Epidemiology of tick-borne encephalitis (TBE) in international travellers to Western/Central Europe and conclusions on vaccination recommendations

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Abstract

Background: Tick-borne encephalitis (TBE) endemicity is spreading in Europe becoming an increasing health risk also for travellers. Previous reviews on TBE in civilian travellers lacked of numerator data and offered at most rough estimates on denominator data. An evidence-based quantification of the risk so far has been impossible; that resulted in fundamentally differing vaccination recommendations.

Methods: A standard internet search was conducted with a focus on the data used to formulate vaccination recommendations. As TBE became notifiable at the European Union (EU) level the databases of European Center for Disease Prevention and Control (ECDC) were analysed for cases imported from abroad 2012. Since these included only 19 EU countries, individual experts were contacted in countries, which had not submitted data and additional surveillance databases were investigated to obtain a comprehensive account on travel-associated TBE in Central and Western Europe.

Results: In 2012, the ECDC and other data sources included 38 reported cases of internationally acquired TBE. Basing on estimates of the exposed number of visitors, the attack rate for an undefined period of time could be very roughly extrapolated to be 0.5–1.3 per 100 000 (1 per 77 000–200 000) overall in Western/Central Europe endemic areas for the exposed at-risk population.

Conclusions: As advised by the World Health Organization (WHO) travellers exposed outdoors in rural endemic areas to a risk of TBE during the period of transmission should be recommended immunization. In contrast, the advice to recommend TBE vaccination for all visitors of endemic areas is inappropriate. Implementation of the risk strategy is compromised by the fact that many at-risk travellers are unaware of the risk, thus they will not consult competent health professionals. Others may consult late, and in some countries of origin no TBE vaccine is marketed.

Key words: Travel, TBE, tick-borne encephalitis, epidemiology, vaccine, prevention

Introduction

The Basics on Tick-Borne Encephalitis TBE

Tick-borne encephalitis (TBE) is a viral infection involving the central nervous system, in the worst-case scenario resulting in long-lasting or permanent neuropsychiatric sequelae or death. This syndrome is associated with the transmission of the TBE virus by tick bites, rarely by ingestion of unpasteurized milk or milk products. Tick habitats are mainly forested and rural areas up to ~1500 m of altitude but ticks may also be found in gardens. In Eastern Europe, TBE endemicity in urban parks has been described. Transmission in Europe is usually limited to the period between April and November, although depending on the meteorological situation few infections may occur in the winter months.

In the European TBE endemic areas (Figure 1) just 0.1–5% (rarely in foci ≤ 30%) of the ticks are infected by the virus.
After an infected tick bite the majority of people will remain asymptomatic and only (2 to) 30% of the individuals will develop an initial non-specific febrile illness lasting a few days, followed by an asymptomatic interval.\textsuperscript{3,4} Approximately one-third of those who initially had symptoms will develop neurological symptoms.\textsuperscript{5} The older the patient the more serious the symptoms will be. According to a 10-year follow-up survey, 80% of patients with primary myelitis manifestation will remain with sequelae.\textsuperscript{6} The case fatality rate in Europe is 0.5–2%; it is higher in Siberia and in the Far East.\textsuperscript{5}

Preventive Options Against TBE Infection

As there is no effective treatment for TBE, prevention is paramount. It is difficult to avoid exposure in habitats that have a high tick density. Personal protection measures against tick bites, such as by clothing or repellents have a limited effectiveness.\textsuperscript{7,8} A skin inspection (‘tick check’) is not always feasible after exposure.

