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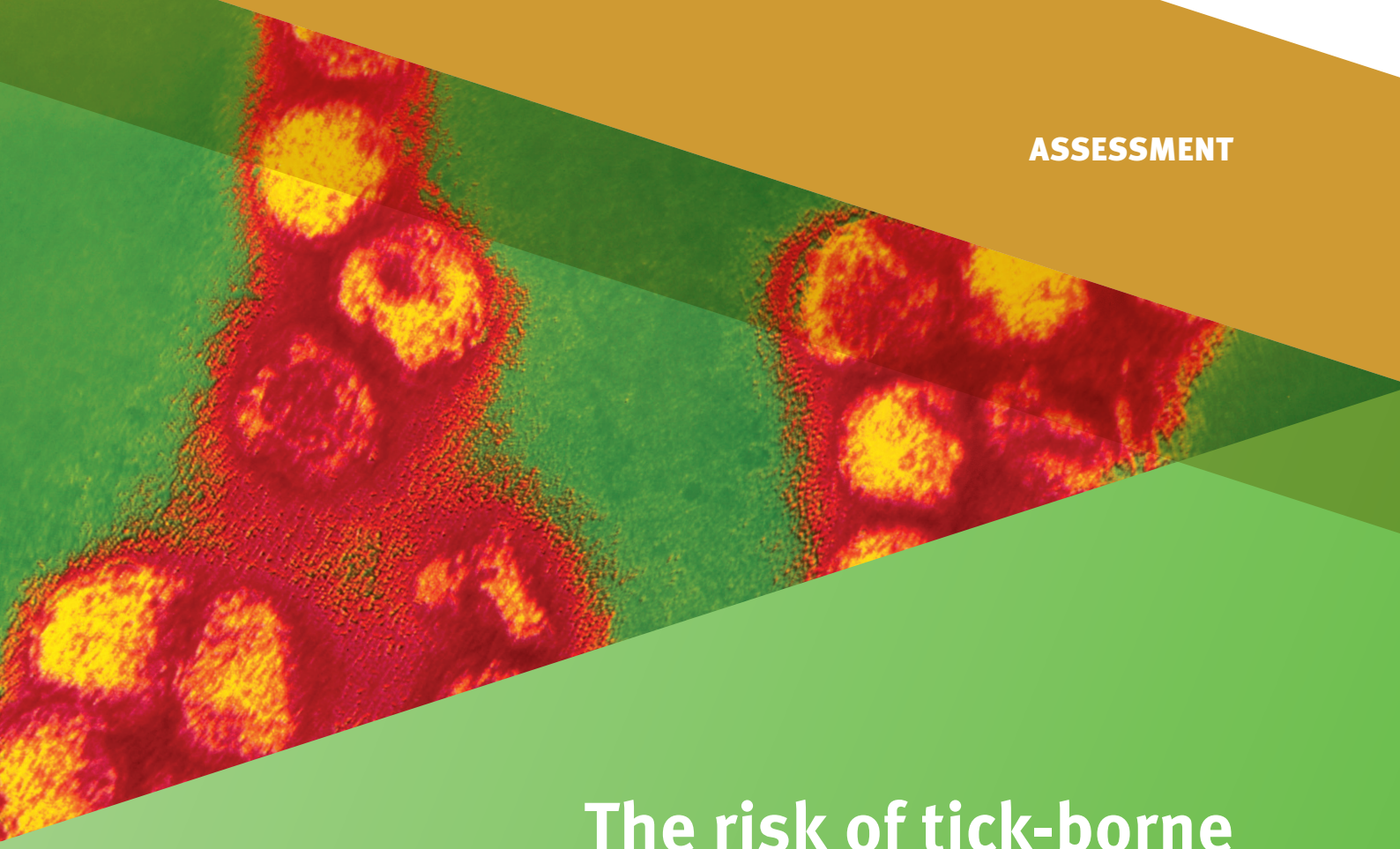

The risk of tick-borne encephalitis virus transmission via substances of human origin

ECDC EVIDENCE ASSESSMENT

The risk of tick-borne encephalitis virus transmission via substances of human origin

This report was written and produced by the European Centre for Disease Prevention and Control (ECDC) and coordinated by Francois-Xavier Lamy.

Authors
Francois-Xavier Lamy, Mohammed Afzal, Tamas Bakonyi, Jenny Mohseni Skoglund and Céline Gossner.

Contributors
The contribution of the Erasmus Medical Centre, Rotterdam, the Netherlands was provided under specific contract No 3 ECD.14393 ID 26009 implementing Framework contract No ECDC/2020/010 (EVD-LabNet). The contributors were Corine Geurts van Kessel, Marion Koopmans, Zsofia Igloi, Richard Molenkamp and Reina Sikkema.

Raquel Llorente and Ramon Molinero Parejo, GIS PHF, ECDC who supported with the production of maps.

Acknowledgements
ECDC would like to thank the following SoHO-Network members for their input and review of the report: Paolo Antonio Grossi (University of Insubria, Infectious and Tropical Diseases Unit, Varese, Italy), Sophie Lucas-Samuel (Agence de la Biomedecine, Saint-Denis, France), Niina Putkuri (Finnish RedCross Blood Service, Vantaa, Finland), Imad Sandid (Agence nationale de sécurité du médicament et des produits de santé, Saint-Denis, France).

ECDC would also like to thank Tatjana Avšič-Županc and Misa Korva (University of Ljubljana, Faculty of Medicine, Institute of Microbiology and Immunology, Ljubljana, Slovenia) and Olli Vapalahti (University of Helsinki, Department of Virology, Helsinki, Finland) for their input to this report.

Suggested citation: European Centre for Disease Prevention and Control. The risk of tick-borne encephalitis virus transmission via substances of human origin. Stockholm: ECDC; 2024

Stockholm, September 2024

ISBN 978-92-9498-746-4
doi 10.2900/4129451
Catalogue number TQ-01-24-002-EN-N

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Figures and tables

Abbreviations

BBB	blood-brain barrier
CNS	central nervous system
CSF	cerebrospinal fluid
EU/EEA	European Union/European Economic Area
IgM	immunoglobulin M
IgG	immunoglobulin G
NAT	nucleic acid testing
NUTS	nomenclature of territorial units for statistics
PCR	polymerase chain reaction
RNA	ribonucleic acid
SoHO	substances of human origin
TBE	tick-borne encephalitis
TBEV	tick-borne encephalitis virus
TESSy	The European Surveillance System
WNV	West Nile Virus

Executive summary

Tick-borne encephalitis (TBE) is a viral infection transmitted primarily through tick bites or consumption of unpasteurised dairy products from infected livestock. It represents a growing public health concern in Europe, with thousands of cases reported annually. This report aims to assess the available evidence on the risk of tick-borne encephalitis virus (TBEV) transmission through substances of human origin (SoHO) such as blood, organs, tissues, and cells, and proposes potential safety measures. The target audience for this document is professionals in the European Union/European Economic Area (EU/EEA) working in SoHO establishments, and other professionals involved in SoHO donor selection.

