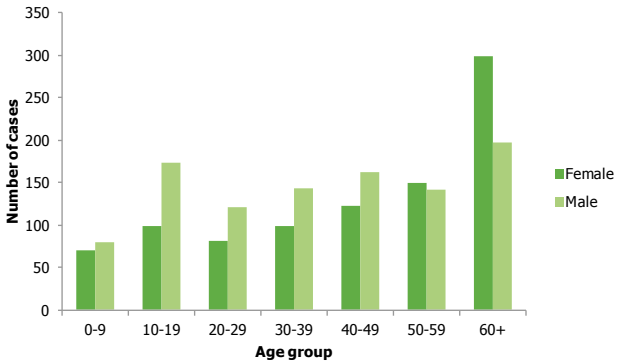
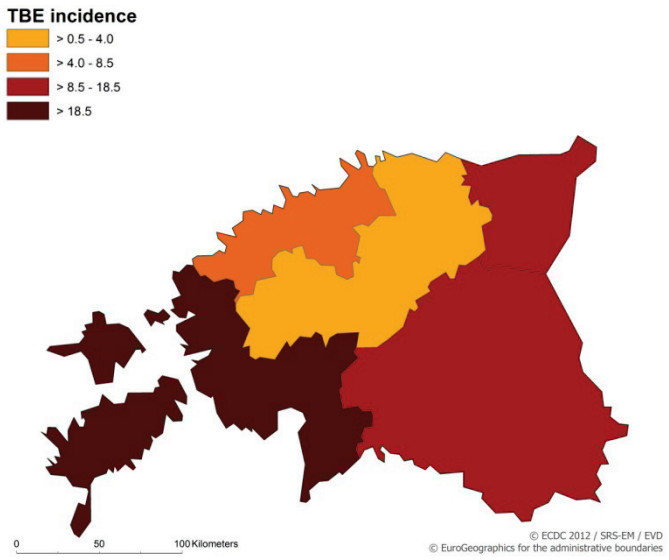


Figure 16. TBE average annual incidence rate per 100 000 inhabitants by NUTS3, Estonia (n=469, period 2008–2010)



Finland

The information in Table 17 below is based on the TBE surveillance survey and case-based surveillance data provided by the country (n=304). In Finland, TBE is endemic, with 20–40 cases reported annually (Figures 17 and 18), the majority of which come from the Åland Islands (Figure 19).

There are between two and five laboratories offering TBE diagnosis.

Data on human cases were extracted from five articles [13, 23, 24, 47, 48]. During the period 2000–2010, five papers investigated TBE risk using alternative methods to human surveillance. Three of them focused on mapping the distribution of the tick species and the different TBE virus subtypes [49–51]. A total of 3 128 ticks were collected: the prevalence of the TBE virus ranged from 0.1% in the Turku archipelago to 3.3% in the Kokkola archipelago. The remaining two papers discussed the screening of rodents and wild birds for viral pathogens such as the TBE virus. The TBE virus infection was confirmed in 24 out of 202 rodents [52]. None of the birds examined tested positive for the TBE virus [53]. The study concluded that the role of migratory birds in transmitting ticks infected with the TBE virus should not be underestimated.

Table 17. Overview of TBE surveillance in Finland

Indicator	Description
Type of surveillance	Comprehensive
Type of reporting	Mandatory
Type of data recorded	Case-based
Cases routinely reported	All cases
Case definition	Yes
Provision of surveillance data	Case-based (2000–2010)
Estimated sensitivity of surveillance	National, fair sensitivity
Reference laboratory	No

Figure 17. Number of TBE cases (bars) and incidence per 100 000 inhabitants (line) by year, Finland (304)

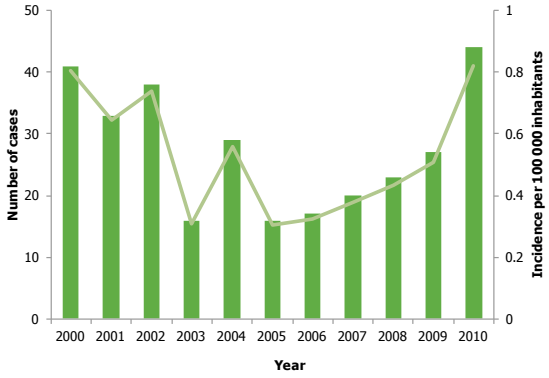


Figure 18. Number of TBE cases by gender and age, Finland (n=304, data from 2000–2010 pooled)

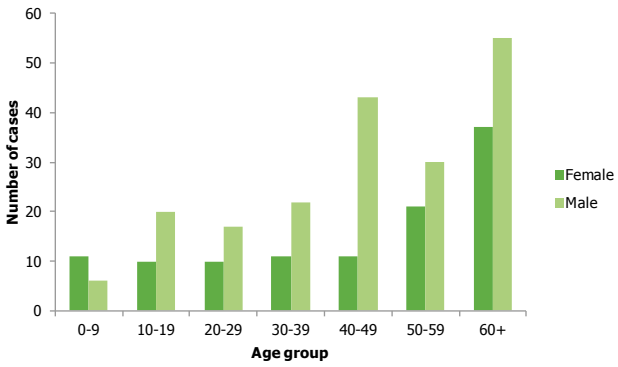
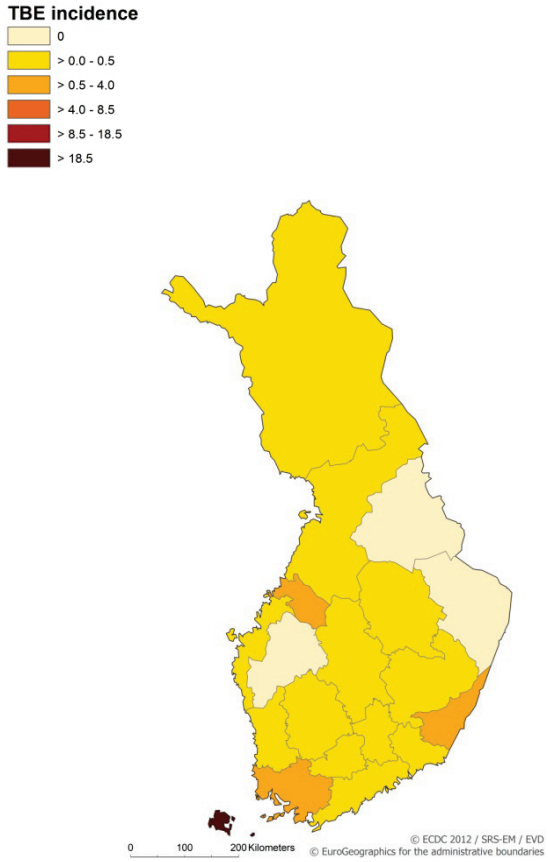


Figure 19. TBE average annual incidence rate per 100 000 inhabitants by NUTS3, Finland (n=304, period 2000–2010)



France

The information in Table 18 below is based on the TBE surveillance survey. A few cases of TBE are reported in France annually. There are between two and five laboratories offering TBE diagnosis, processing around 100–250 samples annually. One reference laboratory is located at the National Reference Centre for Arboviruses in Paris.

Data on human cases were extracted from three articles [23, 54, 55]. One article investigated TBE risk on the basis of the seroprevalence of TBE virus among occupationally exposed forest workers in eastern France [56]. Overall, 2 975 individuals were examined for the presence of the TBE virus. The prevalence of the TBE virus was estimated at 3.4%. Among the provinces included in the study, the highest seroprevalence was observed in Alsace (26.9%) and Lorraine (16.5%).

Table 18. Overview of TBE surveillance in France

Indicator	Description
Type of surveillance	Other (National Reference Centre for Arboviruses)
Type of reporting	Not well defined
Type of data recorded	Case-based
Cases routinely reported	Cases with CNS infection
Case definition	No
Provision of surveillance data	N/A
Estimated sensitivity of surveillance	N/A
Reference laboratory	National Reference Centre for Arboviruses, Paris http://www.pasteur.fr

Germany

The information in Table 19 below is based on the TBE surveillance survey and summary figures provided by the country (Figures 20 and 21). TBE is known to be endemic in Germany and high-risk areas are located in Bavaria and Baden-Württemberg. There are more than five laboratories offering TBE diagnosis and they process over 1 000 samples annually. A veterinary reference laboratory is located at the Friedrich Löffler Institute in Jena, and a consultant laboratory for human disease at the Robert Koch Institute in Berlin.

Data on human cases were extracted from sixteen articles [13, 23, 24, 57–69]. Thirteen papers investigated TBE risk using alternative methods to human surveillance during the period 2000–2010. One of the articles investigated seroprevalence in patients with suspected meningitis in Rhineland-Palatinate [70]. A total of 163 individuals were included in the study. No TBE virus specific antibodies were detected. Another paper discussed the role of roe deer as a host for *Ixodes* ticks [71]. A total of 91 roe deer were examined to estimate tick abundance. The objective of five studies was to assess the prevalence of the TBE virus in ticks [72-76]. Overall, 11 640 ticks were collected in the states of Thuringia, Saxony-Anhalt, Mecklenburg-Western Pomerania, Bavaria and Baden-Württemberg. The latter two regions are regarded to be TBE high-risk areas. The remaining five articles discussed serological investigation for the presence of the TBE virus in animals [77–81]. The observed seroprevalence was: 2.9% in horses, 2.6% in monkeys, 9% in sheep, 4.8% in goats, 42.7% in dogs and 10% in rodents.

