A survey on cases of tick-borne encephalitis in European countries

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The European Network for Diagnostics of "Imported" Viral Diseases (ENIVD) is finalising a project to improve the diagnostic and monitoring of encephalitis viruses in Europe. Part of this study was to analyse the present surveillance situation for tick-borne encephalitis (TBE), which is the most important flavivirus infection of the central nervous system in the European Union (EU) and Russia. A questionnaire was mailed to contact points in all Member States of the EU and three non-EU countries (Norway, Russia and Switzerland) to summarise their TBE surveillance and prevention activities. Information was requested on case definition, type of laboratory tests for TBE diagnostics, investigations regarding tick-transmitted diseases, mapping of endemic foci, vaccination programmes, and recommendations for travellers. The survey gives an overview of the existing epidemiological and laboratory sources of information and the number of TBE cases from 2004 until 2007, but also showed that, in particular, case definitions, diagnostic assays for confirmation, and methods/indicators for mapping risk areas differ widely across the participating countries. The data will help to develop recommendations for the standardisation and quality control of TBE surveillance and diagnostics.

Introduction

Tick-borne encephalitis (TBE) is the most important flavivirus infection of the central nervous system (CNS) in Europe and Russia. The total annual number of cases is estimated to be up to 10,000 in Russia and about 3,000 in European countries [1-4]. According to the International Committee for Taxonomy of Viruses, TBE virus is classified as one species with three subtypes, namely the European subtype (which comprises almost all known isolates from Europe), the Siberian subtype (mainly isolates from Urals, Siberia and far-eastern Russia) and the Far Eastern subtype (mainly isolates from far-eastern Russia, China and Japan).

The three TBE virus subtypes are associated with varying degrees of disease severity [2-4]. Human infections with Far Eastern subtype viruses are usually severe, frequently with encephalitic symptoms (focal meningoencephalitis or polyencephalitis), with an associated fatality rate between 5 and 35%. This type does not cause chronic disease. In contrast, TBE virus infections of the Siberian subtype cause a less severe disease (fatality rate between 1 and 3%), with a tendency for patients to develop chronic or extremely prolonged infections accompanied by diverse neurological and/or neuropsychiatric symptoms. In contrast to these two forms, infections caused by European strains typically take a biphasic course [5]: after a short incubation period (usually 7–14 days, with extremes of 4–28 days), the first (viraemic) phase presents as an uncharacteristic influenza-like illness lasting 2–4 days (range 1–8 days) with fever, malaise, headache, myalgia, gastrointestinal symptoms, leukocytopenia, thrombocytopenia and elevated liver enzymes, often followed by a symptom-free interval of about one week (range 1–33 days). The second phase of TBE occurs in 20–30% of infected patients and is marked by four clinical features of different severity (meningitis, meningoencephalitis, meningoencephalomyelitis or meningoencephalo-radiculitis) and the appearance of specific antibodies in the serum and cerebrospinal fluid (CSF). This is usually the time when patients with high fever and severe headache seek medical advice. The fatality rate in adult patients is less than 2%. However, severe courses of TBE infection with higher mortality and long-lasting sequelae often affecting the patient's quality of life have been correlated with increased age [6-8]. More detailed information on the clinical picture, case definition and other issues of interest are available in a TBE fact sheet on the ENIVD website [http://www.enivd.org].

The epidemiology of TBE is closely related to the ecology and biology of ticks [2,3,9,10]. In nature, TBE virus is propagated in a cycle involving permanently infected ticks and wild vertebrate hosts. Virus transmission occurs horizontally between tick vectors and vertebrates, especially between spring and autumn, with small mammals (mainly rodents) serving as virus reservoirs. In addition, trans-stadial and trans-ovarial transmission of the virus, as well as co-feeding of infected and non-infected ticks on the same host play a major role in virus transmission [11]. In contrast to other tick-transmitted diseases, such as Lyme borreliosis, TBE is distributed in an endemic pattern of so-called natural foci over a wide geographical area focussed on central Europe, the Baltic states and Russia. The distribution of TBE is determined by the occurrence of the respective tick vectors in certain regions [3,10]. While Ixodes ricinus is the prevalent hard tick species across Europe and therefore the most important transmitter of the European TBE virus subtype, Ixodes persulcatus occurs in forest regions of the Urals, Siberia and far-eastern Russia and is the main vector of the other subtypes. Co-circulation of two or all three subtypes could be shown for Finland and the Baltic states where the distribution areas of the two main tick species overlap [12,13].

