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 a 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 meningoencephaloradiculitis) 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 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)](image-url)
### Table 1

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

<table>
<thead>
<tr>
<th>Member State</th>
<th>Notifiable disease</th>
<th>Case definition</th>
<th>Diagnostic assays</th>
<th>Investigations regarding tick transmitted diseases</th>
<th>Mapping of endemic foci/risk area</th>
<th>Vaccination programme</th>
<th>Recommendations for traveller</th>
</tr>
</thead>
<tbody>
<tr>
<td>Austria</td>
<td>Yes(^1)</td>
<td>Serological proven hospitalised TBE cases are counted</td>
<td>ELISA</td>
<td>Survey on TBE and borreliosis</td>
<td>For human cases</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Belgium</td>
<td>No</td>
<td>No</td>
<td>ELISA, PCR</td>
<td>Research project on arbovirology, TBE</td>
<td>In development for human cases, vectors and hosts (rodenats, roe deer)</td>
<td>No (optional)</td>
<td>Yes</td>
</tr>
<tr>
<td>Czech Republic</td>
<td>Yes, since 1971</td>
<td>Clinical and laboratory signs of aseptic meningitis/meningoencephalitis and positive TBE virus serology</td>
<td>Mostly ELISA, in NRI, for arboviruses: CFT and VNT</td>
<td>Tick surveillance in natural foci (TBE and borreliosis) for human cases and infected ticks</td>
<td>No (optional) Not known</td>
<td>No (optional)</td>
<td>Yes</td>
</tr>
<tr>
<td>Estonia</td>
<td>Yes, since 1970</td>
<td>Possible cases: typical clinical case history (aflamphictic course of infection), clinical (i.e., tick bites) confirmed cases, laboratory confirmation not less than four-fold increase in antibody titre in pair sera or IgM-antibodies in serum/CSF or positive PCR(^2)</td>
<td>IGM microcapture ELISA and IHA (PCR only for tick studies)</td>
<td>Tick field surveys (TBE, babesia and anaplasma)</td>
<td>For human cases Yes, only Raad islands (since 2006)</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Finland</td>
<td>Yes, since 1996</td>
<td>TBE virus-IgM positive with suitable clinical and anamnetic data (not exposed to other flavivirus)(^3)</td>
<td>ELISA, VNT only in four cases (PCR not in routine)</td>
<td>Survey on patients with risk of exposure in infected areas as well as outside</td>
<td>For human cases for people at occupational risk No (optional)</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>France</td>
<td>No</td>
<td>For the diagnosis of TBE, a double check on a pair of serum samples is required (not further specified)</td>
<td>ELISA, IFA, ELISA, VNT, PCR, SEAL, VI, WB, HIA</td>
<td>Survey on TBE</td>
<td>For human cases No (optional)</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Germany</td>
<td>Yes, since 2001</td>
<td>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(^4)</td>
<td>ELISA</td>
<td>Tick surveillance (TBE) surveys on borreliosis and rickettiosis</td>
<td>For human cases</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Greece</td>
<td>Yes(^5)</td>
<td>Clinical CNS symptomatic case with positive PCR in clinical sample, increased IgG and IgM antibody titres of IgG detection in CSF, virus isolation</td>
<td>ELISA, IFA, PCR, VI</td>
<td>Survey on TBE (human cases, serosurvey, ticks); survey on arboviruses; tick survey</td>
<td>For human cases and ticks in northern Greece No (optional) Yes, if requested</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Hungary</td>
<td>Yes since 1977</td>
<td>Aseptic meningitis, encephalitis or meningocerebrophalomyelitis confirmed by laboratory tests</td>
<td>ELISA, IFA, ELISA</td>
<td>Regular human cases, serosurvey (TBE); project on tick survey (until 2008)</td>