Table 19. Overview of TBE surveillance in Germany

Indicator	Description
Type of surveillance	Comprehensive
Type of reporting	Mandatory
Type of data recorded	Case-based
Cases routinely reported	All cases
Case definition	Yes
Provision of surveillance data	No, summary figures for this report
Estimated sensitivity of surveillance	N/A
Reference laboratory	Consultant Laboratory on TBE, Robert Koch Institute, Berlin www.rki.de/konsiliarlabor-fsme

Figure 20. Number of TBE cases (bars) and incidence per 100 000 inhabitants (line) by year, Germany (3 126)

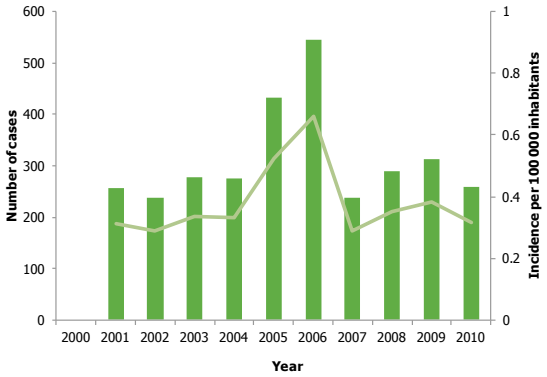
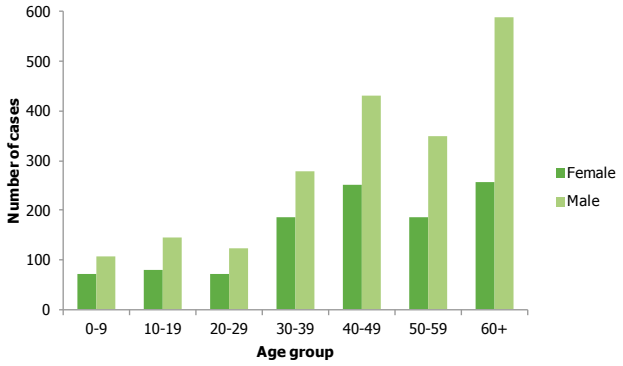


Figure 21. Number of TBE cases by gender and age, Germany (n=3 125, data from 2001–2010 pooled)



Greece

The information in Table 20 below is based on the TBE surveillance survey. During the period 2000–2010, there were no TBE cases reported. Information on the epidemiology of TBE in Greece is limited.

During the period 2000–2010, one paper investigated the risk of TBE in humans. The objective of the study was to identify TBE cases among healthy individuals and patients with central nervous system infection residing in the prefectures of northern Greece [82]. A total of 1 223 individuals were examined for the presence of the TBE virus. Among the healthy individuals seropositivity was estimated to be 2.06%. None of the patients was diagnosed as a TBE case.

Table 20. Overview of TBE surveillance in Greece

Indicator	Description
Type of surveillance	Comprehensive
Type of reporting	Mandatory
Type of data recorded	Case-based
Cases routinely reported	Cases with CNS infection
Case definition	Yes
Provision of surveillance data	N/A
Estimated sensitivity of surveillance	National, fair sensitivity
Reference laboratory	No

Hungary

The information in Table 21 below is based on the TBE surveillance survey (and aggregated surveillance data provided by the country (n=686, Figures 22 and 23). TBE is endemic in Hungary. Natural foci of TBE are present in Transdanubia and the northern part of the country (Figure 24).

There is only one laboratory offering TBE diagnosis and it processes more than 1 000 samples annually. One reference laboratory is located at National Reference Laboratory for Viral Zoonoses in Budapest.

Data on human cases were extracted from three articles [13, 24, 83]. One paper investigated the seroprevalence of the TBE virus in domestic animals across north eastern Hungary [84]. A total of 400 subjects were examined for the presence of the TBE virus. TBE infection was documented in 26.5% of cattle, 7.0% of sheep and 0% of horses.

Table 21. Overview of TBE surveillance in Hungary

Indicator	Description
Type of surveillance	Comprehensive
Type of reporting	Mandatory
Type of data recorded	Case-based
Cases routinely reported	Cases with CNS infection
Case definition	No
Provision of surveillance data	Aggregated (2000–2010)
Estimated sensitivity of surveillance	National, overall low sensitivity
Reference laboratory	National Reference Laboratory for Viral Zoonoses, Budapest http://www.oek.hu

Figure 22. Number of TBE cases (bars) and incidence per 100 000 inhabitants (line) by year, Hungary (n=686)

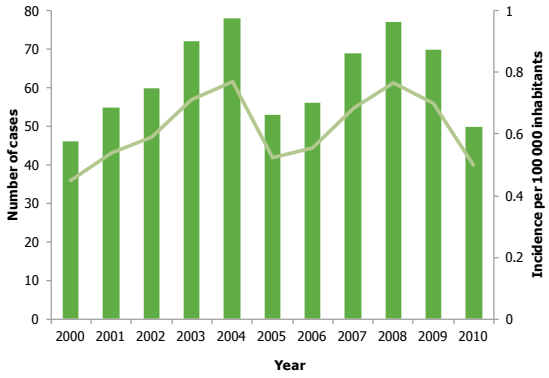


Figure 23. Number of TBE cases by gender and age, Hungary (n= 686, data from 2000–2010 pooled)

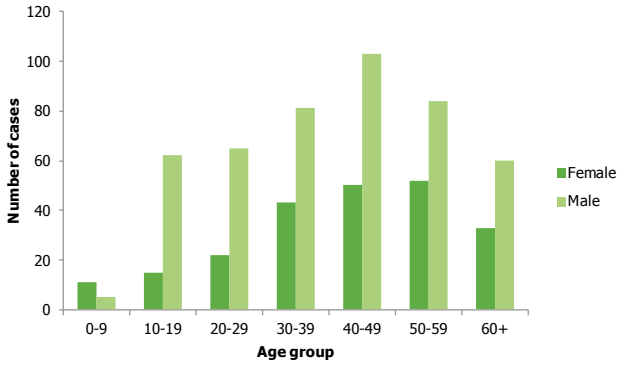
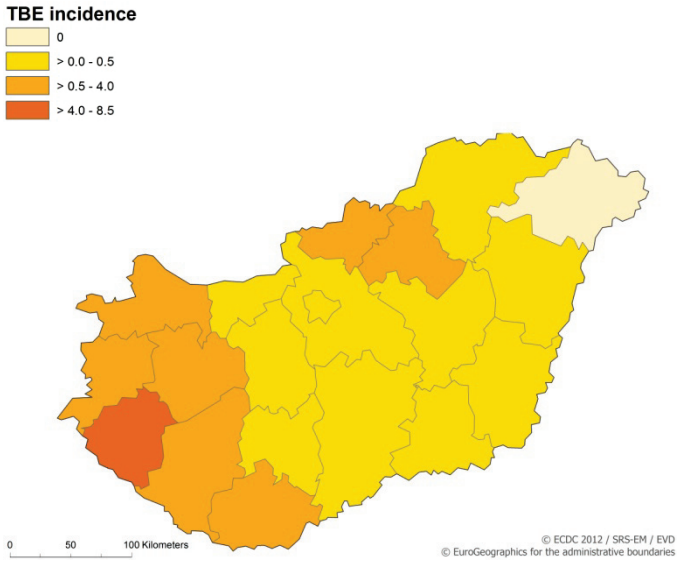


Figure 24. TBE average annual incidence rate per 100 000 inhabitants by NUTS3, Hungary (n=686, period 2000–2010)



Italy

The information in Table 22 below is based on the TBE surveillance survey (and aggregated surveillance data provided by the country (n=159, Figures 25 and 26). TBE incidence in Italy is very low and is restricted to the central and north eastern part of the country (Figure 27). There are over five laboratories offering TBE diagnosis and more than one reference laboratory in Italy: one national and several regional laboratories.

Data on human cases were extracted from six articles [23, 24, 85–88]. During the period 2000–2010, ten papers investigated TBE risk using alternative methods to human surveillance. All studies were performed at regional level. Four seroprevalence surveys were performed in humans, involving a total of 1 694 subjects in central and northern Italy [89–92]. According to the results of these studies, the proportion of inhabitants positive for TBE virus antibodies ranged from 0.1% in Tuscany to 4.3% in the Friuli-Venezia region. Additionally, four studies of TBE virus detection in ticks [93–96] and four animal seroprevalence surveys were performed [94, 96–98], exclusively in northern regions of Italy, where TBE cases are reported to the surveillance system. Results of the studies confirmed circulation of the TBE virus in this region. In the south of Italy there is no evidence of disease presence, but neither is there much evidence of its absence.

Table 22. Overview of TBE surveillance in Italy

Indicator	Description
Type of surveillance	Comprehensive
Type of reporting	Not well defined
Type of data recorded	Case-based
Cases routinely reported	All symptomatic cases (including tick-borne fever)
Case definition	No
Provision of surveillance data	Aggregated (2001–2010)
Estimated sensitivity of surveillance	Regional, fair sensitivity
Reference laboratory	Department of Infectious, Parasitic and Immune Mediated Diseases, Istituto Superiore di Sanità, Rome http://www.iss.it

Figure 25. Number of TBE cases (bars) and incidence per 100 000 inhabitants (line) by year, Italy (n=159)

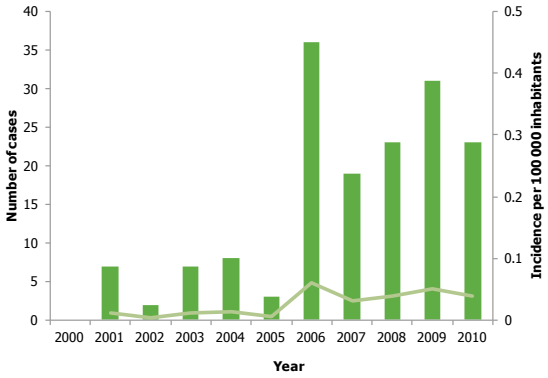


Figure 26. Number of TBE cases by gender and age, Italy (n= 159, data from 2001–2010 pooled)

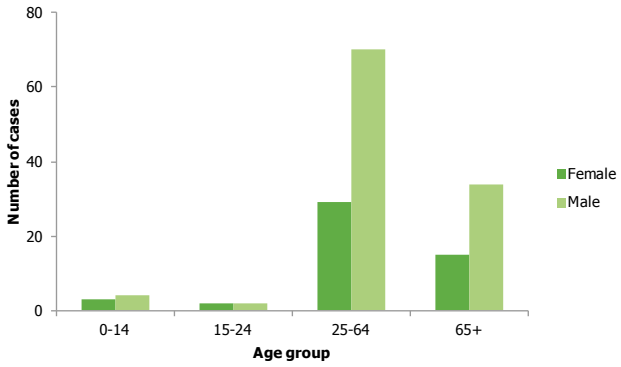
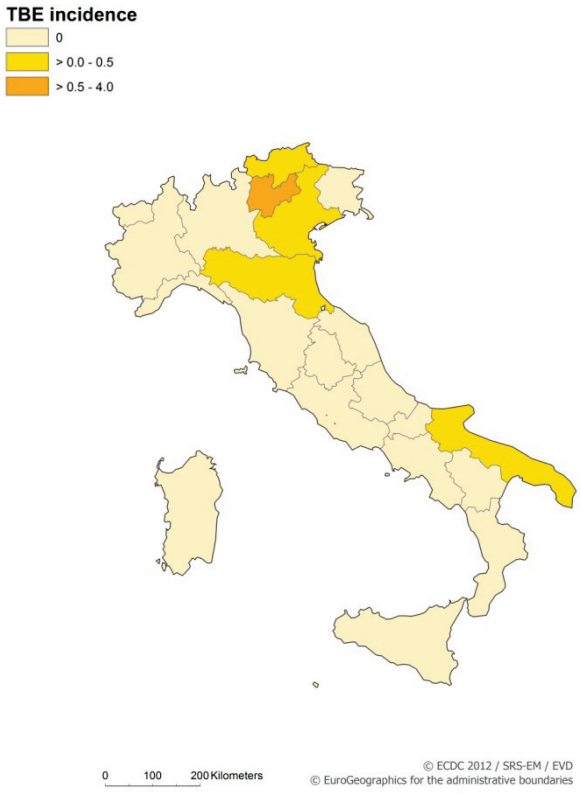


Figure 27. TBE average annual incidence rate per 100 000 inhabitants by NUTS2, Italy (n=159, period 2001–2010)



Latvia

The information in Table 23 below is based on the TBE surveillance survey and case-based and aggregated surveillance data provided by the country (n=3105, Figures 28 and 29). TBE is endemic in Latvia (Figure 30).