However, the virus prevalence in ticks as well as the prevalence of infected ticks within the risk areas can vary [4,9,14,15]. Countries with high-risk areas are Russia, Latvia, Lithuania and Estonia. TBE is also a significant issue in Germany, the Czech Republic, Poland, Switzerland, Sweden, Finland, Slovakia, Hungary and Slovenia. Even in Austria, the only country with progressively decreasing

incidences since 1981 (due to high vaccination coverage [16]), the occurrence of TBE may be of relevance for unvaccinated tourists. In France, Italy, Greece, Norway and Denmark, TBE is of minor importance. In the United Kingdom, Ireland, Belgium, the Netherlands, Luxembourg, Spain and Portugal, TBE is not indigenous. Detailed epidemiological statistics from 1990 onwards can be obtained from the website of the International Scientific Working Group on TBE [http://www.isw-tbe.info].

An increase of TBE incidence has been observed in the risk areas (both high- and low-risk) in some of the endemic countries mentioned above, especially in the last decade [15,17-20]. In addition, new TBE foci have appeared in Europe. This is due to a complex interrelation of several factors, such as social (e.g. socio-political changes, human leisure activities), ecological (e.g. effects of climate changes on vectors) and/or technological factors (e.g. advanced diagnostics and increased medical awareness) [20-24]. The collection of epidemiological data is indispensable in order to predict endemic foci and to recommend preventive measures. Several methods can be employed to investigate the epidemiological situation of TBE [10]:

1. examination of ticks and animal reservoirs for the presence of TBE virus (especially by molecular diagnostic techniques);
2. seroprevalence study of people exposed to ticks; and
3. describing clinical cases and their geographical location.

TBE is a growing concern in Europe, but the surveillance and notification schemes are not uniform and not always mandatory and may affect the prevalence estimates for the disease in certain regions [25,26]. Main problems are the lack of a Europe-wide standard case definition, wide differences in the quality of national surveillance of TBE cases, and varying diagnostic procedures. Thus, surveillance data from different countries are difficult to compare. Furthermore, little is known about the true TBE virus prevalence in tick populations or about the circulation of new subtypes in Europe.

Currently, the European Network for Diagnostics of "Imported" Viral Diseases (ENIVD) is finalising a project to improve the diagnostic and monitoring of encephalitis viruses in Europe. Its tasks are being defined in several working groups [27]. Here, the ENIVD-working group for TBE virus describes the results of a questionnaire survey on the present TBE surveillance situation in Europe, which will help to develop recommendations for the standardisation and quality control in TBE surveillance and diagnostics.

Methods

To request information on TBE surveillance and prevention activities in national surveillance systems, a questionnaire with 10 questions was mailed to contact points in all member states of the European Union (EU) and three non-EU countries (Norway, Russia and Switzerland) based on an ENIVD database of expert microbiologists and epidemiologists. The questions were the following:

1. Is TBE a notifiable disease in your country? (Since when?)
2. Is there an official reference base to which the annual number of cases is reported?
3. Does a clear case definition for TBE exist? (If yes, what is it?)
4. What kind of diagnostic assays are used most often to diagnose TBE?
5. Is there an expert or reference laboratory for TBE infections in your country? (If yes, what are their contact details?)
6. What was the annual number of human cases between 2004 and 2007?
7. Are there any regular investigations regarding tick-transmitted diseases? (If yes, what kind of investigations?)
8. Do you map endemic foci/risk areas? (If yes, based on what kind of data?)
9. Is there an official vaccination programme for TBE in your country?
10. Are there official recommendations regarding TBE vaccination for travellers to TBE endemic areas?

Results

Of 30 contacted countries, 19 EU member states and three non-EU countries (Norway, Russia and Switzerland) participated in this survey (recovery rate: 73%) (Figure 1). All contributors are listed in the acknowledgements section. The completed questionnaires were returned during the summer trimester of 2007. The TBE case numbers for 2007 were added afterwards in February/March 2008. Therefore, the results of this survey reflect national surveillance systems and case numbers for TBE up to these dates.

FIGURE 1

Form of notification for tick-borne encephalitis in Europe and Russia (survey participants)