Vaccines offer the best protection against TBE. Two TBE vaccines are mainly available in Western Europe\textsuperscript{9} and also in a limited number of travel clinics in Australia.\textsuperscript{10} In Canada, the vaccine has been withdrawn from the market and the respective Public Health Agency Statement has been archived\textsuperscript{11} but another firm apparently has reapplied for a licence. Also in USA, no vaccination is available.\textsuperscript{12}

The two Western European vaccines are Encepur originally developed by Chiron Behring in Marburg, Germany, later produced and marketed by Novartis Vaccines, now by GlaxoSmithKline (GSK) and FSME-IMMUN developed by Immuno, later produced and marketed by Baxter, Vienna, Austria, now by Pfizer. These vaccines contain purified TBE virus from a German or an Austrian strain, respectively, both are grown in chick embryo fibroblasts, inactivated by formalin and both have aluminum hydroxide added as adjuvant. Following adverse event reports associated with previous generations of both vaccines, the manufacturers have modified their adult and pediatric formulations and this resulted in improved tolerance basing on clinical trials and post-marketing monitoring.\textsuperscript{7,9} A Cochrane review concluded that, ‘although adverse effects were commonly reported, none was serious or life threatening’.\textsuperscript{13} Accelerated schedules—particularly indicated for travellers requesting protection shortly before departure—have been tested for both vaccines. When a
second dose of FSME-IMMUN was given ~2 weeks after the first, a seroconversion exceeding 90% was demonstrated at least in those below the age of 50 years, for older subjects it was exceeding 80%, similar results were obtained with a rapid schedule using Encepur (0, 7, 21 days). Field effectiveness protection rates of 96–99% were demonstrated for persons vaccinated according to the regular Austrian schedule. Duration of protection is still subject to evaluation and discussion and not subject of this review. Neither widely known additional details about the use of these two vaccines nor the Russian and Chinese TBE vaccines will be discussed in this article.2,5,7,9,13–16

Although the problem of TBE in travellers had been recognized before, mainly since the turn of the century there have been a number of publications on differing vaccination recommendations for this target population. These will be discussed later. Additionally, a broad European expert group determined that ‘reliability of surveillance of TBE in European countries is necessary to improve the quality of vaccine recommendations’ in the general population.20 In 2012, the year following this claim, TBE became notifiable at the European Union (EU) level, including data on imported infections.21

The purpose of this article is to determine what evidence there currently is to recommend TBE vaccination for travellers in Europe excluding Russia, basing on recent notification data and a systematic literature review.

Methods

Literature Search Strategy

From the PubMed, Medline, Cochrane Database of Systematic Reviews and Google Scholar databases, the following combinations were searched (any time, no limitation to the period):

- tick borne encephalitis OR tbe OR tbev AND travel
- tick borne encephalitis OR tbe OR tbev AND military

The titles were reviewed to determine whether they related either to TBE epidemiological issues or vaccination recommendations in travellers. All others were excluded. Bibliographies of articles were used in an attempt to identify additional sources.

European Centre for Disease Prevention and Control, GeoSentinel and World Tourism Organization Databases

The first Annual Epidemiological Report of the European Centre for Disease Prevention and Control (ECDC) to include a chapter on TBE was published in November 2014.22 The published number and rates of TBE reported in EU and in European Economic Area (EEA) countries in the calendar year 2012 were evaluated. Details relating to the probable country of infection in imported cases were requested and data were provided by ECDC extracted from the European Surveillance System—TESSy. As several EU/EEA countries (Bulgaria, Cyprus, Denmark, Italy, Luxemburg, Malta, The Netherlands, Portugal and Iceland) had not submitted any national data, experts there were individually invited to submit data as far as such were available. Since Croatia, Switzerland and Liechtenstein were not included in the ECDC excel table, also those data were collected separately (Table 1).

GeoSentinel, the global surveillance network of the International Society of Travel Medicine (ISTM) in partnership with the Centres for Disease Control had previously recorded cases of TBE in travellers. Thus, it was invited to document recorded TBE cases, and particularly those detected in 2012.

Lastly, to obtain better denominator data on international tourists exposed to TBE risk, the U.N. World Tourism Organization (WTO) in Madrid was asked for guidance and data.