There are between two and five laboratories offering TBE diagnosis and they process more than 1 000 samples annually. There is one reference laboratory, located at the Infectology Center of Latvia in Riga.

Data on human cases were extracted from five articles [13, 23, 24, 99, 100]. During the period 2000–2010, one paper investigated TBE risk using alternative methods to human surveillance. The objective of the study was to discuss the epidemiological situation in Latvia during 1993–2002 and to determine the prevalence of the TBE virus in collected ticks [101]. The TBE virus prevalence observed in *Ixodes ricinus* was 1.8% in 2000, 1.7% in 2001 and 5.2% in 2002. The highest prevalence of TBE virus was observed in the central part of Latvia.

Table 23. Overview of TBE surveillance in Latvia

Indicator	Description
Type of surveillance	Comprehensive
Type of reporting	Mandatory
Type of data recorded	Case-based
Cases routinely reported	All cases
Case definition	No
Provision of surveillance data	Aggregated (2000–2006); case-based (2007–2010)
Estimated sensitivity of surveillance	National, fair sensitivity
Reference laboratory	Infectology Center of Latvia, Riga http://www.lic.gov.lv

Figure 28. Number of TBE cases (bars) and incidence per 100 000 inhabitants (line) by year, Latvia (n=3 105)

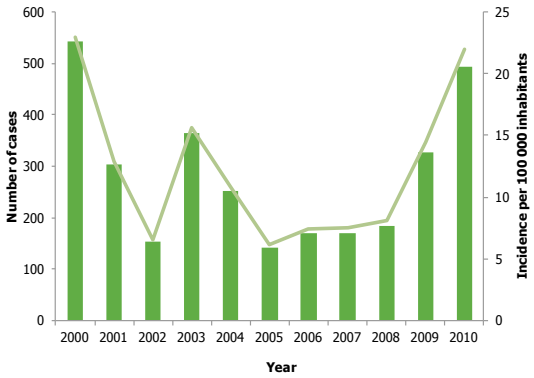


Figure 29. Number of TBE cases by gender and age, Latvia (n= 3 100, data from 2000–2010 pooled)

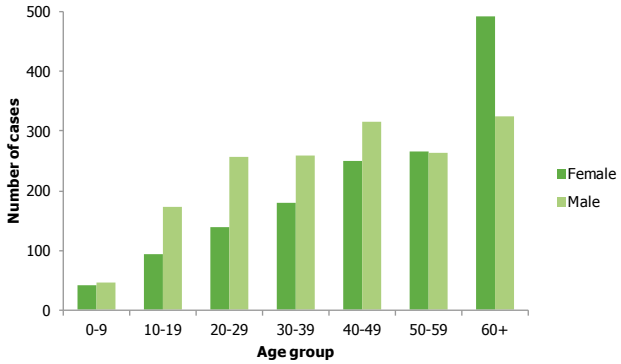
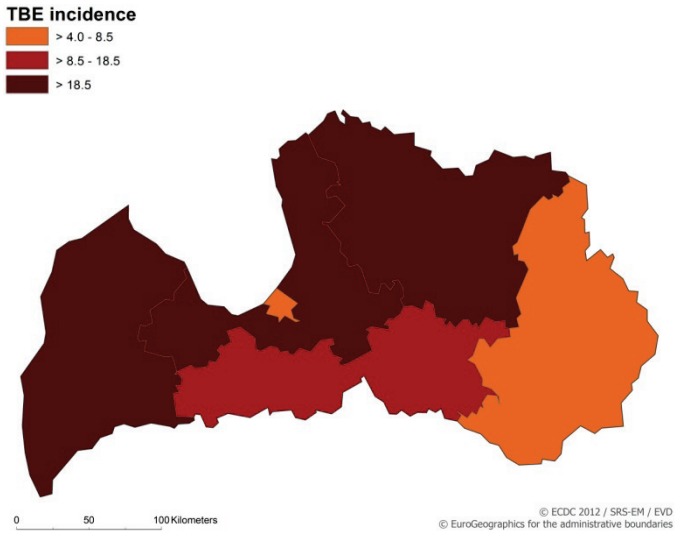


Figure 30. TBE average annual incidence rate per 100 000 inhabitants by NUTS3, Latvia (n=1 177, period 2007–2010)



Lithuania

The information in Table 24 below is based on the TBE surveillance survey, case-based data (n=612) and summary figures provided by the country (Figures 31 and 32). Lithuania is one of the countries with the highest number of reported TBE cases in Europe. TBE is present throughout Lithuania but the northern parts of the country are regarded to be TBE foci (Figure 33). There are between two and five laboratories offering TBE diagnosis, processing between 500 and 750 samples annually. There is one reference laboratory, located at the National Public Health Surveillance Laboratory in Vilnius.

Data on human cases were extracted from four articles [13, 23, 24, 102]. During the period 2000–2010, four papers investigated TBE risk using alternative methods to human surveillance. One of them assessed the distribution of the TBE virus in Lithuania on the basis of virus seroprevalence in healthy individuals from different parts of the country [103]. During 2000, a total of 1 488 serum samples were collected and examined for the presence of TBE virus. In all, 44 (3%) samples were identified as seropositive. The remaining three articles discussed investigations into the presence of TBE virus antibodies in household animals and ticks [104–106]. A total of 2 320 animals and 5 615 ticks were examined. Antibodies to the TBE virus were found in 0.7% of goats, 4.2% of sheep and 2.4% of cows in 2001, 7.0% of horses, 10.8% of cattle, 8.1% of sheep, 8.1% of goats and 7.6% of dogs in 2000–2002 and 11.8% of goats in 2004.

Table 24. Overview of TBE surveillance in Lithuania

Indicator	Description
Type of surveillance	Comprehensive
Type of reporting	Mandatory
Type of data recorded	Case-based
Cases routinely reported	All cases
Case definition	No
Provision of surveillance data	Case-based (2010)
Estimated sensitivity of surveillance	National, fair sensitivity
Reference laboratory	National Public Health Surveillance Laboratory, Vilnius http://www.nvspl.lt

Figure 31. Number of TBE cases (bars) and incidence per 100 000 inhabitants (line) by year, Lithuania (n=4 449)

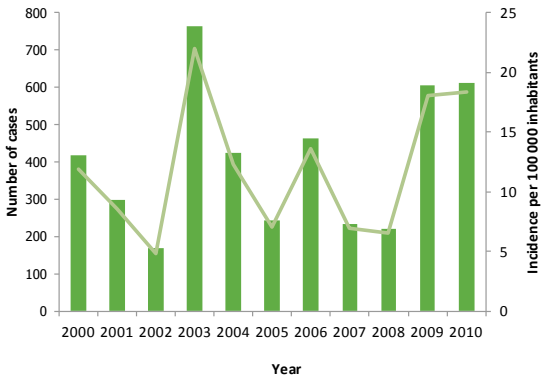


Figure 32. Number of TBE cases by gender and age, Lithuania (n=612, case based data of 2010)

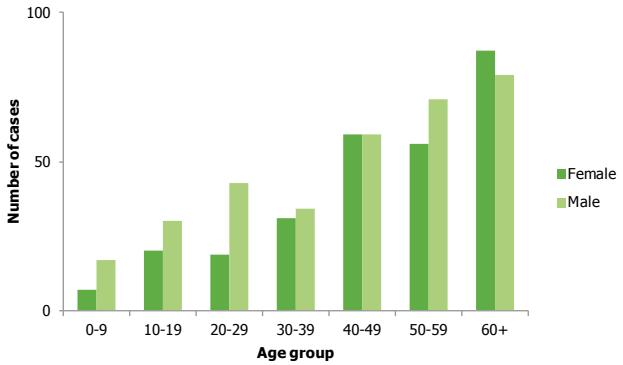
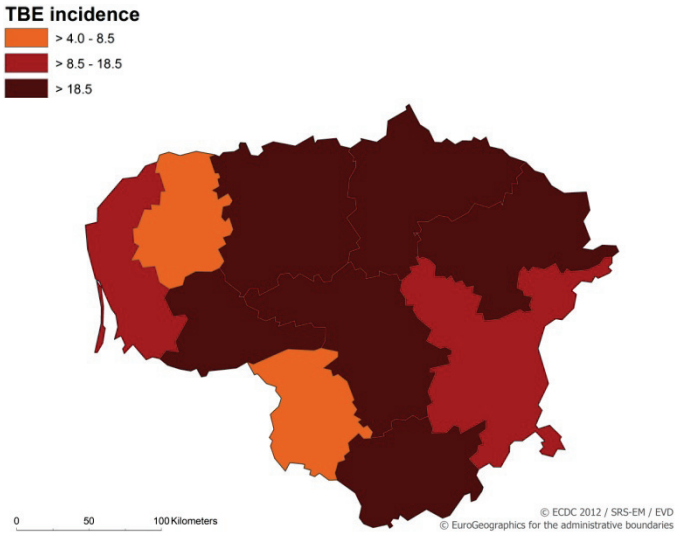


Figure 33. TBE average annual incidence rate per 100 000 inhabitants by NUTS3, Lithuania (n=612, period 2010)



Norway

The information in Table 25 below is based on the TBE surveillance survey and aggregated data provided by the country (n=62, Figures 34 and 35). TBE, which was first diagnosed in 1998, occurs sporadically in Norway although parts of the southern coast have been established as endemic (Figure 36).