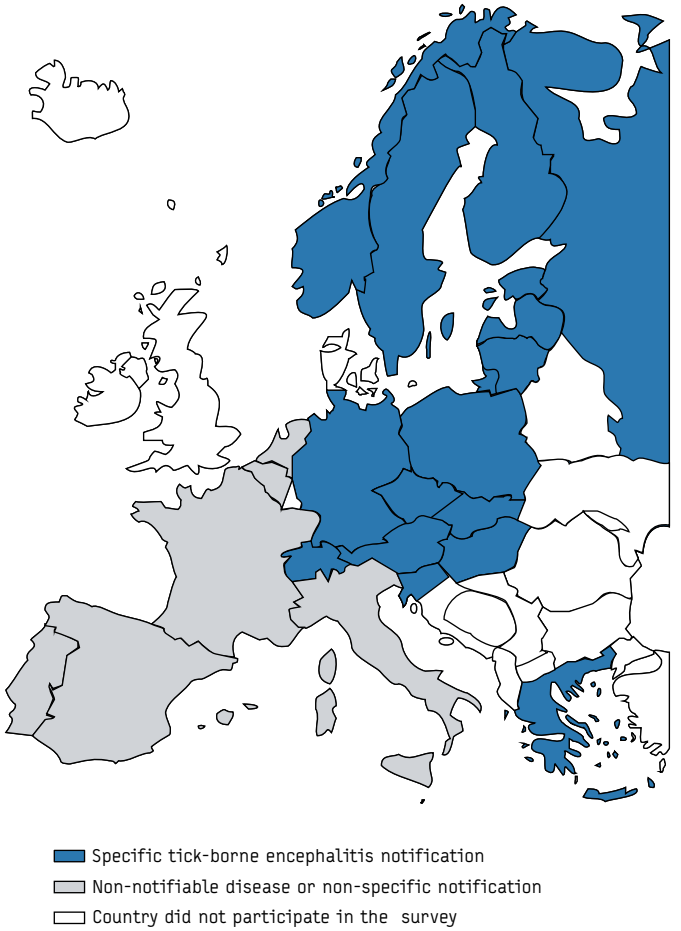


Table 1

Survey data regarding surveillance systems on tick-borne encephalitis in European countries*

Member State	Notifiable disease	Case definition	Diagnostic assays	Investigations regarding tick transmitted diseases	Mapping of endemic foci/risk area	Vaccination programme	Recommendations for travellers
Austria	Yes[1]	Serological proven hospitalised TBE cases are counted	ELISA	Survey on TBE and borreliosis	For human cases	Yes	Yes
Belgium	No	No	ELISA, PCR	Research project on anaplasmosis, babesiosis, TBE (2007-2010)	In development for human cases, vectors and hosts (rodents, roe deer)	No (optional)	Yes
Czech Republic	Yes, since 1971	Clinical and laboratory signs of aseptic meningitis/ meningoencephalitis and positive TBE virus serology	Mostly ELISA, in NRL for arboviruses: CFT and VNT	Tick surveillance in natural foci (TBE and borreliosis)	For human cases and infected ticks	No (optional)	Not known
Estonia	Yes, since 1970	Possible case: typical clinical case history (biphasic course of infection), epidemiological links (e.g. tick bite); Confirmed case: with laboratory confirmation: not less than four-fold increase in antibody titre in pair-sera or IgM-antibodies in serum/CSF or positive PCR[5]	IFA, ELISA, VNT, PCR, SEQ, VI, WB, HIA	Survey on TBE	For human cases	No (optional)	Yes
Finland	Yes, since 1996	TBE virus-IgM positive with suitable clinical and anamnestic data (not exposed to other flaviviruses)[6]	IgM micro-capture ELISA and HIA (PCR only for tick studies)	Tick field surveys (TBE, babesia and anaplasma)	For human cases	Yes, only Åland islands (since 2006)	Yes
France	No	For the diagnosis of TBE, a double check on a pair of serum samples is required (not further specified)	ELISA, VNT only in very few cases (PCR not in routine)	Survey on patients with risk of exposure in infested areas as well as outside	For human cases (only Alsace region)	No (optional)	No
Germany	Yes, since 2001	Clinical CNS symptomatic case with positive PCR in blood/CSF or IgM- and IgG-antibodies in blood/CSF or increase in IgG-antibody titre or intrathecal antibody production[7]	ELISA	Tick surveillance (TBE); surveys on borreliosis and rickettsiosis	For human cases	Yes	Yes
Greece	Yes[2]	Clinical CNS symptomatic case with: positive PCR in clinical sample, increased IgG and IgM antibody titres of, IgM detection in CSF, virus isolation	ELISA, IFA, PCR, VI	Survey on TBE (human cases, serosurvey, ticks); survey on CCHF and on bacterial tick-borne diseases	For human cases and ticks, in northern Greece	No (optional)	Yes, if requested
Hungary	Yes since 1977	Aseptic meningitis, encephalitis or meningoencephalomyelitis confirmed by laboratory tests	IFA, HIA, ELISA	Regular: human cases, serosurvey (TBE); project on tick survey (until 2008)	For human cases and TBE natural foci	Yes, for people at occupational risk	No
Italy	no[3]	No	IFA, VI, PCR, micro-neutralisation	not known	For human cases (only north-eastern Italy)	No (optional)	No
Latvia	Yes, since 1999	No	ELISA	Survey on TBE and borreliosis; tick survey	For human cases and infected ticks	Yes, for children (since March 2007)	Yes
Lithuania	Yes, since 1969	Officially no, but reported cases are serologically proven hospitalised TBE cases	ELISA	Annual tick activity	For human cases	No (optional)	Yes
Poland	Yes, since 1970	Clinical description: typical clinical case history (biphasic course of infection); Laboratory criteria: demonstration of four-fold or greater rise of antibody titre in serum or demonstration of intrathecal antibodies or virus isolation from tissues, blood or CSF (for probable case: demonstration of IgM antibodies in serum with no history of previous flaviviral exposition); classification in possible, probable or confirmed cases[8]	ELISA	Survey on TBE and borreliosis	For human cases	Recommended for high-risk groups, but not reimbursed (optional)	Yes
Portugal	No	No	IFA	Survey on rickettsia, borrelia and arboviruses; tick survey	No	No (optional)	No
Slovakia	Yes, since 1950	Not known	ELISA, HIA (PCR in specific cases)	Survey on TBE and tick survey	No	No (optional)	Yes
Slovenia	Yes, since 1977	A case of TBE is considered to be confirmed by the following findings: fever, clinical signs/ symptoms of meningitis or meningoencephalitis, an elevated CSF cell count (>5x10^5 cells/L), and serum IgM anti-bodies to TBE virus and/or IgG seroconversion	ELISA, PCR	Survey on human cases and in ticks for TBE, borreliosis, rickettsiosis, anaplasmosis and further tick-borne pathogens	For human cases, ticks and reservoirs	Yes	Yes
Spain	No	No	ELISA, PCR	Survey on bacterial tick-borne diseases	No	No (optional)	Yes
Sweden	Yes[4], since 2004	Under discussion, but reported cases are based on clinical picture and positive serology	ELISA	No	Human cases, incidence	No (optional)	No
The Netherlands	No	No	ELISA, PCR	Survey on borreliosis (RIVM, Bilthoven)	For borellia	No (optional)	No
Norway	Yes, since 1975	No	ELISA	Survey on borreliosis	For human cases, serosurvey in dogs (areas of Kristiansand)	No (optional)	No
Russia	Yes, since 1950	No formal case definition	ELISA	Survey on human cases and in ticks forTBE, orreliosis, rickettsiosis, CCHF	For human cases and infected ticks	Federal level: optional; regional level: yes	No
Switzerland	Yes, since 2001	Not known	ELISA	No	For human cases and natural reservoirs	Yes, recommended for high-risk groups	Yes