Results

Literature Review Relating to Civilian Travellers

There were 109 publications reviewed relating to the PubMed travel database. Five were excluded because the language was not understood (Danish, Dutch, Hungarian, Norwegian, Russian); in neither of them the English title indicated that relevant data would be presented. Also 49 articles were excluded, which only had general descriptions of TBE just mentioning the potential relevance to travellers. Further 22 reviews were not included because they were targeted on diagnostics, clinical, vaccine or viral issues or on national epidemiology, some in Asia only. Lastly, there were 17 unrelated publications, describing other viral infections, often dengue, veterinary problems, ticks, climatic changes or insurance issues related to TBE. Finally, there were 16 travel-related publications, 7 of them being anecdotal reports of TBE imported cases, the remaining 9 were relevant reviews.2,7,8,26–31 No additional publications of relevance were detected in the other databases.

Since all these reviews lacked proper data on rates in international travellers, they attempted to demonstrate the need for TBE immunization by using other data. The varying approaches are presented here in a structured manner:

Incidence Rate in the Local Population

Most described the TBE incidence in the local population in European endemic countries.2,7,8,28,31 Essentially in analogy to the risk in the resident population the authors in these articles concluded by indirect evidence on the need for TBE vaccination recommendations for visitors. Some particularly evoked the gradually increasing risk in the past decades, listing multiple associated factors,26,28 while others argued that an artefact related to improved diagnosis and surveillance might also play a role.7 Obviously low incidence rates in Austria or other countries with high vaccine coverage are misleading, and also vaccinated travellers originating in such countries will reduce the toll of TBE acquired abroad.3,7,9,28

Anecdotal Travel-Related TBE Case Reports

Several authors additionally collected anecdotal case reports.8,31 They concluded that this approach is bound to result in underestimation. This is true first because TBE was not notifiable in all EU countries until 2012, and second because of a lack of awareness particularly in non-endemic countries with subsequent failure to diagnose the illness.31 Lastly, imported TBE cases are usually not considered to be worth a publication, unless detected overseas.32–34 This is best demonstrated by the fact that among 8 TBE infections diagnosed and treated in institutions participating in the global GeoSentinel surveillance network 2005–2014...
(unpublished data) only a single had been reported; most of the infections had occurred before required notification.

### Proportion of Imported TBE Infections Among the Nationally Notified Cases

Annually 5–10 cases of imported TBE are noted in Sweden. Basing on Robert-Koch-Institut data 3–9% of cases detected in Germany were acquired abroad; among the 195 cases reported in 2012 that would be 6–18 cases. Among the cases registered in Switzerland and Liechtenstein an estimated 1–2% annually were imported by international travellers (E Altpeter, personal communication; see also Table 1, Notes).

### Population at Risk Estimates

In articles relating to TBE vaccination recommendations, several authors referred to the WTO arrival data, for instance