<td>For human cases and TBE natural foci Yes, for people at occupational risk No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Italy</td>
<td>No(^6)</td>
<td>No</td>
<td>IFA, VI, PCR, micro-neutralisation</td>
<td>not known</td>
<td>For human cases (only north-eastern Italy) No (optional)</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Latvia</td>
<td>Yes, since 1999</td>
<td>No</td>
<td>ELISA</td>
<td>Survey on TBE and borreliosis; tick survey</td>
<td>For human cases and infected ticks Yes, for children (since March 2007)</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Lithuania</td>
<td>Yes, since 1964</td>
<td>Officially no, but reported cases are serologically hospitalised TBE cases</td>
<td>ELISA</td>
<td>Annual tick activity</td>
<td>For human cases No (optional)</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Poland</td>
<td>Yes, since 1970</td>
<td>Clinical description: typical clinical case history (aflamphictic 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 cases: demonstration of IgM antibodies in serum with no history of previous flavivirus exposure; classification in possible, probable or confirmed cases(^7)</td>
<td>ELISA</td>
<td>Survey on TBE and borreliosis</td>
<td>For human cases Recommended for high-risk groups, but not reimbursed (optional)</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Portugal</td>
<td>No</td>
<td>No</td>
<td>IFA</td>
<td>Survey on Rickettsia, borrelia and arboviruses; tick survey</td>
<td>No No (optional) No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Slovak Republic</td>
<td>Yes, since 1950</td>
<td>Not known</td>
<td>ELISA, IFA (PCR in specific cases)</td>
<td>Survey on TBE and tick survey</td>
<td>No (optional) Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Slovenia</td>
<td>Yes, since 1977</td>
<td>A case of TBE is considered to be confirmed by the following findings: fever, clinical signs/symptoms of meningitis or meningocerebrophalmyelitis, an elevated CSF cell count (&gt;5x10(^6) cells/L) and serum IgM anti-body reaction to TBE virus and/or IgG seroconversion</td>
<td>ELISA, PCR</td>
<td>Survey on human cases and in ticks for TBE, borreliosis, rickettiosis, anaplasmosis and further tick-borne pathogens</td>
<td>For human cases, ticks and reservoirs Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Spain</td>
<td>No</td>
<td>No</td>
<td>ELISA, IFA</td>
<td>Survey on bacterial, tick-borne diseases No</td>
<td>No No (optional) No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Sweden</td>
<td>Yes(^8), since 2004</td>
<td>Under discussion, but reported cases are based on clinical picture and positive serology</td>
<td>ELISA</td>
<td>No</td>
<td>Human cases, incidence No (optional) No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>The Netherlands</td>
<td>No</td>
<td>No</td>
<td>ELISA, PCR</td>
<td>Survey on borreliosis (RIVM, Bilthoven)</td>
<td>For borrelia No (optional) No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Norway</td>
<td>Yes, since 1935</td>
<td>No</td>
<td>ELISA</td>
<td>Survey on borreliosis</td>
<td>For human cases, serosurvey in dogs (areas of Kristiansand) No (optional)</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Russia</td>
<td>Yes, since 1950</td>
<td>No formal case definition</td>
<td>ELISA</td>
<td>Survey on human cases and Hf ticks for TBE, borreliosis, rickettiosis, arboviruses</td>
<td>For human cases and infected ticks Federal level; regional level; Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Switzerland</td>
<td>Yes, since 2001</td>
<td>Not known</td>
<td>ELISA</td>
<td>No</td>
<td>For human cases recommended for high-risk groups Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>