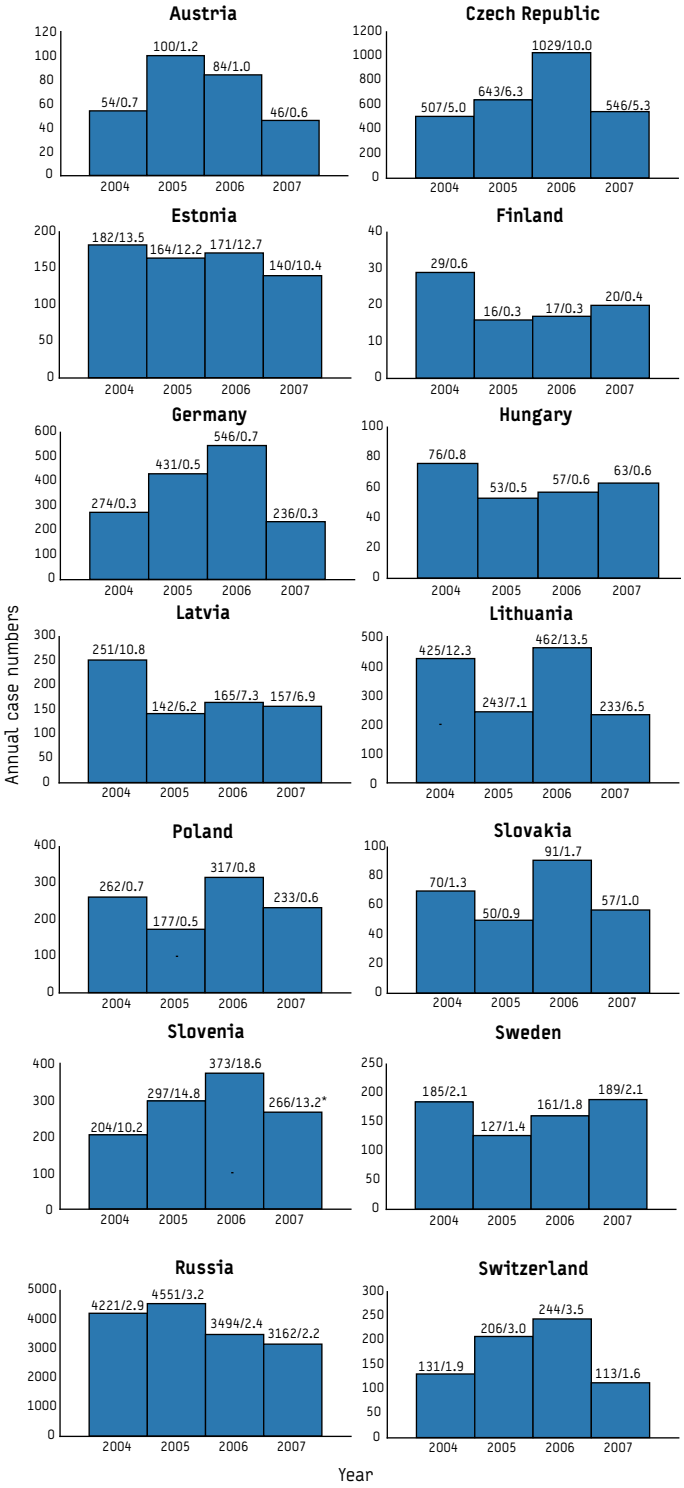
* Data provided by listed contributors.