### Table 1. Number of TBE reported cases and cases in international travellers, 2012

<table>
<thead>
<tr>
<th>Country</th>
<th>TBE total (n)</th>
<th>TBE imported (n)</th>
<th>TBE presumably imported from</th>
</tr>
</thead>
<tbody>
<tr>
<td>EU with report to ECDC</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Austria</td>
<td>49</td>
<td>1</td>
<td>Switzerland</td>
</tr>
<tr>
<td>Belgium</td>
<td>2</td>
<td>2</td>
<td>Austria, Norway</td>
</tr>
<tr>
<td>Czech Republic</td>
<td>573</td>
<td>2</td>
<td>Finland, Slovakia, (The Netherlands)</td>
</tr>
<tr>
<td>Estonia</td>
<td>178</td>
<td>1</td>
<td>?</td>
</tr>
<tr>
<td>Finland</td>
<td>39</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>France</td>
<td>1</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Germany</td>
<td>195</td>
<td>7 (+1 ex Russia)</td>
<td>Aus, Hun, Ita, Lit, Pol, (Rus), Swi</td>
</tr>
<tr>
<td>Greece</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Hungary</td>
<td>44</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Ireland</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Latvia</td>
<td>229</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Lithuania</td>
<td>485</td>
<td>5</td>
<td>Czech Republic, Germany, Latvia, Sweden</td>
</tr>
<tr>
<td>Poland</td>
<td>189</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Romania</td>
<td>3</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Slovakia</td>
<td>102</td>
<td>1</td>
<td>Czech Republic</td>
</tr>
<tr>
<td>Slovenia</td>
<td>164</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Spain</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Sweden</td>
<td>287</td>
<td>3</td>
<td>Finland</td>
</tr>
<tr>
<td>UK</td>
<td>3</td>
<td>3</td>
<td>Latvia, Lithuania, Sweden</td>
</tr>
<tr>
<td>EU Total (ECDC data)</td>
<td>2560</td>
<td>26</td>
<td></td>
</tr>
<tr>
<td>EU without report to ECDC</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bulgaria</td>
<td>N/A</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>Cyprus</td>
<td>N/A</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>Denmark</td>
<td>1</td>
<td>1</td>
<td>Sweden</td>
</tr>
<tr>
<td>Italy</td>
<td>34</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Luxemburg</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Malta</td>
<td>N/A</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>The Netherlands</td>
<td>5</td>
<td>5</td>
<td>Norway, Sweden,</td>
</tr>
<tr>
<td>Portugal</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Non-EU European</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Croatia (non-EU in 2012)</td>
<td>47</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Iceland</td>
<td>N/A</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Norway</td>
<td>8</td>
<td>2</td>
<td>Finland, Germany</td>
</tr>
<tr>
<td>Switzerland/Liechtenstein</td>
<td>96</td>
<td>2</td>
<td>Austria, Estonia</td>
</tr>
<tr>
<td>Select overseas countries</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Australia</td>
<td>0</td>
<td>0</td>
<td>Czech Republic, Finland</td>
</tr>
<tr>
<td>Canada</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Japan</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>USA</td>
<td>2</td>
<td>2</td>
<td>Czech Republic, Finland</td>
</tr>
<tr>
<td>Total (excl. Russia, Asia)</td>
<td>2753</td>
<td>38</td>
<td></td>
</tr>
</tbody>
</table>

**Remarks**

1. Erroneous report to ECDC, case infected in Czech Republic.
2. Annually 3–9% imported.
3. Annually 5–10 imported.
4. Data provided by ECDC extracted from TESSy.
6. Only North-Eastern Italy with 7.1 million population.
7. Diagnosed at Medical University of Vienna/Heinz F.X. p.c.
8. No mandatory reporting; data from national reference laboratory.
9. One each from ECDC and GeoSentinel database, both females, 16 and 40 years old.
10. Annually 1–2% imported/Altpeter E p.c., 1 case also from GeoSentinel database.
mentioning the total number of international arrivals worldwide or in Europe (504 million in 2011).7,31 Many authors also described the increase in tourist numbers to endemic countries. One estimate was more specific relating to ‘more than 78 million people to TBE-endemic areas in 2007’.30 Slightly lower is an earlier estimate of ‘50 million travellers (who) visit tick borne encephalitis virus (TBEV) endemic regions annually’.27 Some articles highlighted a general trend to increasing outdoor activities.2,7,28,31

Incidence Rate Estimation
One author attempted to extrapolate the risk in travellers basing on a provincial incidence rate. That estimate was 1 in 10 000 for a 4-week stay specifically in the highly endemic Austrian province of Styria.2,27 That rate was extrapolated from ‘epidemiologic data available in Austria due to an excellent TBE surveillance system’ with no further details indicated.27 Basing on that estimate, it was extrapolated that annually ‘one should expect a total of 60 travel-associated clinical TBE cases to occur among summer vacationers after their stay in Austria’.27 The same was later misquoted that ‘the small Austrian province of Styria exports probably ~60 cases of TBE during one summer’.28 Basing on unspecified data from 12 European countries, another extremely high incidence estimate of 17 456 TBE cases in international travellers between 1998 and 2007 was presented and later quoted.27