TBE is a notifiable disease in the EU/EEA, with 28 680 confirmed cases reported during the period 2013–2022, most being locally-acquired autochthonous cases. The mean notification rate in EU/EEA countries during this period ranged from 0.01 to 16.83 per 100 000 population. Cases peak during April–November, coinciding with tick activity and outdoor human activities. More than two-thirds of TBEV infections remain asymptomatic, though the exact proportion is uncertain as mild clinical illness is not often diagnosed. Symptomatic cases generally present as a biphasic disease with an initial flu-like phase followed by a second phase characterised by inflammation of the central nervous system. The case-fatality of TBE is below 2%, generally reported at 0.5%. However, long-term sequelae have been reported in 10–40% of patients with neurological symptoms.

TBEV transmission through SoHO is documented but rare, with two cases reported via transfusion from one donor and three cases via organ transplant from another donor.

Reports of transmission are rare despite important TBE notification rates in endemic areas and non-trivial seroprevalence among blood donors. This suggests a very low likelihood of transmission of TBEV leading to symptomatic disease through blood transfusion. The impact of transmission of TBEV through blood transfusion is unknown and the risk of transmission of TBEV through blood transfusion in EU/EEA cannot be assessed.

Transmission of TBEV through organ transplantation has been reported from one donor and all recipients of organs procured from the infected donor were infected by TBE. The likelihood of transmission of TBEV leading to symptomatic disease through organ transplantation is considered low. The severity of the disease course may be associated with immunosuppression, however it is important to note that no specific antiviral treatments are available for TBEV. The impact of a transmission of TBEV through organ transplantation is considered moderate. The risk of TBEV transmission through organ transplantation in the EU/EEA is considered low.

In the absence of reported cases of TBEV transmission through tissue or cell transplantation, the likelihood and impact are unknown, and the risk for these SoHOs cannot be assessed.

Potential measures during TBEV transmission periods could include deferring blood donors reporting recent tick bites in affected areas for a period of 28 days; testing organ, tissue and cell donors for TBEV ribonucleic acid (RNA) and TBEV antibodies, and identifying exposure risks in order to inform the transplant team. A TBEV infection should be considered for recipients of organs, tissues, or cells who exhibit neurological symptoms if the donor had a risk of exposure to TBEV. Increasing vaccination rates in highly endemic areas could improve overall SoHO safety in relation to TBEV.

There are still several areas of uncertainty in relation to TBE and the risk of TBEV infection through SoHO, including the infectious dose and viraemia levels in asymptomatic individuals.

1. Introduction

Ticks are important vectors of pathogens, both for humans and animals, and tick-borne diseases represent a growing public health concern in Europe [1]. Vector-borne infectious agents can also be transmitted by blood transfusion and organ transplantation, which have triggered concerns about the threat posed by tick-borne diseases to the safety of SoHO [2,3]. TBE is regarded as one of the most important tick-transmitted neurological and life-threatening viral diseases, with thousands of cases reported annually in Europe [4,5].

The TBE serocomplex comprises tick-borne encephalitis virus (*Orthoflavivirus encephalitidis* TBEV), Louping ill virus (*Orthoflavivirus loupingi*), Powassan virus (*Orthoflavivirus powassanense*), Kyasanur Forest disease virus (*Orthoflavivirus kyasanurense*) and its related variant Alkhurma virus, and Omsk haemorrhagic fever virus (*Orthoflavivirus omskense*) [6]. The scope of this document is limited to the risk posed by TBEV transmission through SoHO (i.e. blood and blood components, organs, tissues and cells, including reproductive cells). The report aims to assess the available evidence on this topic and propose potential safety measures.

The target audience for this document is professionals in the EU/EEA working in SoHO establishments and other professionals involved in SoHO donor selection.

2. Methods

The content of this technical report was supported by targeted literature reviews for each specific topic section. Cases of TBEV transmission through SoHO were identified through the systematic literature reviews described in the articles by Martello et al. [7] and Giménez-Richarte et al. [8]. The search strategy described in Martello et al. was replicated to identify the publication of any new case of transmission of TBEV through SoHO up to January 2024.

The assessment of the risk of TBEV transmission through SoHO is based on an adaptation of ECDC's operational tool for rapid risk assessment methodology [9].

The proposed safety measures are based on an expert opinion. In February 2024, a call for interest to review the present report was sent to the ECDC SoHO network (SoHO-Net)[1]. The call was open to all interested members of the network based in countries with TBEV transmission, having prior experience of the risk of TBEV transmission through SoHO. Safety measures initially proposed by ECDC were revised and finalised by the SoHO-Net experts during the review process. Due to the rare occurrence of transmission cases being reported and the fact that there are still gaps in research, there is significant uncertainty regarding the effectiveness of safety measures to prevent transmission of TBEV through SoHO. The SoHO-Net experts who replied to the call and participated in the review are listed in the Acknowledgements on p.ii. They have submitted declarations of interest which did not reveal any conflicts of interest.

3. Background

Tick-borne encephalitis virus

TBEV is a member of the *Flaviviridae* family; genus *Orthoflavivirus,* species *Orthoflavivirus encephalitidis* [10]. The TBEV is a spherical, enveloped virus, with polyhedral nucleocapsid symmetry, 40−60 nm in diameter. The virus has a linear, single-stranded positive sense RNA genome, approximately 11.0 kb long [11].

Based on genomic sequences, five main sub-types have been defined. The European sub-type (TBEV-Eu) circulates in western, central, northern and eastern Europe; the Siberian sub-type (TBEV-Sib) is mainly found in Siberia and far-eastern Russia; the far-eastern sub-type (TBEV-FE) circulates mainly in the far-eastern Russia, China and Japan. However, both TBEV-Sib and TBEV-FE have also recently been isolated in north-eastern Europe [12,13]. Recently, two other sub-types have been described [5]: the Baikalian (TBEV-Bkl) and the Himalayan (TBEV-Him). In Europe, TBEV is mainly transmitted to humans by *Ixodes ricinus* ticks. In parts of eastern and north-eastern Europe, Russia, and the far east of Asia, the vector most often described is *Ixodes persulcatus [12].*

Depending on the time of the year and geographical location, the proportion of infected ticks varies; in central Europe approximately 0.1% to 5%, and in Siberia up to 40% of ticks carry TBEV [1,4]. The main reservoirs of the virus are small wild vertebrate hosts (e.g. rodents), although larger mammals, such as wild deer, are also important reservoir hosts for adult ticks [14]. Common infection routes to humans are the bites of infected ticks, usually from April to November, or consumption of unpasteurised milk or milk products from TBEV-infected livestock, the latter generally leading to localised outbreaks [7,15]. Populations at risk of tick bites are those carrying out recreational or occupational outdoor activities (e.g. gardening, hunting, fishing, camping, forestry,

[1] https://www.ecdc.europa.eu/en/about-ecdc/what-we-do/partners-and-networks/disease-and-laboratory-networks/network-microbial

farming, military). Human-to-human transmission is extremely rare and has been reported through blood transfusion or organ transplantation. Transmission from mother to infant through breast milk is probable, but not confirmed [7,16,17]. A few cases of laboratory-acquired TBEV infections have been reported [7].