[1] Notified if meningoencephalitis. Start of notification not further specified.
[2] Notification as arboviral encephalitis since 2002 as part of the Commission decision 2002/253/EC.
[3] Notification of all acute viral encephalitis cases since 1990. Not specifically TBE.
[4] Notifiable 1969-1989, and again from July 2004. Voluntary reporting during the period 1990 - June 2004.
[5] Case definition used since 2004.
[6] A Baltic/Nordic working group on TBE started in October 2007 to discuss an appropriate case definition.
[7] Case definition of the Robert Koch Institute according to the Law for the Prevention of Infections (Infektionsschutzgesetz, IfSG), 2007
[8] Case definition used since January 2005.

CFT: complement fixation test; CSF: cerebrospinal fluid; ELISA: enzyme linked immunosorbent assay; HIA: haemagglutination inhibition assay; IFA: immunofluorescence assay; PCR: polymerase chain reaction; SEQ: sequencing; VI: virus isolation; VNT: virus neutralisation; WB: Western blot. CCHF: Crimean Congo haemorrhagic fever; TBE: tick-borne encephalitis. NRL: National reference laboratory

FIGURE 2

Annual case numbers and incidences (per 100,000 inhabitants) of tick-borne encephalitis in European countries, 2004-2007



* Slovenia 2007. No officially confirmed laboratory data (usually 25% higher than the mandatorily reported cases)

Case reporting

While TBE cases were specifically notifiable in 16 of the 22 participating countries (73%), at the time of the survey, notification of TBE was not mandatory in Belgium, France, Italy, Portugal, Spain and the Netherlands (Figure 1). Of the 16 countries with TBE notification, eight (Austria, Czech Republic, Germany, Greece, Hungary, Poland, Slovenia and Sweden) had a case definition based on clinical criteria and laboratory confirmation, two (Estonia and Finland) also included cases with an epidemiological link (e.g. tick bite), and the remaining six countries (Latvia, Lithuania, Norway, Russia, Slovakia, and Switzerland) had no officially or clearly formulated case definition (Table 1). From Finland and Sweden we know, that the present case definitions are under discussion and will soon be harmonised among the Baltic and Nordic states (the discussion started in October 2007 and is planned to be done by June 2008).

Although clear case definitions were provided by ten countries, differences could be seen in the classification of relevant TBE cases as aseptic meningitis, meningoencephalitis and/or meningoencephalomyelitis (see e.g. classifications in Austria, Czech Republic, Hungary or Slovenia), as well as in the application of laboratory tests for case confirmation (Table 1). Commonly, the routine laboratory diagnosis of TBE is based on the detection of specific antibodies by enzyme linked immunosorbent assay (ELISA) as done in 20 participating countries (91%). Polymerase chain reaction (PCR) is included for particular investigations (e.g. tick studies or severe cases) by 10 countries (45%); followed by other methods like immunofluorescence assay in five countries; haemagglutination assay and virus neutralisation tests in four countries, respectively; and virus isolation in three countries. Other less common methods like complement fixation test, sequencing and Western blot are used in the Czech Republic and Estonia.

Surveillance activities

While for Italy, Sweden and Switzerland information on further investigations regarding tick-transmitted diseases (e.g. TBE, borreliosis, babesiosis, ehrlichiosis, rickettsiosis) were not available, the other 19 countries could provide these data (Table 1). They conduct mainly human serosurvey studies on borreliosis or TBE (10 countries each), followed by surveys on rickettsiosis in five countries. Surveys on the prevalence of TBE virus in tick populations were also performed in seven countries; for anaplasma (the causative agent of ehrlichiosis in Europe) and borrelia in four countries, and for babesia, rickettsia and other relevant pathogens in three countries, respectively. All countries except Portugal, Slovakia and Spain provided information on what kind of data they based their TBE risk assessments on (Table 1). The mapping of risk areas is mainly based on the geographical incidence of autochthonous clinical cases (18 countries), while seven countries also included data on infected ticks in the risk assessment, and only four countries used data from natural reservoirs (e.g. rodents) or indicator hosts (e.g. roe deer, dogs). The Netherlands used this kind of data only for risk assessment of borreliosis.

Trends in TBE incidence

Based on the data from this survey we are able to present an overview of the TBE situation in 14 European countries from 2004 until 2007 (Figure 2). Other participating countries have provided no (Belgium, Greece, Italy, Portugal, Spain) or only few data (France, The Netherlands, Norway).