There is only one laboratory offering TBE diagnosis and it processes less than 100 samples annually. There is one reference laboratory, located at the Norwegian Institute of Public Health, Department of Virology, Division of Infectious Medicine in Oslo.

Data on human cases were extracted from two articles [107, 108]. During the literature search no articles were identified which would help to analyse the risk of TBE in Norway.

Table 25. Overview of TBE surveillance in Norway

Indicator	Description
Type of surveillance	Comprehensive
Type of reporting	Mandatory
Type of data recorded	Case-based
Cases routinely reported	All cases
Case definition	Yes (2008)
Provision of surveillance data	N/A
Estimated sensitivity of surveillance	National, fair sensitivity
Reference laboratory	Norwegian Institute of Public Health, Department of Virology , Division of Infectious Disease Control, Oslo http://www.fhi.no

Figure 34. Number of TBE cases (bars) and incidence per 100 000 inhabitants (line) by year, Norway (n=62)

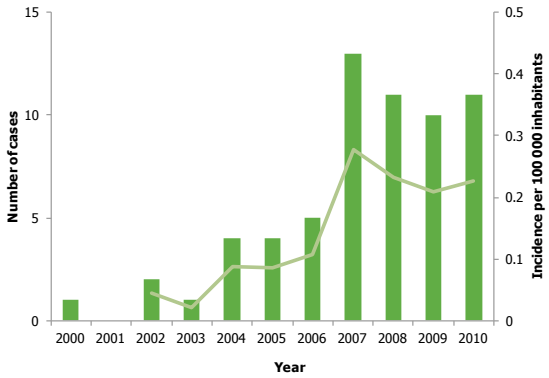


Figure 35. Number of TBE cases by gender and age, Norway (n=61, data from 2000–2010 pooled)

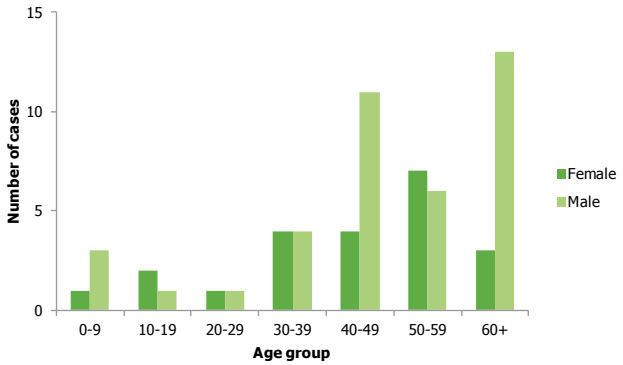
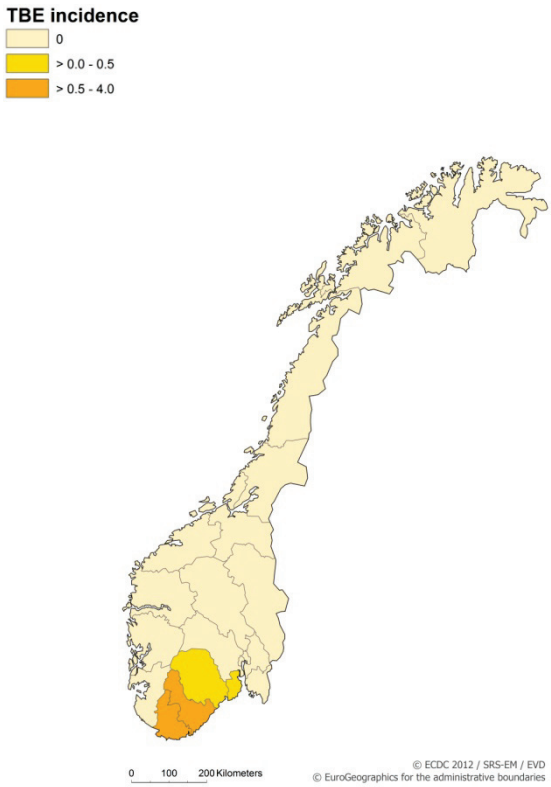


Figure 36. TBE average annual incidence rate per 100 000 inhabitants by NUTS3, Norway (n=53, period 2000–2010)



Poland

The information in Table 26 below is based on the TBE surveillance survey and case-based surveillance data provided by the country (n=2 680). In Poland, TBE is endemic and 200–300 cases are reported annually (Figures 37 and 38), 90% from two provinces neighbouring the Baltic States (Figure 39). A surveillance case definition has been in use since 2005. There are less than five laboratories offering TBE diagnosis and they process between 500 and 1 000 samples annually. There is one reference laboratory, located at the National Institute of Public Health in Warsaw.

Data on human cases were extracted from sixteen articles [13, 109–123]. During the period 2000–2010, seven papers investigated TBE risk using alternative methods to human surveillance. In two studies seroprevalence in occupationally exposed inhabitants of endemic eastern regions ranged from 25% [124] to 81% [125]. One study assessed the prevalence of TBE virus antibodies in the general population [126]. This study revealed that seroprevalence among inhabitants from known endemic regions (27/1037, 2.6%) is similar to that among inhabitants of non-endemic regions (12/461, 2.6%). Two studies investigated the prevalence of TBE virus antibodies in household animals as a proxy for local TBE virus circulation [126, 127]. The proportion of animals tested that had TBE virus antibodies ranged from 1.4% in non-endemic regions [126] to 16% in endemic regions [127]. Three studies investigated the prevalence of TBE virus in host-seeking ticks [128-130]. As a result of these investigations, between 1.6% [129] and 12.2% [130] of ticks collected tested positive, both in endemic regions and regions considered to be TBE-free. To conclude, studies of seroprevalence and tick investigations have identified the TBE virus circulating in areas where no human cases have been reported, thereby indicating variable sensitivity of human TBE surveillance.

Table 26. Overview of TBE surveillance in Poland

Indicator	Description
Type of surveillance	Comprehensive
Type of reporting	Mandatory
Type of data recorded	Case-based
Cases routinely reported	Cases with CNS infection
Case definition	Yes (2005)
Provision of surveillance data	Case-based (2000–2010)
Estimated sensitivity of surveillance	50-75%
Reference laboratory	National Institute of Public Health-National Institute of Hygiene, Warsaw http://www.pzh.gov.pl

Figure 37. Number of TBE cases (bars) and incidence per 100 000 inhabitants (line) by year, Poland (n=2 680)

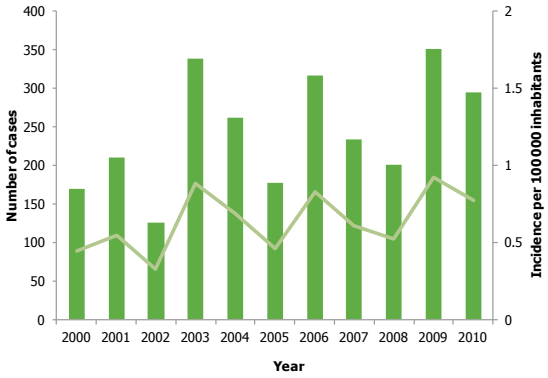


Figure 38. Number of TBE cases by gender and age, Poland (n=2 680, data from 2000–2010 pooled)

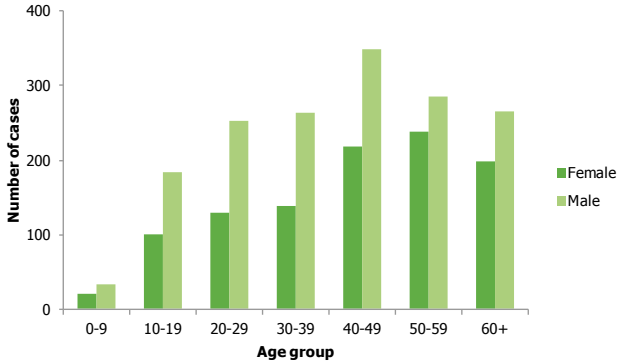
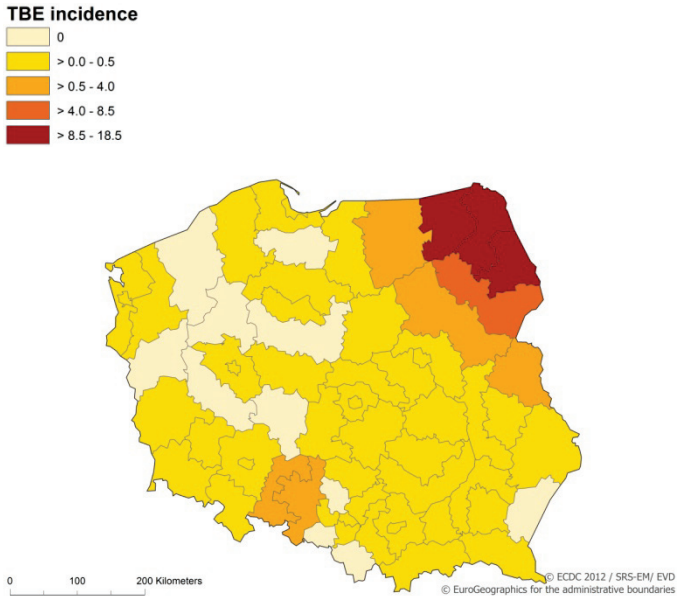


Figure 39. TBE average annual incidence rate per 100 000 inhabitants by NUTS3, Poland (n=2 680, period 2000–2010)



Romania

The information in Table 27 below is based on the TBE surveillance survey (and case-based surveillance data provided by the country (n=14, Figures 40, 41 and 42). In Romania TBE occurs sporadically and information on its epidemiology is limited.

A surveillance case definition has been in use since 2008 and was revised in 2011.

During the literature search no articles were identified which would help analyse the risk of TBE in Romania.