Epidemiology in the EU/EEA

TBE became notifiable at the EU/EEA level in 2012 and human cases should be reported to the European Centre for Disease Prevention and Control (ECDC) according to the EU case definition [18]. The data is collected through The European Surveillance System (TESSy). Confirmed cases are defined as any person with symptoms of inflammation of the central nervous system (CNS) and TBE-specific immunoglobulin M (IgM) AND immunoglobulin G (IgG) antibodies in blood, or TBE-specific IgM antibodies in cerebrospinal fluid (CSF), or seroconversion or four-fold increase of TBE-specific antibodies in paired serum samples, or detection of TBE viral nucleic acid in a clinical specimen, or isolation of TBE virus from a clinical specimen.

Based on data collected through TESSy, there were 28 680 confirmed TBE cases reported between 2013 and 2022 by 29 countries, an average of 2 868 confirmed cases reported every year. The frequency of reporting varied between countries, ranging from reporting data for all years to not reporting data at all. Three EU/EEA countries (Iceland, Malta, and Liechtenstein) reported zero cases during this period and one country (Cyprus) did not provide any data. The vast majority of confirmed cases, 26 823 (93.5%), were acquired locally (also called autochthonous cases), meaning that they were diagnosed in the country where the infection occurred. The highest number of confirmed cases was reported in 2020 (3 751).

The mean notification rates in countries reporting at least one case during the period 2013−2022 ranged from 0.01 (Bulgaria and Greece) to 16.83 (Lithuania) confirmed cases per 100 000 population . In seven EU/EEA countries (Austria, Czechia, Finland, France, Germany, Norway, and Poland), the average annual percentage change in notification rates between 2013−2022 was above 5%, corresponding to an annual increase in TBE notifications of 5% or more on average between 2013 and 2022 in these countries (Table 1). Case counts and notification rates of confirmed locally-acquired cases during the period 2013−2022 are provided in Annex 1.

The number of reported confirmed cases was highest for the age group 45 to 64 years and was consistently higher for males in all age groups. The overall male to female ratio of reported confirmed cases was 1.5:1.

Table 1. Notification rates of confirmed cases of TBE in EU/EEA countries per 100 000 population, by year, 2013–2022