For the presented period of the past four years certain tendencies/changes in the TBE incidence can be extracted. Following clear increases of the annual case numbers in 2004-2006 (approximately two-fold) in the Czech Republic (with more than 1,000 cases in 2006, the highest reported number since notification began), Germany (with an all-time high of 546 cases in 2006), Slovenia (with 373 cases in 2006, the highest number since 1994) and Switzerland (with the highest number, 244 cases, in 2006) the incidences in these countries declined in 2007. A similar trend in annual TBE case numbers could be observed for Austria. However,

Table 2

Survey data regarding surveillance systems on tick-borne encephalitis in European countries*

Member State	Reference	Expert or reference laboratory†
Austria	http://www.virologie.meduniwien.ac.at/home/virus-epidemiologie/virusepidemiologische-information/lang_1-content.html (Institute of Virology, Medical University of Vienna)	Univ.-Prof. Dr. F. X. Heinz Institute of Virology, Medical University of Vienna
Belgium	http://www.iph.fgov.be/epidemio/epien/index0000.htm (Scientific Institute of Public Health, Brussels)	Dr. P. Heyman Research Laboratory for Vector-borne Diseases, Queen Astrid Military Hospital, Brussels
Czech Republic	http://www.szu.cz/cema/epidat/epidat.htm (National Institute of Public Health, Prague)	Prim. Dr. J. Januška NRL for arboviruses, National Institute of Public Health, Ostrava
Estonia	http://www.tervisekaitse.ee/ (Health Protection Inspectorate, Tallinn)	Dr. I. Golovljova National Institute for Health Development, Tallinn
Finland	http://www3.ktl.fi (National Public Health Institute, Helsinki)	Prof. O. Vapalahti Haartman Institute, University of Helsinki
France	http://www.pasteur.fr/sante/clre/cadrecnr/arboFHV-index.html (National Reference Centre for Arboviruses, Lyon)	Dr. H. Zeller Unit for the biology of emerging viral infectious (UBIVE) Institut Pasteur, Lyon
Germany	http://www.rki.de/DE/Content/Infekt/EpidBull/epid__bull__node.html (Robert Koch-Institute, Berlin)	Prof. J. Süss NRL on tick-borne pathogens, Friedrich-Löffler-Institute, Jena
Greece	http://www.keel.org.gr/ (Hellenic Centre for Infectious Disease Control, Athens)	Prof. A. Papa School of Medicine, Aristotle University of Thessaloniki
Hungary	Yearbook of Health Statistics (National Centre for Epidemiology, Budapest)	Dr. E. Ferenczi NRL for viral zoonoses, National Center for Epidemiology, Budapest
Italy	not provided	Dr. L. Nicoletti Arbovirus Laboratory, Italian National Institute of Health,(Istituto Superiore di Sanitá), Rome
Latvia	http://www.sva.lv/epidemiologija/statistika/ (State Public Health Agency, Riga)	Dr. T. Kolupajeva Infectology Centre of Latvia, Riga
Lithuania	http://www.ulpkc.lt (Centre for Communicable Disease Prevention and Control, Vilnius)	Dr. A. Griskevicius Lithuanian AIDS centre laboratory, Vilnius
Netherlands	not provided	Dept. of Virology, Unit Diagnostics, Erasmus MC, Rotterdam and Laboratory of Virology, National Institute for Public Health and the Environment (RIVM), Bilthoven
Poland	http://www.pzh.gov.pl/epimeld/index_a.html (National Institute of Hygiene, Warsaw)	Associate Professor B. Litwińska NRL for arboviruses, National Institute of Hygiene, Warsaw
Portugal	not provided	Dr M.T. Paixão Centre for Vectors and Infectious Diseases Research (CEVDI) National Institute of Health, Lisboa
Slovakia	Regional Public Health Authority, Banska Bystrica	Ing. Z. Sirotná NRC for arboviruses, Public Health Authority of the Slovak Republic, Bratislava
Slovenia	http://www.ivz.si/ (Institute of Public Health Republic of Slovenia, Ljubljana)	Prof. Dr. T. Avšič-Županc Instituteof Microbiology and Immunology, University of Ljubljana
Spain	http://cne.isciii.es (National Centre of Epidemiology, Institute of Health Carlos III, Madrid)	Dr. A. Tenorio CNM Institute of Health Carlos III, Majadahonda-Madrid
Sweden	Annual report of the Department of Epidemiology, Swedish Institute for Infectious Disease Control	Swedish Institute for Infectious Disease Control, SE 171 82 Solna, Sweden
Norway	http://www.msis.no/emsisexternalweb/Forside.htm#_Welcome_to_the (Norwegian Institute of Public Health, Oslo)	not provided
Russia	Annual (or biannual) Book "Infectious morbidity in the provinces of Russian Federation" (Federal Centre of Hygiene and Epidemiology, Moscow)	Dr. A.E. Platonov Laboratory for arboviruses, Central Institute for Epidemiology, Moscow
Switzerland	http://www.bag.admin.ch/k_m_meldesystem/00733/00804/index.html?lang=de (Federal Office of Public Health, Bern)	Dr. D. Schultze Institute for Clinical Microbiology (IKMI), St. Gallen