Target Populations for TBE Immunization Recommendations
As a result of the widely differing incidence estimates, differing vaccination recommendations were repeatedly discussed. Some concluded that ‘TBE vaccination should be recommended for travellers going to TBE endemic countries’.28 Explicitly, it was stated that the ‘50 million travellers per year to European endemic regions indicate a need for (international) recommendations’, although highlighting contact with nature, visiting friends and relatives and rural tourism as risk factors.28 In contrast to such universal advice, the World Health Organization (WHO) and others recommended vaccination for ‘high-risk individuals only’ and specified that the ‘risk of infection is negligible for people who remain in urban areas’.5,7,38 This was contradicted by statements that TBE-infected ticks had been detected in urban parks.2,7

Some deplored ‘there is not even a European-wide consensus on the recommendation for TBE vaccination in travellers’.30 It was requested that internationally recognized recommendations on prophylaxis against TBE in travel medicine should be formulated.2,7,28,31

ECDC Notification Data
Overall 2560 cases, including 2106 confirmed TBE cases were reported by countries in EU and in EEA in 2012. The highest notification rates were reported by

- Estonia 13.35 per 100 000
- Lithuania 11.69 per 100 000
- Slovenia 7.98 per 100 000

The male to female ratio was 1.58–1. The highest notification rate of confirmed TBE was recorded in the 45- to 64-year old age group, followed by those aged over 65 years of age. Most cases were reported between June and October but reports were submitted in every month. It is questionable whether reports in December and January reflect late onset, delayed diagnosis, late reporting—or exposure during winter.21

Basing on the ECDC report, information on the importation status was available for 1967 cases, of which 26 (1.20 %)22 were acquired abroad. Table 1 shows the origin of these cases. Other sources provided an additional 12 to a total of 38 cases of internationally acquired TBE infections in Europe (including 1 case from Russia) and USA. Included herein are also cases detected by national authorities not reporting to the ECDC, reference laboratories in countries which also did not report to the ECDC, the Global GeoSentinel Surveillance and the Centres for Disease Control and Prevention in USA.

Literature Review Relating to Military Cohorts
In the ‘military’ PubMed database, 32 articles were detected. After the exclusion of 9 for language reasons (Chinese, Polish, Russian) and another 14 for being not relevant for this survey (pure diagnostics, non-European epidemiology, TBE incidence in ticks, description of symptoms, vaccination uptake), 9 articles were analysed in detail. Among these, 2 had no data, 2 were cost-benefit analyses basing on the cohort studies summarized later, 1 reviewed data from an earlier study. Three cohort studies were conducted in the 1980’ and early 1990s in the US military.39-41 One additional small study was performed in 56 Austrian recruits, none of whom had clinical or laboratory evidence of TBE-virus infection.42 In summary, in a population with several thousand person-months of exposure the infection rate was slightly below 1 per 1000 per month and not a single clinical case of TBE was observed.

WTO and Other Denominator Data
Basing on the latest report from the WTO,36 in 2014 there were 581.8 million international tourist arrivals in Europe, including 214.9 million in Southern/Mediterranean Europe, where TBE endemicity is limited to few regions, e.g. in Croatia and Italy (Figure 1). But also, the remaining 366.9 million are no indicator for potential exposure as in large parts of Northern and Western Europe (most of France 83.7 million, all of the Benelux States 22.9 million, UK 32.6 million) there is no risk of TBE infection. That leaves us with 227.7 million travellers having visited countries with widespread endemicity (2014; for 2012 even 234.8 million).