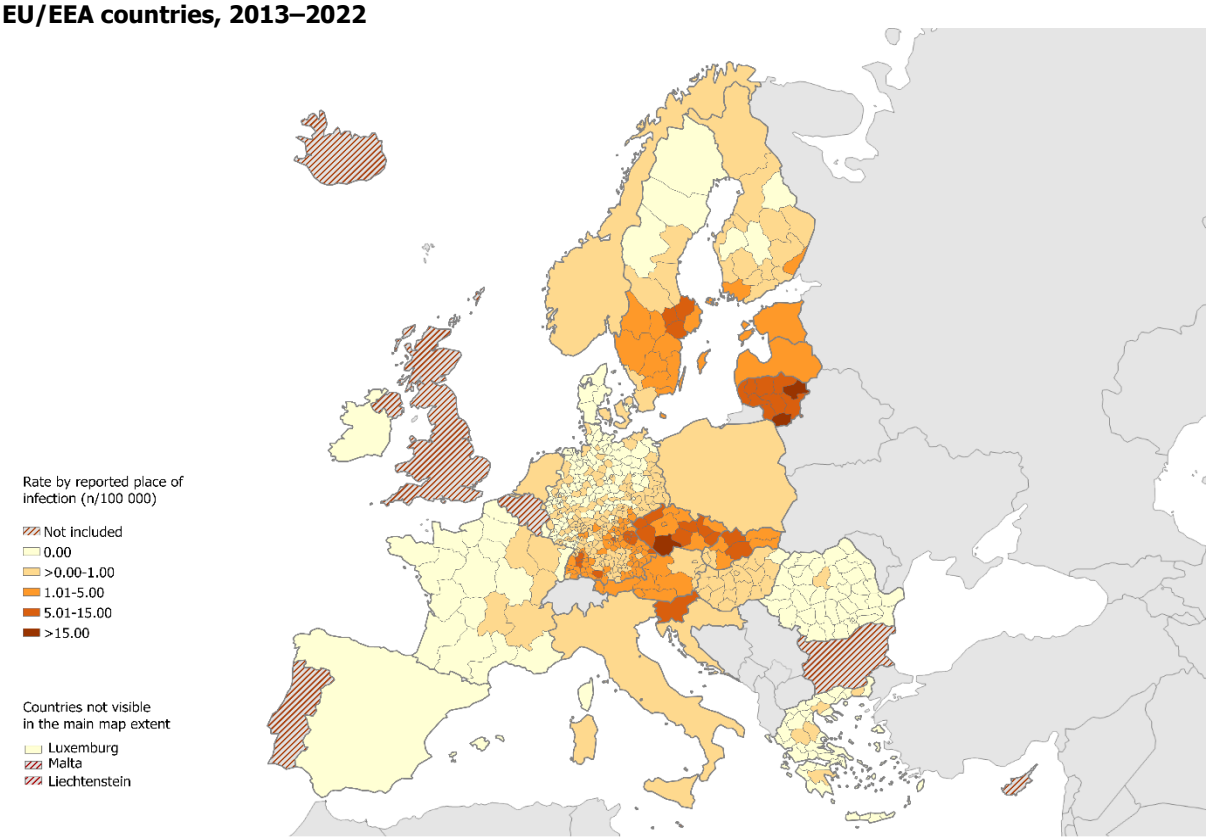
Reporting country	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022	Mean notification rate (2013–2022)	Annual percentage change[a] (95% CI)
Austria	1.18	0.95	0.92	1.10	1.40	1.94	1.20	2.81	1.51	2.29	1.53	9.30 (2.60 to 15.99)
Belgium	0.01	0.00	0.01	0.01	0.03	0.03	0.03	0.06	0.02	0.02	0.02	NC
Bulgaria	ND	0.00	0.03	0.00	0.01	0.00	0.01	0.03	0.01	0.00	0.01	NC
Croatia	1.03	0.54	0.62	0.14	0.24	0.54	0.32	0.34	0.10	0.60	0.45	-10.02 (-27.61 to 7.57)
Cyprus	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	NC	NC
Czechia	5.94	3.90	3.31	5.34	6.49	6.73	7.24	7.95	5.65	6.74	5.93	5.49 (-0.44 to 11.42)
Denmark	ND	ND	ND	ND	ND	0.07	0.09	0.09	0.12	0.09	0.09	NC
Estonia	8.64	6.23	8.75	6.08	6.38	6.44	6.19	5.27	6.17	10.51	7.07	-0.47 (-6.26 to 5.32)
Finland	0.70	0.86	1.24	1.11	1.54	1.43	1.25	1.65	2.89	2.23	1.49	12.49 (7.67 to 17.30)
France	0.00	0.01	0.02	0.02	0.00	0.04	0.01	0.07	0.04	0.05	0.03	27.93 (2.16 to 53.69)
Germany	0.52	0.33	0.27	0.43	0.59	0.70	0.53	0.86	0.51	0.67	0.54	7.20 (-0.14 to 14.54)
Greece	0.00	0.01	0.01	0.00	0.00	0.02	0.00	0.00	0.04	0.01	0.01	NC
Hungary	0.27	0.26	0.22	0.14	0.14	0.31	0.17	0.18	0.06	0.30	0.21	-5.40 (-17.76 to 6.96)
Iceland	ND	ND	ND	ND	ND	ND	ND	ND	ND	0.00	0.00	NC
Ireland	0.00	0.00	0.00	0.00	0.00	0.00	0.02	0.00	0.00	0.00	0.00	NC
Italy	0.00	0.00	0.01	0.08	0.04	0.06	0.06	0.09	0.03	0.18	0.06	NC
Liechtenstein	ND	ND	ND	ND	ND	ND	ND	ND	0.00	0.00	0.00	NC
Lithuania	16.39	11.99	11.50	21.91	16.64	13.67	25.45	24.30	13.06	13.44	16.83	1.70 (-6.10 to 9.49)
Luxembourg	ND	0.00	0.18	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.02	NC
Latvia	11.36	7.44	7.10	4.62	9.13	5.17	9.11	7.81	11.73	ND	8.16	NC
Malta	ND	ND	ND	ND	ND	ND	ND	ND	ND	0.00	0.00	NC
Netherlands	ND	ND	ND	0.02	0.02	0.03	0.02	0.03	0.02	0.03	0.02	NC
Norway	0.12	0.25	0.17	0.23	0.30	0.49	0.66	0.76	1.32	1.55	0.59	27.65 (22.22 to 33.08)
Poland	0.36	0.34	0.30	0.56	0.52	0.39	0.52	0.30	0.48	0.97	0.47	6.55 (-1.46 to 14.55)
Portugal	ND	ND	ND	ND	ND	ND	ND	0.00	0.00	0.01	0.00	NC
Romania	0.01	0.01	0.00	0.00	0.01	0.02	0.00	0.00	0.01	0.00	0.01	NC
Spain	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	NC
Sweden	2.19	1.85	2.75	2.42	0.00	3.55	3.47	2.59	5.14	4.45	2.84	NC
Slovakia	2.99	2.12	1.48	3.11	1.38	2.83	2.97	3.39	1.32	2.91	2.45	0.69 (-9.33 to 10.70)
Slovenia	14.96	4.85	3.01	4.02	4.94	7.40	5.33	8.92	2.94	5.93	6.23	-3.11 (-16.22 to 10.00)

ND: No data reported. NC: Not calculated

[a] *Log-linear regression of notification rates over the period 2013–2022. Log-linear regression was performed only for countries that reported data and had more than zero cases for each year.*

TBE is focally endemic in the northern, central and eastern parts of the EU/EEA. Figure 1 provides the geographical distribution of notification rates for confirmed locally-acquired cases of TBE by country at the NUTS-3[2] level, where available. Notification rates per country should be interpreted carefully as TBE has a focal endemicity. For example, in Germany the majority of cases are reported in the southern regions, whereas in Lithuania cases are reported throughout the country.

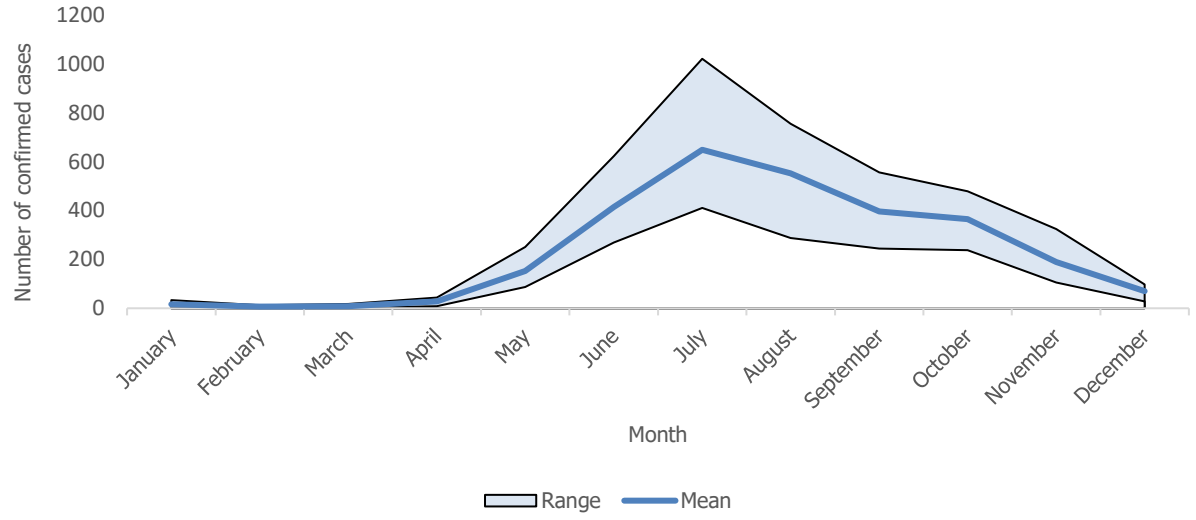
Figure 1. Mean notification rates of confirmed locally-acquired TBE cases per 100 000 population, EU/EEA countries, 2013–2022



NUTS-3 levels are shown whenever available. Specifications for the map are presented in Annex 2.