Table 27. Overview of TBE surveillance in Romania

Indicator	Description
Type of surveillance	Comprehensive
Type of reporting	Mandatory
Type of data recorded	Case-based
Cases routinely reported	Cases with CNS infection
Case definition	Yes (2008, revised in 2011)
Provision of surveillance data	Case-based (2008-2010)
Estimated sensitivity of surveillance	Regional, fair sensitivity
Reference laboratory	N/A

Figure 40. Number of TBE cases (bars) and incidence per 100 000 inhabitants (line) by year, Romania (n=14)

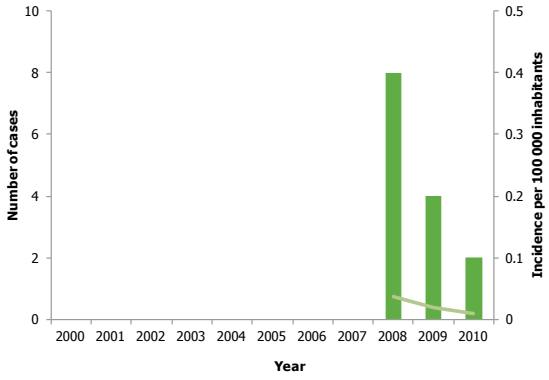


Figure 41. Number of TBE cases by gender and age Romania (n=14, data from 2008–2010 pooled)

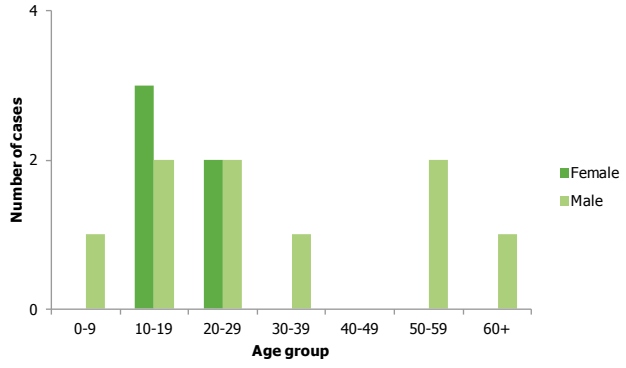
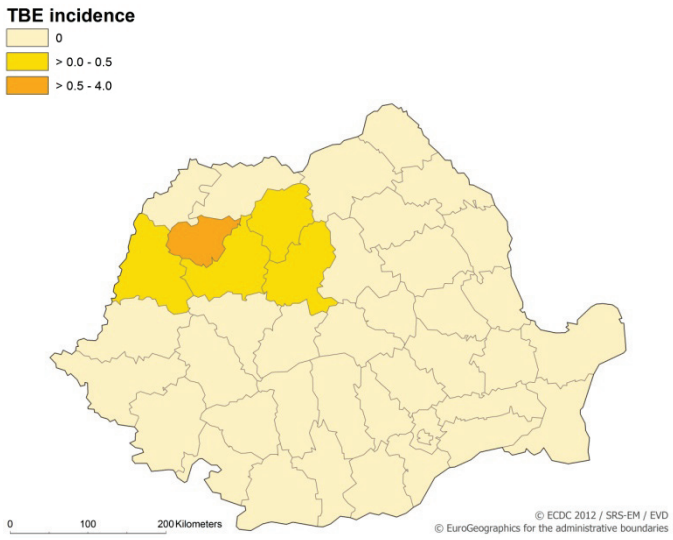


Figure 42. TBE average annual incidence rate per 100 000 inhabitants by NUTS3, Romania (n=14, period 2008–2010)



Slovakia

The information in Table 28 below is based on the TBE surveillance survey and case-based surveillance data provided by the country (n=790). In Slovakia TBE is endemic. Around 60–80 cases are reported annually (Figures 43 and 44). TBEV foci are found in the Carpathian and Pannonian regions (Figure 45).

There are more than five laboratories offering TBE diagnosis, processing between 250 and 500 samples annually. There is one reference laboratory, the NRC for Arboviruses, located at the Public Health Authority of the Slovak Republic in Bratislava.

Data on human cases were extracted from four articles [13, 23, 24, 131]. During the literature search no articles were identified which would help to analyse the risk of TBE in Slovakia.

Table 28. Overview of TBE surveillance in Slovakia

Indicator	Description
Type of surveillance	Comprehensive
Type of reporting	Mandatory
Type of data recorded	Case-based
Cases routinely reported	All cases
Case definition	No
Provision of surveillance data	Aggregated (2000), case-based (2001–2010)
Estimated sensitivity of surveillance	National, important regional differences in sensitivity
Reference laboratory	NRC for Arboviruses, Public Health Authority of the Slovak Republic, Bratislava http://www.uvzsr.sk

Figure 43. Number of TBE cases (bars) and incidence per 100 000 inhabitants (line) by year, Slovakia (n=790)

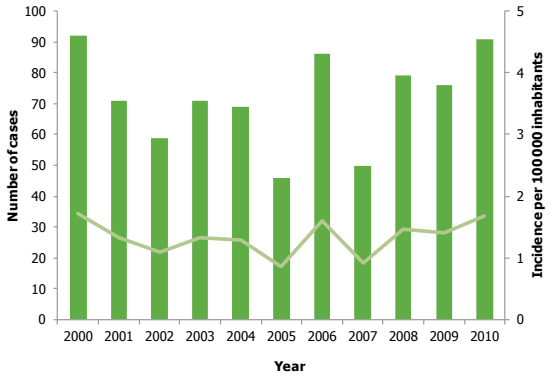


Figure 44. Number of TBE cases by gender and age Slovakia (n=698, data from 2000–2010 pooled)

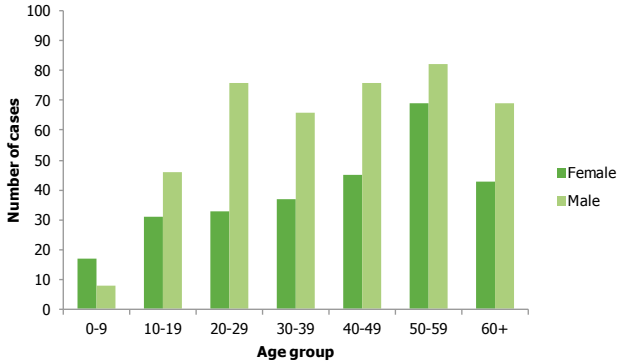
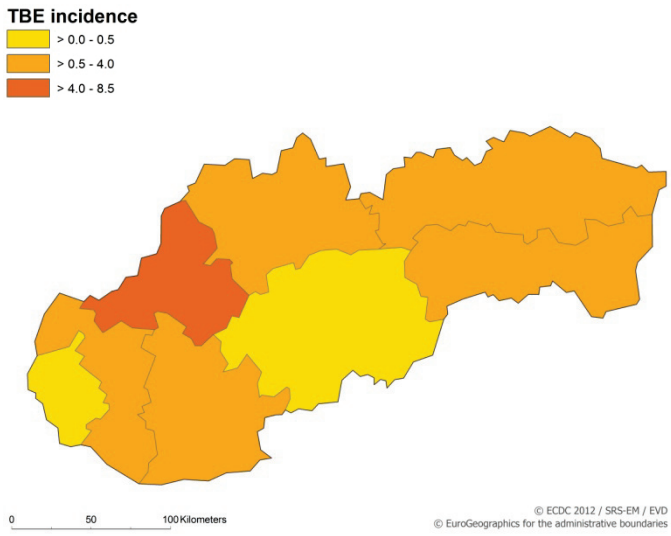


Figure 45. TBE average annual incidence rate per 100 000 inhabitants by NUTS3, Slovakia (n=698, period 2000–2010)



Slovenia

The information in Table 29 below is based on the TBE surveillance survey and summary figures provided by the country. Slovenia is one of the countries with the highest reported number of TBE cases (Figure 46) and a large part of the country is known to be endemic. The risk of infection is particularly high in the Gorenjska and Koroška regions.

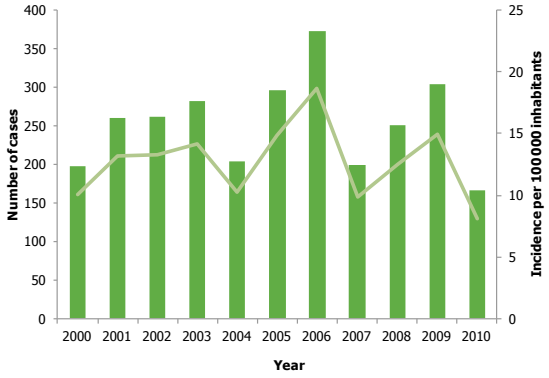
There is only one laboratory offering TBE diagnosis and this processes between 250 and 500 samples annually.

Data on human cases were extracted from nine articles [13, 23, 24, 132-137]. During 2000–2010 there was one paper which investigated TBE risk using alternative methods to human surveillance. The objective of the study was to estimate TBE virus infection in Slovenian ticks [138]. A total of 4 785 ticks were collected and examined during a two-year period. The sampling was conducted in eight different parts of Slovenia. The presence of the TBE virus was assessed at 0.54% in 2005 and 0.43% in 2006.

Table 29. Overview of TBE surveillance in Slovenia

Indicator	Description
Type of surveillance	Comprehensive
Type of reporting	Mandatory
Type of data recorded	Case-based
Cases routinely reported	Cases with CNS infection
Case definition	No
Provision of surveillance data	No, summary figures for this report
Estimated sensitivity of surveillance	National, fair sensitivity
Reference laboratory	No

Figure 46. Number of TBE cases (bars) and incidence per 100 000 inhabitants (line) by year, Slovenia (n=2 795)



Sweden

The information in Table 30 below is based on the TBE surveillance survey and case-based surveillance data provided by the country (n=1,086). In Sweden 100–200 cases are reported annually (Figures 47 and 48). The majority of cases come from the central and eastern parts of the country (Figure 49).

A surveillance case definition has been in use since 2004. There are more than five laboratories offering TBE diagnosis and there is one reference laboratory, located at the Swedish Institute for Communicable Disease Control.

Data on human cases were extracted from eight articles [13, 23, 24, 139-142]. During the period 2000–2010, five papers investigated TBE risk using alternative methods to human surveillance. The objective of one study was to estimate the seroprevalence of the TBE virus in inhabitants of Aspö island [143]. A total of 642 blood samples were examined for the presence of the TBE virus. TBE-virus-specific antibodies were documented in 53 individuals. In the follow-up 24 out of 200 participants were found to be TBE-virus positive. The other study focused on screening migrating birds and determining their role in the transmission of ticks infected with the TBE-virus [144]. Overall, 1 155 ticks were collected from 447 of the 13 260 birds examined. TBE virus was detected in six ticks. The remaining three articles discussed TBE virus prevalence in the tick population [145–147]. A total of 8 167 ticks were examined. The sampling was conducted in the eastern and western part of Sweden. The results of the studies confirmed the circulation of the TBE virus.