Basing on 2008 statistics, there were more than 8.4 million international camping trips lasting 4-7 nights in Europe (e.g. missing data from Estonia, Latvia, Poland), which at the time corresponded to 5.7% of all holiday trips43 or ~4% of all international travels. To note, ‘20% of all holiday trips by Dutch residents were camping trips’.43 Countries with widespread TBE risk have a comparatively small tourism volume, e.g. the three Baltic States have 6.8 million arrivals. Among 1.9 million foreign visitor arrivals in Lithuania 2012, 26% were registered December to March,44 leaving 1.4 million for the period of transmission. Of these, 22 600 stayed in rural tourism farmsteads45 and additionally 33 400 (2008)43 spent camping vacations. Thus, in this high-risk country at least 56 000 (4%) foreign visitors clearly were at
TBE risk by outdoor rural exposure; in all three Baltic States roughly 200,000 would be at risk (data not shown).

Various countries publish more detailed regional (by state, province, canton, etc., also by month) statistics including separate data for foreigners and duration of stay (e.g. Switzerland, Germany), some including also data on the reason for travel or camping (e.g. France). However, as these databases are limited and not comparable they cannot serve to establish a comprehensive and reliable estimate on the population truly at risk of TBE in Europe.

Discussion

General Epidemiology

The 2560 total and 2106 confirmed TBE cases in the EU/EEA countries are slightly less than expected for Europe excluding Russia, however, only 19 EC plus 1 EEA countries submitted data. Including all information sources, the total of 2753 is still slightly below previous estimates, between 3000 and 4000 for this period. Giss documented 2805 average TBE cases in Europe excluding Russia for the 1990–2007 period as compared with 1452 for the 1976–1989 period; a maximum of 3914 cases was recorded in 2006. This increase illustrates how besides improved diagnostic means, awareness and reporting, TBE is an emerging infection. The ECDC summarizes that ‘the number of human cases of TBE in all endemic regions of Europe has increased by almost 400%’. The surface of endemicity is expanding in many countries reaching higher altitudes, raising temperatures and increased humidity may result in more favourable conditions for ticks, and behavioural changes with more outdoor recreational activities may also have contributed to this increase, which apparently is continuing. Lastly, the migration of population to suburban areas may play a role. The very considerable annual fluctuation associated with climatic conditions is not to be discussed here.

Imported Cases—Numerator Data

The ECDC report and numerous other sources for the first time allow to present evidence that in 2012 a total of 38 cases of TBE (plus one case from Russia) were documented in Central/ Western Europe among international travellers. That is a very substantial number of patients. However, in view of the four cases exported from Austria in that year, the >60 travel-associated clinical TBE cases to occur among summer vacationers after their stay in Austria are apparently an exaggerated estimate. Most likely some additional cases were not properly diagnosed and others were not reported, as illustrated by a single case, which was only recorded by GeoSentinel. But, it seems very unlikely that we face a 15-fold underreporting.

Denominator Data

Denominator data are essential to calculate an attack rate per stay or even better an incidence rate per month, week or day of exposure abroad. Basing on WTO statistics, some 230 million international travellers visit countries with widespread areas of TBE endemicity every year. About a quarter of the journeys take place between December and March, when there is hardly any transmission, and many visit only regions in these countries where there is no endemicity. It has been previously proposed that 50–78 million travellers visit TBE endemic regions each year.

Besides the 5.7% of holiday camping trips in relation to all holiday trips (4+ nights), also hotel guests in rural areas will have outdoor activities and be exposed to a risk of TBE. Business travellers were not accounted for in these statistics. Overall, it appears that only a minority of travellers is at risk for an undetermined number of days, let us assume that this proportion is between 4 and 10%.

Attack Rates

Since there are no data on the duration of exposure to risk among travellers, it is impossible to determine incidence rates for a defined period of time. At best, we can estimate attack rates per travel but that may also be relevant as some visitors may get infected during a brief exposure.

Among the annually 230 million visitors to countries with widespread TBE endemicity, ~175 million will travel between April and November. Basing on the 38 TBE cases in 2012, the overall attack rate would be 1 per 4.5 million. Basing on the estimated 50–78 million travellers who visit the TBE endemic regions, the attack rate would still 1 per 1.3–2 million.