During the period 2013–2022, although cases were reported throughout the year, the large majority were reported between April and November (Figure 2) [19], which coincides with the period of most tick-activity and human outdoor activity. The most frequent peak in cases occurred in July. A bimodal pattern with a second, smaller peak in September or October has been observed in Europe during this period which coincides with the second peak of the *I. ricinus* questing (host-seeking) activity that occurs in autumn in central Europe [20,21].

Figure 2. Mean, range of confirmed cases of TBE in EU/EEA countries, by month, 2013–2022



[2] NUTS 2 = a geographical nomenclature subdividing the economic territory of the EU into regions at three different levels (NUTS 1, 2 and 3 respectively, moving from larger to smaller territorial units).

Among the 23 953 confirmed TBE cases reported between 2013 and 2022 with information on hospitalisation, 91.3% (n=21 875) were hospitalised due to TBE. The proportion of hospitalised cases each year ranged from 84.0% to 94.5%. This high proportion is explained by the fact that surveillance mostly captures cases with clinical manifestations indicative of TBEV infection (i.e. meningitis, meningoencephalitis, or meningoencephalomyelitis). It should be noted that the majority (more than two-thirds) of individuals infected with TBEV remain asymptomatic or pauci-symptomatic and are therefore undiagnosed and not reported [22].

Information on vaccination status during the 2013−2022 period was available for 20 286 confirmed cases, of which 94.9% (n=19 251) were reported to unvaccinated; 2.1% (n=428) had received one or two doses of vaccine and 2.2% (n=444) had received three or more doses. The dose was unknown for 0.8% (n=163). These results should be interpreted with caution as the available data does not indicate whether the immunisation schedule complied with requirements (e.g. interval between doses). Vaccination uptake rates across Europe vary considerably [23].

Clinical picture

Similar to infections with other flaviviruses, more than two-thirds of individuals infected with TBEV may remain asymptomatic, although the exact proportion is unknown because mild clinical illness is often not diagnosed [22,24]. The incubation period ranges from 2−28 days and is usually 7−14 days. Symptomatic infections with TBEV can present with a biphasic or monophasic course. The first phase is usually characterised by a flu-like illness with fever, headache, and myalgia. The disease can then progress to a second phase involving inflammation of the central nervous system (CNS), typically with aseptic meningitis, meningoencephalitis, or meningoencephalomyelitis. An intermediate, afebrile phase may occur between both phases. Meningitis is the most common manifestation of the CNS inflammation, while just under 50% of patients with CNS involvement will develop encephalitis. Encephalitis may occur in conjunction with myelitis in less than 10% of patients with neurological symptoms [1]. The monophasic form of the disease presents either with rapid CNS involvement or, conversely, with a self-limiting form of the disease without CNS inflammation, described as 'febrile headache' [15,25]. The biphasic form of the disease is more frequently reported than the monophasic form among symptomatic patients.

In Europe, reported TBEV-Eu infections generally result in a mild form of TBE with a biphasic course in up to 70% of infected patients [26]. The reported case-fatality rate is below 2%, generally reported at around 0.5% [1,5,24]. In patients with CNS involvement, TBE can cause long-term sequelae, also known as post-encephalitic syndrome [27]. Common symptoms of these sequelae, include depression and anxiety, persistent headache, hearing loss or tinnitus, ataxia, and impaired cognitive function. Among those with neurological symptoms (less than 30% of all TBE cases) the proportion of individuals affected by long-term sequelae varies from 10% to 40%, but different study designs and definitions make it difficult to compare and consolidate estimates [22,27-30]. TBEV-Sib infections are usually considered to result in mild forms of TBE, while TBEV-FE infections are associated with more frequent severe forms of the disease, including haemorrhagic forms, and increased case-fatality rates [5,24]. A chronic progressive form of TBE has been reported in 1.7% of the infected patients in Siberia and far-eastern Russia but is rarely seen in Europe. However, there is a knowledge gap in relation to the epidemiology of this presentation [5,22]. The severity of the disease is not entirely determined by the viral sub-type responsible for infection, but may also be influenced by age, immune status, and viral dose [1,27,29].

4. Assessment

Tropism

European sub-type

The virus introduced via tick saliva first replicates at the entry site in skin neutrophils, Langerhans cells, local dendritic cells and macrophages [31], before the macrophages move to local lymph nodes [32]. The underlying molecular mechanisms for broad flavivirus cell tropism [33] are not yet fully understood. TBEV is transmitted within one hour of the bite because it is already present in the salivary glands at the start of the blood meal. Tick saliva increases the virulence of the virus and facilitates its transmission [34,35]. Following replication in these lymph nodes, the virus can reach and infect other organs via the circulation (spleen, liver and bone marrow) (viraemic phase) [36]. The host's viremia persists for a few days, but ticks remain infected all their lives and are the main reservoir for this virus. TBEV also reaches the brain through the circulation and can cross the blood–brain barrier (BBB) [37,38]. It is not known how TBEV crosses the BBB. Once in the CNS, TBEV can replicate in the large neurons of the anterior horns, dentate nucleus, Purkinje cells, medulla oblongata, pons, and striatum [5]. In patients with the biphasic illness, the virus can also be detected in the blood in the paucisymptomatic or asymptomatic/intermediate phase [39]. In the second phase, after the appearance of antibodies, the probability of detecting the virus in the blood or cerebrospinal fluid (CSF) is lower and the role of serological testing is crucial [39,40]. In the second phase, haematological and metabolic parameters (i.e. leukocyte counts, thrombocyte counts and liver enzyme measurements) typically return to normal as the infection clears from the bone marrow and liver [25].

The risk of vertical transmission of TBEV is uncertain. In a limited number of reported cases, umbilical cord blood and amniotic fluid from a small number of infected women were negative for viral RNA (n=3). Foetuses in the reported cases were healthy and uninfected [41]. Probable cases of transmission via breastmilk have been described [16,17].

If initial TBEV infection occurred via the alimentary route, the virus first infects intestinal epithelial cells (microfold or M cells) of the Peyer's patches and is then transported by the intestinal M cells by transcytosis to the sub-epithelium [42,43], from where dendritic cells take the virus to the intestinal lymphoid tissue. The next phase of the infection proceeds as described above [5,15,44].

Other sub-types

The scientific literature is more abundant on the European TBEV sub-type and detailed studies on other sub-types are rare. Animal studies in the 1970s suggest higher affinity of TBEV-FE sub-type with neurons of the brain and spinal cord compared to the European sub-type [24]. However, it is unknown to what degree animal studies mimic human infections. Furthermore, in experimental models, infections are rarely introduced via the natural exposure route (tick bites).

Different receptor usage was suggested for the TBEV-Eu and the TBEV-Sib and-FE-sub-types which could account for some differences in pathogenesis [24].