Table 30. Overview of TBE surveillance in Sweden

Indicator	Description
Type of surveillance	Comprehensive
Type of reporting	Mandatory
Type of data recorded	Case-based
Cases routinely reported	Cases with CNS infection
Case definition	Yes (2004)
Provision of surveillance data	Case-based (2005–2010)
Estimated sensitivity of surveillance	National, fair sensitivity
Reference laboratory	Swedish Institute for Communicable Disease Control, Solna http://www.smittskyddsinstitutet.se

Figure 47. Number of TBE cases by year, Sweden (n=1 086)

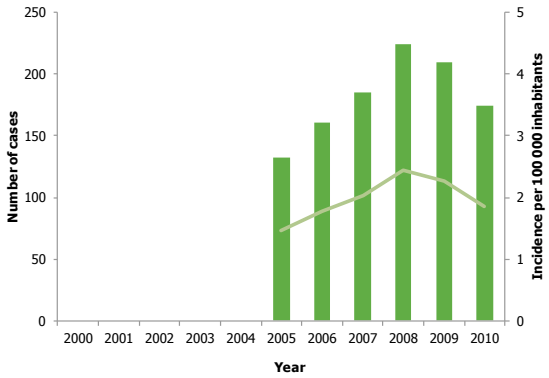


Figure 48. Number of TBE cases by year, Sweden (n=1 086, data from 2005–2010 pooled)

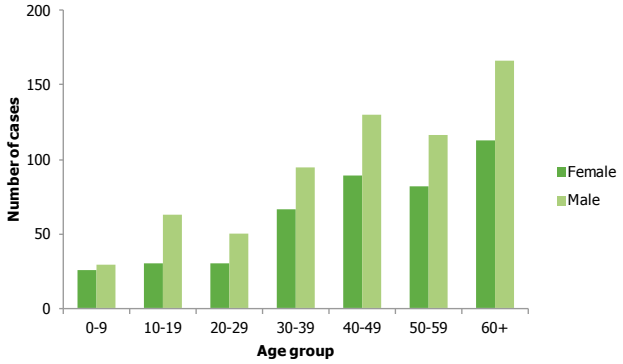
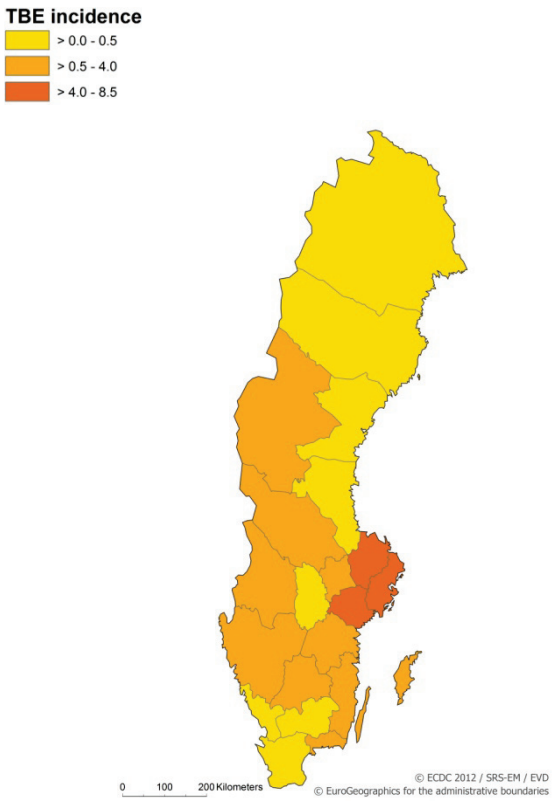


Figure 49. TBE average annual incidence rate per 100 000 inhabitants by NUTS3, Sweden (n=1 086)



Switzerland

The information in Table 31 below is based on the TBE surveillance survey. TBE is endemic in areas of northern Switzerland.

A surveillance case definition has been in use since 1988 and was revised in 2007. There are more than five laboratories offering TBE diagnosis. There is one reference laboratory, located at the National Reference Centre for Tick-borne Diseases in Neuchâtel.

Data on human cases were extracted from eight articles [13, 22–24, 148–151]. During the period 2000–2010, two papers investigated TBE risk using alternative methods to human surveillance. One study discussed the national screening of ticks for the presence of TBE virus using a high-throughput method [152]. Overall, 62 343 ticks were examined. The TBE virus was found to be endemic in 38 localities and the mean virus prevalence was estimated at 0.46%. The aim of the other study was to estimate TBE virus prevalence in the tick population of the Bern Canton [153]. A total of 307 ticks were screened for the presence of the TBE virus and infection was determined in 14 nymphs, 18 male and 12 female adults.

Table 31. Overview of TBE surveillance in Switzerland

Indicator	Description
Type of surveillance	Comprehensive
Type of reporting	Mandatory
Type of data recorded	Case-based
Cases routinely reported	All symptomatic cases (including tick-borne fever)
Case definition	Yes (1988, revised in 2007)
Provision of surveillance data	N/A
Estimated sensitivity of surveillance	National, fair sensitivity
Reference laboratory	National Reference Centre for Tick-borne Diseases, Neuchâtel http://www2.unine.ch/cnrt/

Discussion

The aim of the project was to provide an overview of data sources and availability regarding TBE and to obtain a better understanding of the current magnitude of TBE in the EU and EFTA countries. An online survey, surveillance data collection, and literature searches were used to identify data on TBE and describe the data sources (including type of surveillance systems, case definitions, and surveillance performance) and published seroprevalence surveys providing supplementary data on human risk. A number of countries provided summary figures instead of surveillance data to illustrate their situation. Additionally, several countries decided not to share their surveillance datasets. Moreover, given the zoonotic nature of the evaluated diseases, human surveillance cannot be perceived as the only source of information for interpretation of human risk. When considering data availability, we took into account the indirect evidence provided by animal surveys and tick studies.

Although human surveillance systems for TBE have been implemented in the majority of EU/EFTA countries, important differences exist in terms of case definitions used, clinical syndromes reported and variables collected at national level. Additionally, important differences exist between countries as regards access to laboratory diagnosis. For example, the two tests enabling differentiation of TBE virus infection from other flaviviral infections (neutralisation test and haemagglutination inhibition assay) are only available in eight EU countries. These factors may hamper valid interpretation of human and animal surveillance and their comparisons at an international level. Despite these drawbacks, it is clear that TBE information is consistently and systematically collected in several EU/EFTA countries, enabling a description of the extent of TBE endemic regions and general surveillance trends. Moreover, the information available for particular countries is in most instances consistent and reliable.

The literature review showed that published studies were more common for high-risk countries. During the evaluated 10-year period, 72% of the publications on TBE risk came from 20% (six) of the countries with high levels of endemic TBE virus circulation: Czech Republic, Germany, Lithuania, Slovenia, Sweden and Switzerland. Yet, among 12 countries which had not published studies there were three high-risk areas reported (Bulgaria, Romania and Slovakia).

The key risk areas for TBE are located in central and eastern Europe and the Baltic and Nordic countries. The area extends to Switzerland and the French region of Alsace in the west of Europe, and to northern Italy and the Balkan countries in the south of Europe. Based on the available data, the highest risk of TBE was among males aged 40–60 years, indicating that persons working outdoors may be at increased risk of TBE. However, an accurate identification of high-risk populations would necessitate collection of more detailed surveillance data and performing epidemiological studies to assess the TBE risk factors at individual level.

As with many diseases under surveillance in Europe, there is a need to prioritise surveillance activities. This is already done in two thirds of European countries in relation to TBE, which is a vaccine-preventable disease and can result in severe outcomes.

This report was a first effort to collect existing data on TBE in EU/EFTA countries. The data, covering the period 2000–2010, were collected from different sources using different case definitions, time scales, and spatial units and do not reflect the complete picture or the complexity of TBE's epidemiology. Therefore a number of recommendations have been made to improve the surveillance and to increase our understanding of TBE in EU/EFTA countries.

Recommendations

- There is a need to improve surveillance throughout Europe, with emphasis on obtaining homogenous, comparable data at EU level.
- ECDC should encourage data collection at sub-national levels and make it possible to register the data, including the place of residence and of infection, at least at NUTS-3 geographical level. Collection of TBE data at country level is irrelevant for a European approach to TBE risk assessment, as it needs to take into account several geographically variable biotic and abiotic determinants of disease risk.
- Uniform use of diagnostic methods for detection of TBE pathogens should be encouraged, i.e. by promoting implementation of reference laboratories in all EU/EFTA countries. The reference laboratories should have the appropriate diagnostic tools available, including methods for distinguishing TBE from other flaviviruses.
- The following is recommended for TBE surveillance:
  - implementation of the standard EU case definition for TBE;
  - initiating routine collection of surveillance data from EU countries;
  - use of data from tick and animal surveys in addition to human case surveillance to define TBE endemic areas.
- There is a need to develop vaccination recommendations for EU citizens as well as for travellers to endemic regions.

Annex 1 – General description of the project

The main goal of the project was to summarise existing data on TBE. To achieve these goals, a consortium of experts was created, with expertise in communicable disease surveillance, tick biology, microbiology and clinical medicine. First, a thorough literature review was performed in order to identify gaps in knowledge on burden of TBE. Secondly, surveys were prepared to evaluate the implementation of surveillance systems in particular countries, laboratory methods used, and data availability. In the final phase, the data collected were assessed in terms of completeness and possibility to fill data gaps.

The following steps have been taken to achieve the goals:

Identification of experts – survey respondents

Respondents to the survey on TBE surveillance and data availability were identified in the preparatory phase through an existing network of experts: EU-FP6 EDEN; Med-Vet-Net, VENICE II or ENIVD. Consortium members assured appropriate links with existing or past networks. The head of the ECDC Surveillance Unit approved the list of experts and the invitations were sent by the ECDC Surveillance Unit via ECDC competent bodies in each country.

Literature review

The consortium members shared the task of collecting all published evidence on risk for TBE based on infection in humans, wild hosts and ticks. First, a set of keywords were agreed during the initial teleconference performed in November 2010. The period of the review was limited to 2000–2010. The information on TBE risk was extracted from papers identified by the reviewers and entered into standardised tables. Ten independent reviewers selected the abstracts that met the preliminary inclusion criteria and filled the summary table for each selected abstract.