If in contrast, we assume that only 4–10% of the 50 million are at risk, the attack rate increases to 1 per 50,000 or 1 per 130,000, respectively. In the high risk Baltic States basing on 5 cases, only the attack rate in 2012 would have been 1 per 40,000.

These crude estimates on attack rates appear to be lower than the incidence rate of 1 per 10,000 per month previously published but one must take into account that the duration of stay of visitors usually is <1 month, and that locals may have a higher exposure when compared with visitors, as they often work in tick infested areas.

Also the data from the three American military cohort studies must be interpreted with caution. First, they were conducted several decades ago in a period when TBE incidence rates were lower and less widespread. Second, there may have been a low virus endemicity in areas occupied by the US forces and exposure to ticks may have been limited, as there was no combat situation, even if the troops trained extensively in TBE endemic areas. Third, the period of exposure was not always clearly described and there were uncertainties with respect to interpretation of laboratory data particularly in one of the studies. But these cohort studies still illustrate that the majority of infections remain asymptomatic and that before the turn of the century the risk of TBE was comparatively small.

Limitations

Most agree that there is underreporting of TBE cases. This certainly is still the case but a single case only included in Table 1 had not been reported to the national health authorities in the countries with required notification. The total number of TBE reported to ECDC was slightly lower than previous estimates but this difference was not dramatic. There is no recorded information what proportion of the 38 cases belonged to what type of risk groups. Obviously the asymptomatic infections are not recorded.
Figure 2. TBE decision algorithm for travellers

On the other hand, there also may be some overreporting: as documented by ECDC only 82.2% of the cases were confirmed.\textsuperscript{22} It has not been determined whether and by what laboratory method the cases from the other sources were confirmed—the case definitions still vary.\textsuperscript{49,51,52}

As described earlier, the denominator data, particularly those relating to the population, which is exposed to a substantial TBE risk, are far more uncertain. First, we have only a vague idea about the proportion of travellers visiting endemic countries during the months when there is hardly any transmission (that may vary from country to country), second, we only have rough estimates what proportion of visitors stays in areas with transmission as opposed to those in areas without endemicity (e.g. in Switzerland the Ticino Canton with zero risk).\textsuperscript{53} Third, we have very incomplete data on the proportion of visitors with outdoor exposure in rural areas and fourth we lack data on the duration of exposure. Consequently, the attack rates presented earlier at most illustrate a low and high estimate on the order of magnitude.

Conclusions on TBE Vaccination Recommendations for Travellers

Strategy

Two strategies have been discussed in the past relating to TBE immunization for travellers: a universal recommendation to immunize all visitors to endemic countries or at least endemic areas in these countries vs a risk-group strategy. With the universal approach more than a million travellers would need to be immunized to avoid one symptomatic TBE. The at-risk strategy is more reasonable; it is endorsed by the WHO.\textsuperscript{58} Besides general measures to reduce exposure, specific advice is formulated: ‘The vaccine should be offered only to at-risk travellers’. These are described as those ‘to endemic areas during April to November. The risk is highest when hiking or camping in forested areas up to an altitude of \textasciitilde 1500 m’.\textsuperscript{38} Elsewhere, it is stated that ‘people travelling from non-endemic areas to endemic areas should be offered vaccination if their visits will include extensive outdoor activities’.\textsuperscript{59} Basing on a clear risk perception, 18 out of 28 European countries and one regional group have issued recommendations relating to TBE prevention and specifically immunization for travellers.\textsuperscript{54,55} Various authorities overseas also issued specific travel health advice.\textsuperscript{56,57}

Figure 2 is a summary algorithm; besides the aforementioned risk groups particular attention should be given to migrating work-force in agriculture and long-term foreign residents living anywhere in endemic countries.