Viraemia

European sub-type

The duration of viraemia for TBEV is not well documented, but the length of the various disease phases may provide an indication. The first and the intermediate phase are typically the viraemic phases [39]. The first phase is reported to last from 1–19 days (mean around 4–7 days) [5,25,27,29] and the intermediate afebrile phase lasts from 1–21 days (mean around 8.5 days) [1,39,45]. The second phase is non-viraemic and lasts from 4–28 days (mean 13 days).

Following a tick bite, symptom onset appears to take longer (7–14 days on average, range 1–28 days) than if infection occurs via unpasteurised milk and dairy products (3.5 days on average, range 2–14 days) [46]. Viraemia has been shown to occur prior to the onset of symptoms, but this observation is based on a single example of transfusion-transmitted TBEV [47]. The virus can be detected in the blood, occasionally in CSF and in urine; however, detection period or kinetics have not been established [48-50]. The presence of antibodies is generally associated with a lower probability of detecting viral RNA in blood [25]. In immunosuppressed patients, viraemia may persist and be easier to detect for longer [40,50].

Viral load kinetics have been described for the first phase in a few large studies but not for the asymptomatic/paucisymptomatic phase or for the second phase. Levels of TBEV-Eu sub-type RNA in serum, determined by PCR, have been reported in a few case studies, ranging from 10^2 copies/mL to 10^9 copies/mL [50-52] of TBEV RNA. In the largest case series (n=80), on average 310^3 to 10^6 copies of TBEV RNA/mL have been detected during the first stage of illness, for a range of 1–14 days from the onset of symptoms during the first phase [39]. Another study, consisting of 62 patients, found between 10^4 and 10^5 copies/mL in serum

samples [25]. In a sequencing study, twenty-one samples were selected with a range 10^3 to 10^9 copies/mL during the first phase (days not specified) [53].

In one study (98 patients included), viral load was found to be higher in hospitalised patients than in outpatients. However, there was no significant difference according to age, sex, duration of illness pre-testing, or total duration of the first phase of the illness [25]. In another study, the level of viral RNA in serum of patients with or without CNS involvement was comparable, although viraemia was found to be higher in females [39].

Based on the few studies available, kinetics and viraemia in the blood and milk of relevant livestock (sheep, cows, goats) differ from humans and between animal species. The virus can be detected in milk and milk products for a longer period and with higher titres than for blood. However, pasteurisation is considered to completely inactivate the virus in milk and milk products [15]. The infectious dose for TBEV is unknown, whether for infections from feeding ticks [1] or from contaminated milk/milk products [46].

Other TBEV sub-types

With regard to infections involving non-European TBEV sub-types in humans, the scientific literature in English is scarce and was often published before the routine use of PCR.

Treatment

There is no specific treatment recommended for TBE and the care of patients with TBE is primarily supportive, including intensive care for more severe forms [38,54]. Anti-TBE intravenous immunoglobulin and steroid therapy have been administered for both post-exposure prophylaxis and treatment, mainly in Russia. In Europe, anti-TBE immunoglobulin use has been discontinued due to concerns regarding the possibility of more severe clinical manifestations due to antibody-dependent enhancement [5].

Infection with TBEV can be prevented by avoiding tick bites (using insect repellents, wearing protective clothing and inspecting body and clothing for ticks after exposure), and the consumption of unpasteurised milk and milk products.

Immunity

Natural immunity

During the initial phase (i.e. in the first couple of weeks), specific TBEV antibodies can be detected in both the serum and the CSF. In the serum, IgM reaches peak levels early after neurological symptom onset, while IgG peaks later, during convalescence (at around six weeks). However, the IgM response peaks later in CSF than in serum [55] and large variations are seen in kinetics between patients [56]. IgM antibodies are detectable for several months after infection (up to 10 months) and IgG antibodies are thought to persist for a lifetime and seem to prevent symptomatic reinfection [37]. The intensity and length of antibody production does not seem to depend on the severity of the disease course [44]. Natural infection results in higher titres of neutralising antibodies than vaccination, however the boosting effect of undiagnosed reinfection cannot be excluded [57,58].

There is also an innate immune response against TBEV, however the description of this response is beyond the scope of this document.

Vaccination-induced immunity

The TBEV vaccines contain cell culture grown, formalin-inactivated TBEV strains. Two vaccines using the European sub-type TBEV strains are currently licenced in Europe for adults or children, with a similar immunisation schedule [59]. There are two additional widely-used vaccines, licenced outside of Europe, effective against the far-eastern sub-type [60]. Following the primary vaccination schedule, booster vaccinations are recommended at various intervals, 3−5 years post primary vaccination, depending on the country, age or immune status [57]. Vaccination against the European sub-type is thought to induce cross-reactive antibodies, protecting against infection with the far-eastern and Siberian sub-types [61], although data from epidemiological or immunological studies is sparse.

Following vaccination, IgM antibodies are detectable for months, and neutralising antibodies were found to persist for 5−10 years, both in children and young adults. There is no standardised method and limit for assessing protective levels of antibodies, which supports the recommendation for regular booster doses. Vaccine breakthroughs are rare but do occur [57,62,63]. Pre-existing vaccination against yellow fever was shown to decrease immune response against TBEV vaccination, highlighting potential issues caused by flavivirus cross reactivity in vaccinated individuals [64].

Survival/persistence outside the host

The stability of the infectious virus outside of the human host has mainly been investigated in cell culture medium, milk and milk products. TBEV is sensitive to high temperature, low pH, non-ionic detergents, UV light, gamma-irradiation, and disinfectants [65]. The virus is stable at low temperatures, especially at -60°C or below.

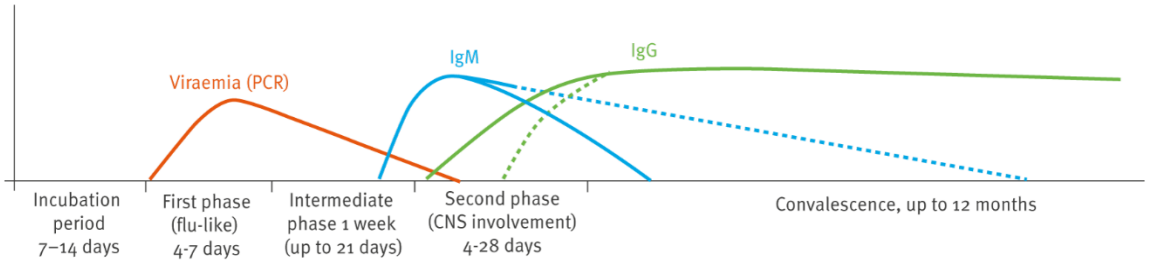
One study showed that there was no decrease in TBEV infectivity in Eagle's minimal essential medium and phosphate-buffered saline over a period of 10 days at 8°C [66]. Complete inactivation of the virus in blood can be achieved at temperatures above 50°C. In freeze-dried form, the virus will retain infectivity almost indefinitely at room temperature [24]. A study showed that virus remained infectious in raw milk for a period of three weeks (20-25 days) at 4 °C and for two weeks in cheese made from raw milk (10−15 days) [67]. No studies were identified reporting on the persistence of TBEV in blood or blood-derived products, outside of the human or animal body.