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*Data provided by listed contributors.*

1. Notified if meningitis/encephalitis. 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 1989. Not specifically TBE.
5. Case definition used since 2000.
7. A Baltic/Nordic working group on TBE started in October 2007 to discuss an appropriate case definition.
8. Case definition of the Robert Koch Institute according to the Law for the Prevention of Infections (Infektionsschutzgesetz, IfSG), 2007
**Figure 2**

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

**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 or indicator hosts (e.g. roe deer, dogs). The Netherlands used this kind of data only for risk assessment of borreliosis. Or indicator hosts (e.g. rodents) were also performed in seven countries; for anaplasma infection 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 (the causative agent of ehrlichiosis in Europe) and borrelia in four countries. They conduct mainly human serosurvey studies on borreliosis (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.

Table 2
Survey data regarding surveillance systems on tick-borne encephalitis in European countries*

<table>
<thead>
<tr>
<th>Member State</th>
<th>Reference</th>
<th>Expert or reference laboratory†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Austria</td>
<td><a href="http://www.virologie.meduniwien.ac.at/home/virus-epidemiologie/virusepidemiologieboche-information/lang_1-content.html">http://www.virologie.meduniwien.ac.at/home/virus-epidemiologie/virusepidemiologieboche-information/lang_1-content.html</a> [Institute of Virology, Medical University of Vienna]</td>
<td>Univ.-Prof. Dr. F. X. Heinz Institute of Virology, Medical University of Vienna</td>
</tr>
<tr>
<td>Belgium</td>
<td><a href="http://www.lph.fgov.be/epidemiologie/epen/Indextweis00.htm">http://www.lph.fgov.be/epidemiologie/epen/Indextweis00.htm</a> [Scientific Institute of Public Health, Brussels]</td>
<td>Dr. P. Heyman Research Laboratory for Vector-borne Diseases, Queen Astrid Military Hospital, Brussels</td>
</tr>
<tr>
<td>Finland</td>
<td><a href="http://www3.ktl.fi">http://www3.ktl.fi</a> [National Public Health Institute, Helsinki ]</td>
<td>Prof. O. Vapalahti Haartman Institute, University of Helsinki</td>
</tr>
<tr>
<td>Greece</td>
<td><a href="http://www.skeel.org.gr/">http://www.skeel.org.gr/</a> [Hellenic Centre for Infectious Disease Control, Athens]</td>
<td>Prof. A. Papa School of Medicine, Aristotle University of Thessaloniki</td>
</tr>
<tr>
<td>Hungary</td>
<td>Yearbook of Health Statistics [National Centre for Epidemiology, Budapest]</td>
<td>Dr. E. Ferenczi NNL for viral zoonoses, National Center for Epidemiology, Budapest</td>
</tr>
<tr>
<td>Italy</td>
<td>not provided</td>
<td>Dr. L. Nicoletti Arbovirus Laboratory, Italian National Institute of Health, [Istituto Superiore di Sanitá], Rome</td>
</tr>
<tr>
<td>Latvia</td>
<td><a href="http://www.sva.lv/epidemiologijasstatistikas/">http://www.sva.lv/epidemiologijasstatistikas/</a> [State Public Health Agency, Riga]</td>
<td>Dr. T. Kolupajeva Infectology Centre of Latvia, Riga</td>
</tr>
<tr>
<td>Lithuania</td>
<td><a href="http://www.slpk.lt">http://www.slpk.lt</a> [Centre for Communicable Disease Prevention and Control, Vilnius]</td>
<td>Dr. A. Griskevičius Lithuanian AIDS centre Laboratory, Vilnius</td>
</tr>
<tr>
<td>Netherlands</td>
<td>not provided</td>
<td>Dept. of Virology, Unit Diagnostics, Erasmus MC, Rotterdam and Laboratory of Virology, National Institute for Public Health and the Environment ([RIVM], Bilthoven</td>
</tr>
<tr>
<td>Portugal</td>
<td>not provided</td>
<td>Dr. M.T. Paixão Centre for Vectors and Infectious Diseases Research (CEVSI) National Institute of Health, Lisboa</td>
</tr>
<tr>
<td>Slovakia</td>
<td>Regional Public Health Authority, Banska Bystrica</td>
<td>Ing. Z. Strotná NNL for arboviruses, Public Health Authority of the Slovak Republic, Bratislava</td>
</tr>
<tr>
<td>Slovenia</td>
<td><a href="http://www.zv.si/">http://www.zv.si/</a> [Institute of Public Health Republic of Slovenia, Ljubljana]</td>
<td>Prof. Dr. T. Avšič-Zupanc Institute of Microbiology and Immunology, University of Ljubljana</td>
</tr>
<tr>
<td>Sweden</td>
<td>Annual report of the Department of Epidemiology, Swedish Institute for Infectious Disease Control</td>
<td>Swedish Institute for Infectious Disease Control, SE 171 82 Solna, Sweden</td>
</tr>
<tr>
<td>Norway</td>
<td><a href="http://www.msis.no/ens/externalweb/Forside.html#_Welcome_to_the">http://www.msis.no/ens/externalweb/Forside.html#_Welcome_to_the</a> [Norwegian Institute of Public Health, Oslo]</td>
<td>not provided</td>
</tr>
<tr>
<td>Russia</td>
<td>Annual [or biannual] Book “Infectious morbidity in the provinces of Russian Federation” [Federal Centre of Hygiene and Epidemiology, Moscow]</td>
<td>Dr. A.E. Platonov Laboratory for arboviruses, Central Institute for Epidemiology, Moscow</td>
</tr>
</tbody>
</table>

* 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 vaccines
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and non-endemic (e.g. Spain) countries with endemic (e.g. Germany) or

CNS diseases should handle the relevant tests and establish widely

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, potable 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.

*On behalf of the Working Group for Tick-borne encephalitis virus in the European Network for Diagnostics of "Imported" Viral Diseases (ENIVD)

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