The inclusion criteria adopted for the literature review were:

- Time limits: years 2000–2010
- Geographical limits: EU and EFTA countries (27 Member States and three EFTA countries - Switzerland, Norway and Iceland). Cases imported from other countries were excluded.
- Language: English, French, Italian, Czech, German, Hungarian, Polish, Russian, Slovak, Slovenian, Spanish and Swedish. If there were abstracts written in languages that could not be understood by the reviewers then the nominated expert from that particular country was asked to review the text.

Inclusion criteria for papers were as follows:

- includes numbers (human case counts) which can be extracted with geographic reference
- data source (surveillance system, special 'ad hoc' study) is described
- provides information important for interpreting disease risk in humans:
  - serological survey of humans or animals;
  - predictive model using environmental variables;
  - other information on pathogen occurrence.

Exclusion criteria for papers were as follows:

- incompatible time period
- different disease
- country not on the list
- only imported cases
- language not understood
- not addressing the aim of the study
- other.

For each included article the full text was retrieved. Reference lists of the selected papers, as well as citation of selected articles in Google Scholar were used to identify papers not included by the original query.

In order to verify the applied methods a pilot study of summary tables was conducted. The reviewers were to evaluate the first 30 abstracts and send the results to project co-ordinator. The co-ordinator team checked summary tables' compliance with procedure and provided feedback to the reviewers. Any additional identified paper was reviewed. Published papers and reports provided by the respondents of the survey were also reviewed using the same criteria.

Development of questionnaires

The surveys covered issues that were not addressed in recent VENICE II and ENIVD questionnaires. Along with the survey on TBE surveillance and data availability, TBE surveillance contact people were asked to provide information on unpublished evidence of TBE risk at tick, animal, and human levels.

Web-based survey administration

The technical co-ordinator prepared the questionnaires in an electronic form, using the platform VoozaNoo (http://www2.voozanoo.net/fr). EpiConcept was subcontracted to provide technical assistance for the design of the on-line surveys, and solve technical problems during survey administration. The technical coordinator of the project was responsible for sending reminders to each contact point. Access to the survey was by user name and password and the access rights varied according to user profile. The respondents in each participating country entered data directly on-line.

Analysis of reporting systems

The availability of reporting systems was summarised and selected indicators evaluated. The possibility of underreporting, depending on the type of surveillance system, was discussed.

Analysis of epidemiological data

The EU and EFTA countries were requested to provide surveillance data on TBE. The data was then analysed and presented individually for each country and for the whole of Europe.

Working group constitution

- Pawel Stefanoff, National Institute of Public Health – PZH, Warsaw, Poland
- Fortunato D'Ancona, Istituto Superiore di Sanità, Rome, Italy
- Wiebke Hellenbrand, Robert Koch Institut, Berlin, Germany
- Luisa P. Sánchez Serrano, National Centre for Epidemiology, Instituto de Salud Carlos III, Madrid, Spain
- Sarah Randolph, Oxford University, Oxford, UK
- Annapaola Rizzoli, Edmund Mach Foundation, Trento, Italy
- Maria Kazimirova, Institute of Zoology, Slovak Academy of Sciences, Bratislava, Slovakia
- Matthias Niedrig, Robert Koch Institut, Berlin, Germany
- Oliver Donoso-Mantke, Robert Koch Institut, Berlin, Germany
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- Pedro Anda, Laboratory of Spirochaetes and Special Pathogens, National Centre for Microbiology, Instituto de Salud Carlos III, Madrid, Spain
- Franc Strle, Department of Infectious Diseases, University Medical Center, Ljubljana, Slovenia
- Joanna Zajkowska, Białystok Medical University, Białystok, Poland.

Timeline

September 2010	Distribution of tasks for development of the questionnaire content and protocol for the literature review
December 2010	Development of the questionnaire content and protocol for literature review
March 2011	Initiation of the online survey on TBE data availability in EU/EFTA countries
May 2011	Review of abstracts selected for literature review on TBE data availability in EU/EFTA countries
June 2011	Collection of surveys from countries First call for surveillance data from countries consenting to provide their data
July 2011	Extraction of data on cases from articles selected by reviewers and through supplementary literature review
August 2011	Preparation of the final report for ECDC.

Annex 2 – Questionnaire on tick-borne encephalitis data availability in EU/EFTA countries

Surveillance of tick-borne diseases

1. Which of the following diseases are subject to epidemiological surveillance in your country at national or sub-national level?

- Tick-borne encephalitis
- Tick-borne rickettsioses
- Q fever
- Lyme borreliosis

Surveillance of tick-borne encephalitis

2.1 Is there one or more surveillance systems for tick-borne encephalitis operating in your country?

- One system
- Two systems
- Three systems
- Four systems
- Five or more systems

2.2 The type of surveillance system is:

- Comprehensive
- Sentinel
- Other (please specify …….)

2.3 This surveillance system operates:

- At national level
- At sub-national level (e.g. regional level)
- Only in endemic areas
- Other (please specify …….)

2.4 Reporting in the surveillance system is:

- Mandatory
- Voluntary
- Not well-defined

2.5 The sources of data used in the surveillance system are (check all that apply):

- Reporting by general practitioners
- Reporting by hospital physicians
- Reporting of deaths from infectious diseases
- Laboratory reporting
- Hospital discharge records
- Death register records
- Other (please specify …….)

2.6 Which cases are routinely reported within the surveillance system?

- All cases (including asymptomatic)
- Tick-borne fever
- Only cases involving central nervous system
- Other (please specify …….)

2.7 Is there a case definition for tick-borne encephalitis used in the surveillance system?

- Yes
- No
- Don’t know.

2.7.1 Is this surveillance case definition used to classify each reported case?

- Yes
- No
- Don't know.

2.7.2 How are reported cases classified?

- Possible (typically only clinical criteria)
- Probable (typically clinical criteria with epidemiological link or confirmation using less specific laboratory test)
- Confirmed (typically require laboratory confirmation)

2.7.3 Please provide the surveillance case definition for tick-borne encephalitis.

2.7.4 In which year was the current surveillance case definition implemented and, where relevant, revised?

2.8 How is data recorded at the highest level of the surveillance system operation?

- Case-based
- Aggregated
- Don't know.

2.8.1 If case-based, what data are collected?

- Notification source (GP, hospital, lab, other)
- Date of notification
- Presumed data of infection
- Case classification (according to the case definition)
- Demographic variables (age, gender)
- Geographical location of residence
- Eurostat NUTS1 (usually country regions)
- Eurostat NUTS2 (usually country provinces)
- Eurostat NUTS3 (usually districts or counties)
- Geographical location of presumed exposure
- Eurostat NUTS1 (usually country regions)
- Eurostat NUTS2 (usually country provinces)
- Eurostat NUTS3 (usually districts or counties)
- Exposure to tick-bite(s)
- Occupational exposure
- Information on presumed vehicle of infection (uncooked dairy products)
- Hospitalisation
- Laboratory test details
- Clinical signs/symptoms
- Clinical complications
- Outcome (dead/alive)
- Vaccination status
- Import related case
- Other (please specify…..)

2.8.2 If aggregated, which aggregation levels are used?

- Age group (please provide the age groups used)
- Gender
- Residence (urban/rural)
- Season/month
- Case classification
- Geographical location of residence
- Eurostat NUTS1 (usually country regions)
- Eurostat NUTS2 (usually country provinces)
- Eurostat NUTS3 (usually districts or counties)
- Vaccination status
- Hospitalisation
- Outcome (dead/alive)
- Importation status
- Other (please specify……)

2.9 Where there attempts to measure the sensitivity of the surveillance system (i.e. estimation of underreporting)?

- Yes
- No
- Don't know.

2.9.1 If yes, what method was used:

- Capture-recapture analysis
- Mathematical modelling of disease burden
- Simply comparison among different sources
- Other (please describe…..)

2.9.2 Please provide the estimate of tick-borne encephalitis surveillance sensitivity:

- <50%
- 50-75%
- >75%

2.9.3 Please provide below the appropriate references or links to the sensitivity assessments.

2.10 How would you assess the surveillance system sensitivity?

- National, fair sensitivity
- National, important regional differences in sensitivity
- National, overall low sensitivity
- Regional, fair sensitivity
- Regional, very low sensitivity
- Other (please describe…)
- Don't know.

2.11 Is another case definition for tick-borne encephalitis used for the clinical management of cases, other than that previously described?

- Yes
- No
- Don't know.

2.11.1 If yes, please describe.

2.12 If surveillance data are available for your country, could you provide them to ECDC under this project (data format will be provided)?

- Yes
- No.

Microbiological methods for tick-borne encephalitis

3.1. Is laboratory confirmation used to ascertain tick-borne encephalitis cases in your country?

- Yes
- No
- Don't know.

3.2 What laboratory tests are used to diagnose suspected tick-borne encephalitis cases?

- ELISA (enzyme-linked immunosorbent assay)
- CFT (complement fixation test)
- VNT (virus neutralisation test)
- PCR (polymerase chain reaction)
- HIA (haemagglutination inhibition assay)
- IFA (immunofluorescence assay)
- WB (Western blot)
- VI (virus isolation)
- SEQ (sequencing)
- LUM (Luminex antibody test)
- Other- specify……

3.3 How many laboratories perform diagnostic tests to diagnose suspect tick-borne encephalitis cases in your country?

- 1
- 2-5
- >5
- Don't know.

3.4 Could you estimate how many samples are processed each year for diagnosis of tick-borne encephalitis cases in the country laboratories?

- <100
- 100 -< 250
- 250 -< 500
- 500 -< 750
- 750 -< 1000
- 1000
- Don't know.

3.5 Are the microbiological testing results reconciled (linked) with epidemiological case reports and available at the national level?

- Yes
- No
- Don't know.

3.6 Is there a reference laboratory for tick-borne encephalitis in your country?

- Yes
- No
- Don't know.

3.6.1 How many?

- One
- More than one (please specify the number…..)

3.6.2 Is the laboratory officially nominated to provide reference microbiological methods for the local laboratories?

- Yes
- No.

3.6.3 What reference methods are performed in the reference laboratory?

- ELISA
- IFA (immunofluorescence assay)
- VNT (virus neutralisation test)
- HIA (haemagglutination inhibition assay)
- PCR (polymerase chain reaction)
- VI (virus isolation)
- SEQ (sequencing)
- Luminex test
- Other (please specify ……)

3.6.4 Did the reference laboratory participate in international External Quality Assurance (EQA) in relation to tick-borne encephalitis diagnosis?