Laboratory tests methods

Note: Most of the statements in this section are applicable to the diagnosis of the European sub-type.

Viraemia occurs during the first and intermediate phases. However, due to the considerable proportion of asymptomatic infections and initial non-specific symptoms, TBEV-RNA is often not tested for in patient samples. As a result, serological methods are the main diagnostic tools (Figure 3). Nevertheless, early after onset of disease or in immunocompromised patients, TBEV-RNA can be detected, and nucleic acid testing (NAT) can be of added value [40].

Figure 3. Dynamics of detectable molecular and serological markers for tick-borne encephalitis virus



Molecular detection of TBEV

Most studies describe better detectability in whole blood than in serum [68]. TBEV detection in CSF is rare [40,48] but could be considered in patients with neurological symptoms [38]. Detection in urine has been described, but kinetics have not been established and detection in urine is generally considered unreliable. Both commercial and in-house tests for TBEV exist. Based on a European-wide external quality assessment (EQA), most assays were able to detect 10^5 TBEV RNA copies/mL [55], which fell in the range of viral load detected in most reported cases. Genomic sequencing was also used successfully to detect TBEV in blood and organs [53,69]. Sequencing is less often used, due to the cost and difficulty of acquiring patient samples in the viraemic phase, however it is still important for determining sub-types and lineages.

Serology

A majority of patients have TBEV-specific IgM and IgG antibodies in serum when neurological symptoms commence. Detecting IgM in serum alone is not sufficient to be able to confirm a recent infection as these antibodies can be cross-reactive or unspecific and can be detected upon vaccination or up to 10 months post-infection. The presence of only IgG in blood is also insufficient as a diagnostic tool, since it is an indicator of either prior infection or vaccination. Routine laboratory testing for TBEV neurological disease is therefore based on the detection of TBEV-specific IgM and IgG antibodies in serum and/or CSF, commonly by means of enzyme-linked immuno-sorbent assays (ELISAs), immune fluorescence (IF) [70,71], a lateral flow IgM test [72], or multiplex immunoassays, specifically developed to distinguish vaccinated individuals from those naturally infected (presence of NS1 only with natural infection) [72].

In all TBEV serological tests the potential for cross reactivity with other flaviviruses should be considered. Flavivirus cross-reactive antibodies can be induced upon infection or vaccination. This may pose a challenge for diagnosis in people vaccinated against yellow fever or Japanese encephalitis with an unknown TBE vaccination history. Individuals with a previous infection (e.g. dengue, Zika, West Nile or Usutu viruses) may also trigger cross-reactivity. Although TBEV belongs to a different serocomplex, the potential complications posed for TBEV serodiagnostics need to be considered when interpreting serology test results. Quantification of IgM antibodies can be helpful in interpreting serology results: high IgM values point to a recent TBEV infection while lower IgM levels might need a follow-up sample to test antibody dynamics, and/or a TBEV-specific virus neutralisation assay. A TBEV neutralisation assay will increase the specificity of TBEV serology, although cross neutralisation with other flaviviruses cannot be completely ruled out [22,55].

Cases of TBEV transmission through SoHO

TBEV transmission through SoHO is rare, but has been documented. To date, only two cases of TBEV transmission via transfusion – both from the same blood donor – and three cases via organ transplantation – all three from the same organ donor – have been reported in the literature.

In 1989, Finish authors described two cases of transfusion-transmitted TBEV infection among 126 cases of the disease in the Åland islands during the period 1959–1987 [47]. The authors did not disclose the exact year of the transmission events. Neither of the transfusion-associated cases, one female and one male, visited areas endemic for TBEV but they received blood from an asymptomatic donor who had been to an endemic area (Kumlinge, Finland). One transfused patient exhibited a monophasic course with CNS involvement; the other patient had a classic biphasic course with immediate onset of the first phase, followed by the second phase 14 days later. As described in the report, the diagnosis of TBEV infection in patients and donor was serological and, given the EU case definition currently in use, it should be noted that these cases would be classified as probable TBE cases. The uncertainty in the assessment of the cause of these events, due to the limited information provided in the report, should also be considered.

Another report describes three patients who received solid organ transplants from a single donor (each of two patients received a kidney, and one received a liver), developed encephalitis 17–49 days after transplantation and subsequently died [69]. The organ donor was a 44-year-old male who was hospitalised in September 2012 for multiple injuries related to a traffic accident. The patient was declared braindead after five days and his organs were recovered on the same day. The donor lived in an area endemic for TBEV in north-eastern Poland and it is unclear whether he had any symptoms of infection before the accident. The presence of TBEV was confirmed by RT-PCR in all recipients and in the donor, but TBEV was only detected after the death of all three recipients. TBEV RNA was detected in the brain tissue of three recipients (and in the CSF of one recipient), as well as in the brain tissue of the donor [69]. Direct sequencing showed the presence of the same viral strain in patients and donor. The very severe course of the disease in the recipients was attributed by the authors to the immunosuppression treatment of the recipients.

Risk assessment

Data, though limited, indicate that there is a risk of TBEV transmission through SoHO. There have been two cases of transfusion-transmission of TBEV from a single donor and three cases from transplanted organs, also from a single donor, reported in the literature. These reports indicate that it is possible that TBEV is transmissible through transfusion and transmission has been confirmed through organ transplantation. Based on these reports, it is suggested that the virus may remain infectious in donated blood for at least eight days [47] as well as in retrieved organs [47,69]. Furthermore, as the virus is at least transiently present in the blood of infected individuals who are, in the majority of cases, either asymptomatic or have only a mild febrile illness, it would be possible that an infected asymptomatic donor could donate blood or organs which, if used, may lead to TBE in recipients. It should be noted that information on the level and duration of viraemia mainly comes from symptomatic cases.