* Data provided by listed contributors.
† Further contact information can be provided on request.
NRL: National Reference Laboratory; NRC: National Reference Centre

the incidence in Slovenia changed dramatically from 10.2 cases per 100,000 inhabitants in 2004 to 18.6 cases per 100,000 in 2006, and is now similar to incidences in Lithuania and Estonia, countries that are usually among the countries with the highest incidence rates. In Latvia, the incidence has decreased significantly in 2005 and since remained stable with approximately seven cases per 100,000 inhabitants. Among the Nordic countries, Sweden had the highest incidences with a gradual increase from 127 cases in 2005 to 189 cases in 2007. While Lithuania, Poland and Slovakia showed considerable fluctuations in the annual TBE case numbers, the trends in the remaining countries were more or less stable. However, we found high incidence levels in the Czech Republic, Estonia, Latvia, Lithuania and Slovenia in 2007 (5.3-13.2), considerable incidence levels for Slovakia, Sweden, Russia and Switzerland (1.0-2.2), and incidence levels under 1.0 cases per 100,000 inhabitants for Austria, Finland, Germany, Hungary and Poland. The epidemiological and laboratory sources of information for the TBE surveillance data are listed in Table 2.

Vaccination policy

Only in Austria, Finland, Germany, Hungary, Latvia, Slovenia, Russia and Switzerland, TBE vaccination is included in an official governmental vaccination programme under certain conditions. In the remaining 14 countries, it is available as an optional vaccination, partly recommended, but not reimbursed by health insurance companies (Table 1). In Austria (with a successful vaccination campaign since 1981), Germany and Switzerland, health insurance companies cover the vaccination costs for people who are at risk of exposure to ticks in risk areas [28-30]. In Finland, TBE vaccination has been offered for free since 2006 only for the Åland islands which have the highest incidence rate of the country. Hungary has a programme only for people at occupational risk. Also in Slovenia, vaccination is only obligatory for forest workers, farmers, military personnel and other occupationally exposed people. In Latvia, a free vaccination programme was started for children from regions with high incidences in March 2007. TBE vaccination in Russia is recommended, but currently not financed by federal budget. There are some programmes on regional level based on province budget or other financial sources.

Travel recommendations

Austria, Belgium, Estonia, Finland, Germany, Greece, Latvia, Lithuania, Poland, Slovakia, Slovenia, Spain and Switzerland stated that they had more or less official recommendations regarding TBE vaccination for people travelling to endemic areas, the other nine participating countries did not provide information on this issue (Table 1). Although the responses to this part of the questionnaire suggested that the contact points had not interpreted the question in the same way, it can be deduced that information for travellers is given for following purposes:

a) General information included in national vaccination programmes for citizens coming from non-endemic regions (e.g. in Austria and Poland);
b) Information on the endemic status of a country for citizens and visitors (limited information in the Baltic states, Slovakia and Slovenia, and comprehensive information in Finland, Germany and Switzerland);
c) Information on the endemic status of foreign countries for citizens travelling abroad (e.g. in Belgium and Spain).

Discussion

TBE is an emerging disease which occurs and spreads among central and western European countries, Scandinavia, countries from the former Soviet Union, and Asia where it has a significant impact on public health. The epidemiology of TBE is very complex, and closely related to the distribution of ixodid ticks. Based on this survey which comprises updated information on TBE surveillance in Europe since the last overview published in 2004 [31], TBE is a notifiable disease, namely in Austria, the Baltic states, Czech Republic, Finland, Germany, Greece, Hungary, Norway, Poland, Russia, Slovakia, Slovenia, Sweden and Switzerland.

While we were able to present an overview of the TBE situation in 14 European countries (based on annual case numbers from 2004 to 2007) in which the disease poses a major threat to public health, other participating countries provided no or only very few data for this survey. A reason for this could be that TBE is not indigenous or a disease of minor importance in these countries. However, single cases of TBE have been documented in France in the Alsace region and more recently in Bordeaux [32], in the northern as well as central part of Italy [1], in northern Greece [33], and also in Norway (southern coast area) and Denmark (Bornholm) [34]. Unfortunately, details about the TBE annual case numbers in Romania and other eastern European countries could not be obtained and remain unclear.