- Yes
- No
- Don't know.

3.6.4.1 How often did the reference laboratory participate in international External Quality Assurance (EQA) from 2005–2010?

- >5
- 5
- 2-4
- 1

3.6.4.2 When was the latest EQA exercise performed?

- 2010
- 2009
- More than two years ago.

3.6.5 Please provide the addresses of reference laboratories (postal address, contact name, email, telephone number).

Annex 3 – Tick-borne encephalitis case definitions used in surveillance systems in EU/EFTA countries

Country	Definition	Details
Austria	Clinical criteria	Clinical picture of acute TBE, defined as at least one of the following criteria: • Flu-like symptoms • CNS symptoms (such as meningitis, encephalitis, myelitis)
	Laboratory criteria	Positive findings with at least one of the following four methods: • Direct detection of pathogens: Nucleic acid detection (e.g. PCR) in blood or cerebrospinal fluid, post-mortem organ tissues • Indirect (serological) evidence: IgM and IgG antibody detection (once much higher value, e.g. ELISA, NT) only in blood or CSF; significant change between two samples with IgG antibody detection (e.g. ELISA, NT); evidence intrathecal TBE-specific antibodies (raised CSF/serum index)
	Confirmed case	Any person who meets the clinical and laboratory criteria
Czech Republic	Unknown	
Estonia	Clinical criteria	Specific two-phase disease: the febrile in the first phase and meningitis or encephalitis in the second phase
	Laboratory criteria	Tick-borne encephalitis virus specific antibody response (IgM in serum or CSF; IgG four-fold in serum); Detection of tick-borne encephalitis virus nucleic acid in the clinical specimen; laboratory results need to be interpreted according to the vaccination status.
	Case classification	• Probable case: any person meeting the clinical criteria and history of tick bite/other epidemiological link; • Confirmed case: any person meeting the clinical and laboratory criteria.
Finland		Diagnostic antibody finding or detection of nucleic acid in clinical specimen
Germany	Clinical criteria	Clinical picture of acute TBE, defined by at least one of the following two criteria: • Influenza-like symptoms, • CNS symptoms (meningitis, encephalitis, myelitis). Additional information • A biphasic clinical course is typical, with initial influenza-like symptoms followed by CNS-symptoms after a symptom-free interval of four to 10 days. However, either phase can occur without the other. • For vaccine-preventable diseases the vaccination history (number of previous vaccine doses, type and date of last vaccine dose) should be ascertained (e.g. by checking vaccination record) and notified.
	Laboratory criteria	Positive diagnosis using at least one of the following four methods: (Direct detection of pathogen only in blood, CSF, haemorrhagic skin infiltrations or clinical specimens from a normally sterile site): • nucleic acid detection (e.g. PCR) only in blood or CSF, post mortem in other organs. Additional information • Detection of TBE-specific IgM- AND IgG-antibody (single elevated level, e.g. ELISA, NT) only in blood or CSF: • Four-fold increase in TBE-specific IgG-antibody (e.g. ELISA, NT) • Detection of intrathecal production of TBE-specific antibodies (elevated CSF/serum index) • Interpretation of antibody detection must consider possible TBE vaccination preceding the test.
	Case classification	• Fulfilling clinical AND laboratory criteria (reference case definition) • Fulfilling laboratory criteria but not clinical criteria (or clinical criteria unknown).
Norway		Laboratory detection of virus in CSF by isolation of nucleic acid, or detection of specific antibodies in serum and/or CSF indicating infection with a virus which has known ability to cause encephalitis.
Poland	Clinical criteria	Any persons with neurological symptoms
	Epidemiological criteria	Consumption of unpasteurised milk from this same source as confirmed case
	Laboratory criteria	Probable case – detection of specific IGM antibodies in serum with no history of vaccination against any flaviviral disease in previous three months. Confirmed case – at least one of the following: • detection of specific IgM and IgG antibodies • detection of specific antibodies in central nervous system • confirmation of anti-TBE antibodies by neutralisation test.

Country	Definition	Details
	Case classification	• Possible case: Any persons with neurological symptoms having visited endemic areas in previous six weeks, during a period of increased tick activity (between April and November) • Probable case: Any person meeting the clinical criteria and epidemiological criteria, OR laboratory criteria for a probable case • Confirmed case: Any person meeting the clinical criteria and laboratory criteria for a confirmed case
Romania	Suspected case	Suspected case: (possible case): any person with fever and meningitis/meningoencephalitis/encephalitis with CRF clear.
	Probable case	Suspected case and one or more of the following epidemiological links: • Recognition of the tick bite 7–14 days before onset in an endemic area • Parasitic ticks 7–14 days before onset, in an area of unknown endemicity, during a specific seasonal period (April-–November) • Person at occupational risk (shepherds, foresters, farmers, etc.) • Consumption of raw milk or uncooked dairy products which come from animals heavily infested by ticks. • Case that received blood form a donor recently diagnosed with TBE OR The suspected case and a positive IgM serology (when unique serum sample is obtained during the acute phase or during the convalescence).
	Confirmed case	A TBE case is a person with clinical criteria and with one of the following laboratory criteria: • Detection of TBE nucleic acid in serum, CSF or tissue by RT PCR • Detection IgM specific antibody in serum and seroconversion, or significant increase in titer of specific antibody IgG up to six months after onset.
Sweden	Suspected case	Epidemiological link • + Clinical criteria • + Pleocytosis in CSF or neurologic symptoms consistent with encephalitis, also with no pleocytosis.
	Confirmed case	Lab confirmed by at least one of the following findings: • Isolation of TBE virus in CSF (or post mortem in brain tissue) • Demonstration of TBE virus nucleic acid in CSF (or post mortem in brain tissue) • Demonstration of specific virus nucleic acid in serum • Demonstration of specific antibody response against TBE virus in serum or in CSF which indicates a current infection.
Switzerland	Case classification	Possible: Febrile illness (ILI) and IgM Probable: Neurological symptoms and IgM Confirmed: Febrile illness (ILI) with/without meningitis, meningoencephalitis or meningoencephalomyelitis, and: • IgM+IgG or • seroconversion or • significant increase in IgG (4x) or • demonstration of TBE virus nucleic acid.

Annex 4 – Variables collected for TBE cases by EU/EFTA countries

Variable	Austria	Belgium	Czech Republic	Denmark	Estonia	Finland	France	Germany	Greece	Hungary	Italy	Latvia	Lithuania	Norway	Poland	Romania	Slovakia	Slovenia	Sweden	Switzerland
Notification source (GP, hospital, lab, other)	✓	✓	✓	✓	✓	✓		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Date of notification	✓	✓	✓		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Presumed date of infection	✓	✓	✓		✓		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓		✓	✓
Case classification (according to case definition)	✓					✓		✓		✓					✓	✓				✓
Demographic variables (age, gender)	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Geographical location of residence: Eurostat NUTS1 (usually country regions)	✓		✓			✓	✓	✓	✓	✓	✓	✓		✓	✓		✓	✓		✓
Geographical location of residence: Eurostat NUTS2 (usually country provinces)	✓							✓		✓	✓	✓		✓	✓		✓		✓	✓
Geographical location of residence: Eurostat NUTS3 (usually districts or counties)	✓	✓	✓	✓	✓		✓	✓		✓	✓	✓	✓	✓	✓	✓	✓		✓	✓
Geographical location of presumed exposure: Eurostat NUTS1 (usually country regions)	✓	✓	✓	✓				✓			✓	✓		✓	✓					✓
Geographical location of presumed exposure: Eurostat NUTS2 (usually country provinces)	✓				✓			✓			✓	✓		✓	✓				✓	✓
Geographical location of presumed exposure: Eurostat NUTS3 (usually districts or counties)	✓		✓					✓			✓	✓	✓	✓	✓	✓			✓	✓
Exposure to tick-bite(s)	✓	✓	✓	✓	✓			✓		✓		✓	✓		✓	✓	✓		✓	✓
Occupational exposures		✓	✓	✓						✓		✓	✓	✓		✓	✓			✓
Information on presumed vehicle of infection (uncooked dairy products)	✓		✓	✓	✓					✓		✓	✓	✓		✓	✓			
Hospitalisation	✓	✓	✓		✓			✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓		✓
Laboratory test details	✓	✓	✓	✓	✓	✓		✓	✓	✓		✓	✓	✓	✓	✓	✓		✓	✓
Clinical signs/symptoms	✓	✓	✓					✓	✓			✓		✓	✓	✓	✓			✓
Clinical complications	✓	✓						✓				✓		✓		✓	✓			✓
Outcome (dead/alive/disabled)	✓		✓		✓			✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓		✓
Vaccination status	✓	✓	✓		✓			✓	✓	✓		✓		✓	✓		✓	✓	✓	✓
Imported case	✓	✓	✓	✓	✓			✓	✓	✓		✓	✓	✓	✓	✓	✓		✓	✓

Annex 5 – Additional information on TBE data availability literature review

Each of the abstracts that met the inclusion criteria was characterised by the following variables: article identification number, availability of denominator concordant with geographical region, first author, country from which the data originate, year of publication, language, study period, study type, setting, subject of the study, sample size, confirmatory testing used and comments facilitating interpretation of the data.

Summary of literature review on TBE

Abstracts on TBE		Number
Total abstracts reviewed		1050
Selected abstracts	Human cases	66
	Animals and vectors	48
	Serological survey	11
Excluded abstracts	Country not on the list	159
	Incompatible time period	61
	Different disease/vectors	77
	Not addressing the aim of the study	519
	Non-understandable language	13
	Only imported cases	3
	Duplicated	80
Other	Not available	12

TBE data availability from literature review by country, EU/EFTA countries, 2000–2010

Country	Abstracts on animals and vectors	Abstracts on humans	Cases retrieved from articles*
Austria	2		
Belgium			
Bulgaria			
Cyprus			
Czech Republic	5	9	6556
Denmark	3		
Estonia	2		
Finland	5		
France		3	29
Germany	12	16	2987
Greece			
Hungary	1		
Iceland			
Ireland			
Italy	6	1	34
Latvia	1		
Lithuania	3	4	5480
Luxembourg	1		
Malta			
The Netherlands	1		
Norway			
Poland	4		
Portugal			
Romania			
Slovakia			
Slovenia	1	9	3132
Spain	1		
Sweden	4	8	654
Switzerland	2	8	2327
UK			
Total	54	58	21199

**Only data not duplicating surveillance data provided by countries within the current project.*

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