There is a misconception that an international consensus on the application of other travel vaccines exists\textsuperscript{51} and that for instance ISTM should issue recommendations. First, the WHO is the highest international authority. Second, although the purpose of the ISTM is ‘to develop guidelines’ and ‘to stimulate and promote research’ the Society goes no further then to publish expert reviews in the Journal of Travel Medicine\textsuperscript{58} to avoid interference or even contradiction with existing national recommendations. Also, it is wrong to assume that ‘vaccination against TBE may be required for some tourists’\textsuperscript{28} as such obligation is not compatible with the International Health Regulations.\textsuperscript{59}

Ad hoc expert groups have in the past issued ‘consensus recommendations’ but increasingly such a process has become difficult because of rigid requirements; if such a process is sponsored by the industry there will be reservations relating to potential conflict of interest.\textsuperscript{60}

Relevance of TBE Immunization to Other Travel Vaccines

In absolute numbers, travel-associated TBE cases are markedly more often reported when compared with manifest rabies\textsuperscript{61}—although risk exposure may be much greater\textsuperscript{62}—meningococcal disease,\textsuperscript{63} or Japanese encephalitis\textsuperscript{64}. In contrast, every year \textasciitilde 100 cases of Salmonella enterica subspecies enterica serovar Typhi are imported just to England, Scotland and Wales mainly
by people having visited friends and relatives in India or Pakistan.\textsuperscript{65} Estimates on the attack rates per trip for Japanese encephalitis varied between 1 per 400 000\textsuperscript{66} and 1 per million\textsuperscript{67} or less.\textsuperscript{67} The estimated risk for travel-associated typhoid is \sim \text{per 3000} for destinations in South Asia (high risk) and \text{per 50 000} for travel to any other destination.\textsuperscript{68} For those with outdoor exposure in endemic areas, the risk of symptomatic TBE now must be positioned between the risk of typhoid in South Asia\textsuperscript{28,69} and the risk of the neurological infections mentioned earlier.

The Fundamental Problem

The problem with TBE immunization in travellers is neither the lack of recommendations nor the issue by an internationally recognized authority. The real issue is that at-risk travellers particularly in non-TBE endemic countries lack of awareness for the risk of infection, thus they do not search for any travel health advice.\textsuperscript{7,28,31} Travel clinics are usually consulted by customers planning ‘exotic trips’ but hardly ever when the destination is in another industrialized nation. Primary care physicians will rarely be informed about plans for outdoor vacations but if they are they should ask about destination details to be able to conclude on the risk of TBE and the indication for immunization.

Awareness must be increased, not on arrival at the destination, but weeks before departure in the travel planning stage, so that protection by vaccination may be granted. The sources often consulted at this stage are travel brochures and websites. Probably the greatest impact could be achieved if those offering any type of accommodation or transportation in areas of TBE endemicity would mention the health risk and the possible indication for immunization. This would illustrate that the respective enterprises care for the well being of their customers along with ‘Quality in tourism’ as propagated by the WTO, caring about safety as one of the quality determinants.\textsuperscript{70}

If travellers subsequently consult health professionals these should enforce that recommendation and wherever a vaccine is available immunize all who are at risk of TBE infection, possibly using an accelerated schedule. The second dose should be applied at least 2 weeks before departure unless exposure will be for an extended period of time.\textsuperscript{38}

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NOTE

Data from TESSy, provided by Austria, Belgium, Czech Republic, Estonia, Finland, France, Germany, Greece, Hungary, Ireland, Latvia, Lithuania, Poland, Romania, Slovakia, Slovenia, Spain, Sweden, UK and released by ECDC. The views and opinions of the author expressed herein do not necessarily state or reflect those of ECDC. The accuracy of the authors’ statistical analysis and the findings they report are not the responsibility of ECDC. ECDC is not responsible for conclusions or opinions drawn from the data provided. ECDC is not responsible for the correctness of the data and for data management, data merging and data collection after provision of the data. ECDC shall not be held liable for improper or incorrect use of the data.

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Relating to current and previous TBE vaccine manufacturers R.S. was reimbursed for travel costs, attendance to meetings and/or he obtained honoraria for lectures or advisory boards by Baxter, GSK, Novartis and Pfizer.

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