To understand the described tendencies and changes in the TBE incidence during the past four-year-period as well as the fluctuation in incidence rates observed particularly during the last decade among European countries, a complex interrelation of several factors has to be considered, such as social, ecological and/or technological factors [15, 17-24]. It seems more appropriate to base a discussion of the TBE epidemiology on these factors – the importance of which can vary depending on the country – rather than on climate change alone. In particular, due to the mild winter in 2006/2007, it was not to be expected that the TBE incidences would decline in 2007 for Austria, the Czech Republic, Germany, Slovenia and Switzerland. Similar observations have been discussed in previous publications regarding the increase of incidence and appearance of new foci, for example in Nordic and Baltic states [24,35]. Thus changes of leisure activities in nature, increasing/decreasing mobility to risk areas, changes in wildlife hosts/tick populations, improved diagnostics or vaccination campaigns may have influenced the quantity and quality of epidemiological data. In the case of Latvia, the observed decrease in incidence from approximately 11 cases per 100,000 inhabitants in 2004 to seven cases per 100,000 in 2005 and the following years, probably reflects the initiation of vaccination activities [36].

Knowledge about endemic foci needs to be expanded (also in countries where TBE is of minor importance) and regularly updated in order to identify the risk for the exposed population and to apply TBE vaccines in an optimal way. For an appropriate collection of epidemiological data, a broad standard case definition including all possible clinical signs of laboratory-confirmed TBE should be used in European countries in order to avoid under-ascertainment of cases and to increase the knowledge on the true incidence of TBE [25,26].

Currently, the routine laboratory diagnosis of TBE is based mainly on the detection of specific antibodies in serum and CSF, usually by ELISA. However, certain limitations need to be taken into consideration when using serological methods [37]: An early diagnosis by detecting only IgM is questionable, since IgM antibodies can persist for up to 10 months in vaccinees

or individuals who acquired the infection naturally. Therefore, confirmation by detection of specific IgG is recommended, but may turn out negative in the first phase of infection. Although it is necessary to monitor IgG titres one or two weeks later for a possible increase, this is rarely done. Moreover, a major problem when using ELISA and IFA are cross-reactions of antibodies induced by other flavivirus infections or vaccinations (e.g. Dengue virus, West Nile virus, Yellow fever virus and Japanese encephalitis virus). It is therefore advised to verify positive results by neutralisation test. Due to the use of infectious virus particles, this requires the handling in biosafety level 3 facilities, making the test time-consuming, expensive and only available in highly specialised laboratories. PCR techniques have also been developed in a remarkable way lately and new publications reveal that RT-PCR methods can be of great diagnostic value in the early diagnosis of TBE and in the discrimination among virus subtypes [37]. However, they are mainly restricted to the first phase of infection. Serological and/or molecular testing should be performed using standard operation protocols (SOPs) among European countries and should be regularly monitored by external quality assurance programmes to guarantee the comparability of data from clinical diagnosis, epidemiological surveillance and surveys on the incidence of TBE virus in ticks and vertebrate hosts [38].

While Lyme borreliosis, another tick-transmitted disease of similar epidemiological importance in Europe, can be treated with antibiotics, no specific treatment for TBE is available to date and the administration of TBE immunoglobulin for a passive post-exposure prophylaxis is highly questionable [39] and not recommended anymore for example in Germany. The last application was discontinued many years ago as the preparations for passive immunisation are no longer produced.

Due to the fact that TBE causes high costs for health care systems (intensive care in hospitals, possible long-lasting cognitive and neuropsychiatric sequelae etc.) TBE vaccination should be recommended and reimbursed for residents of and travellers to TBE endemic areas, who are at risk of tick bites. The Austrian example shows that systematically increased vaccination coverage will result in the decrease of morbidity and therefore hospitalised cases [16]. A further important question of great public health impact, not addressed in this survey, is the diagnosis of vaccine failure [25]. The protective efficacy of the widely used TBE vaccines cannot be properly evaluated if no quality assurance exists for the diagnosis of vaccine failures. Since this is a difficult procedure, the question arises of whether national reference laboratories on CNS diseases should handle the relevant tests and establish widely accepted criteria on how to define a vaccine failure. Furthermore, since awareness among tourists as well as consulting doctors is rather rare [22] recommendations for travellers should be provided by state institutions regardless of whether these institutions are in countries with endemic (e.g. Germany) or non-endemic (e.g. Spain) situation. These can be done using country-specific risk profiles based on the epidemiological data. Today, existing risk maps on this issue are mainly distributed through the vaccine manufacturers. Bringing national data on incidences and prevalence together and distributing such maps may therefore be an important role for a European public health institution.

The participating countries mainly applied the surveillance data from clinical cases as an indicator for predicting endemic foci and for recommending preventive measures. Due to the fact that incidences of human cases may decrease in future because of mass vaccination programmes, alternative indicators for risk assessment are necessary. Therefore, the intro-duction of tick or animal reservoir surveys for prevalence studies of TBE virus have a high priority and should be implemented in national surveillance systems as initiated in previous studies [40-42] . So far, methods for measuring virus prevalence in ticks or animal reservoirs have not been standardised, and reliable tools should be introduced to translate epizootic prevalence data into infection risk for humans.

The implementation of the recommendations given in this report could be helpful, to gain more valuable clinical and epidemiological data on TBE, to improve national surveillance systems and to reduce the incidence rate for the most important flavivirus CNS infection in Europe.

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