The transfusion risk is mainly related to red blood cells and whole blood as platelets and plasma undergo pathogen inactivation methods that have been shown to provide more than six log reduction in infectivity for enveloped viruses, which is considered as adequate inactivation [8,73-75]. However, some residual infectivity cannot be ruled out in persons with high viral loads. As such, the risk of transmission through transfusion of plasma and platelets processed with validated inactivation methods for flaviviruses is expected to be very low. It is also important to consider that the transfusion-transmitted cases were reported in a period prior to 1987, and there is significant uncertainty concerning the assessment of these cases. By way of comparison, there have been 42 transfusion-transmitted cases of WNV, and upwards of 25 WNV transmissions through organ transplants published in the literature (up to November 2021) and 18 from dengue virus [8,76,77]. It should be noted that the annual number of WNV cases reported in EU/EEA is lower than that for TBEV [78], with the majority of cases being asymptomatic. Another element to consider is the non-trivial prevalence rates of prior TBEV infections in healthy blood donors in endemic areas, ranging from less than 1% to 7% in specific areas [79-83]. These studies do not explore active infections in blood donors, but they highlight the possibility that a large proportion of TBEV infections are not reported and the actual number of individuals with TBEV infections may be higher than reported, including among blood donors.

The likelihood of TBEV transmission leading to symptomatic disease through blood transfusion is considered very low due to the very low number of cases reported, including in countries with high TBE notification rates. The impact of a transfusion transmission of TBEV is unknown. The risk of TBEV transmission through blood transfusion in EU/EEA cannot be assessed.

The likelihood of transmission of TBEV leading to symptomatic disease through organ transplantation is considered low due to the very low number of cases reported and considering the fact that for those cases reported, all recipients of organs procured from the infected donor were infected by TBE. The impact of a TBEV transmission through organ transplantation is considered moderate due to the availability of tests to detect TBEV in the donor which would inform transplant teams ahead of transplantation. The severity of the disease course may be associated with immunosuppression; however, it is important to note that no specific antiviral treatments are available for TBEV. The risk of TBEV transmission through organ transplantation in the EU/EEA is considered low.

The likelihood of TBEV transmission leading to symptomatic disease through tissue or cell transplantation is unknown and the impact of transmission through transplantation is unknown. The risk of transmission of TBEV infections for tissue or cell transplantation cannot be assessed.

The likelihood of TBEV transmission through SoHO may be increased during outbreaks and seasonal peaks of transmission. However, significant uncertainties remain, in particular the level and duration of viraemia in asymptomatic infected individuals.

5. Safety measures

There are no safety recommendations or standards related to the risk of TBEV transmission via SoHO at EU level. While several EU/EEA countries report including a specific question about tick bites on the donor history questionnaire, these questions are expected to lack the sensitivity to detect potential TBE exposure, since a history of tick bites is provided in less than 50% of TBE cases [84]. There are no approved laboratory tests specifically for the screening of TBEV in living or deceased donors. However, molecular diagnostic tests detecting TBEV-RNA and serological tests detecting specific IgG and IgM in the blood are available and should be considered where there is a suspicion of exposure in SoHO donors. Detection of TBEV in CSF samples is not recommended for SoHO donors due to the risk of the procedure for living donors and the time required to make the results available, which is incompatible with donation from deceased individuals. Current systems for pathogen reduction in plasma and platelets effectively inactivate flaviviruses and the multiple pathogen reduction steps used in the fractionation process of plasma-derived medicinal products have been shown to be robust in the removal of enveloped viruses [75]. Leukoreduction of blood components is unlikely to have an impact on the transmission of TBEV through blood components.

During seasonal periods of TBEV transmission in affected areas (which can be defined as limited geographical areas - e.g. NUTS 3 level - where at least one confirmed locally-acquired case of TBE has been reported in the most recent epidemiological update[3]), the following measures can be considered:

All SoHO

- While a specific question on a history of tick bites will probably lack the sensitivity to detect potential TBE exposure, this question should still be considered relevant for identifying the risk of infection during seasonal TBEV transmission for residents of affected areas, or travellers having stayed in affected areas.
- An important measure to consider, to increase the overall safety of SoHO in terms of TBEV infection, could be to achieve a high TBE vaccination coverage in the general population of highly endemic areas (defined as five or more cases per 100 000 population) in line with national recommendations.

Blood and blood components

- Blood donors reporting a tick bite in a TBE-affected areas could be deferred for a period of 28 days from the day of the bite or the day when the tick is removed, if this happens later.
- A further consideration could be the temporary cancellation of blood and blood component collection in a limited area around a local outbreak associated with the alimentary route, as well as the quarantine of collected red blood cells for several days to monitor for symptoms among donors.
- If a viral inactivation or pathogen reduction procedure is carried out that is specific and adapted to the blood component (in particular platelets and plasma but also possibly red blood cells or whole blood) and validated for flaviviruses by the national competent authority, prospective blood donors could be considered as eligible for apheresis donation.

Organs, tissues, and cells

- In the event an exposure risk, such as a prior tick bite in affected areas in the previous 28 days, is identified through the donor questionnaire (or skin inspection for deceased donation), donors should be tested for TBEV-RNA and both IgG and IgM to confirm the infection. If serological tests are positive, a neutralisation test can be considered to confirm a recent infection.
- For deceased donors, testing could be considered to inform the transplant team before transplantation. If the results cannot be provided before transplantation, the recipient(s) and the medical team(s) should be informed, and a benefit-risk assessment should be considered. It is important to note that no specific antiviral treatments are available for TBEV. Serological and molecular testing for TBEV should be considered in the event of CNS-related symptoms in the recipient.
- For living organs, tissues and haematopoietic progenitor cell donors, testing should be considered to inform the transplant team before transplantation. If transplantation cannot be postponed and the results cannot be provided before transplantation, the recipient(s) and the medical team(s) should be informed, and a benefit-risk assessment should be considered. It is important to note that no specific antiviral treatments are available for TBEV. Serological and molecular testing for TBEV should be considered in the event of CNS-related symptoms in the recipient.
- If viral inactivation procedures validated by a national competent authority for flaviviruses are available for specific tissues (e.g. viro-inactivated bones), no testing is needed for these tissue donors, provided that no other tissues are procured.

Due to the rare occurrence of transmission cases reported and the remaining research gaps, there is a significant uncertainty on the effectiveness of these safety measures to prevent transmission of TBEV through SoHO.

[3] The map describing notification rates for locally acquired TBE in EU/EEA countries using the last available epidemiological update is published at: https://www.ecdc.europa.eu/en/tick-borne-encephalitis/surveillance-and-disease-data

6. Uncertainty and research gaps

Several areas of uncertainty remain regarding the TBE and the risk of TBEV infection through SoHO.

Uncertainty and research gaps on the disease

- The proportion of cases with mild and severe symptoms, and CNS symptoms for the Eu-sub-type is still uncertain.
- The level of viraemia in asymptomatic cases remains unknown, as well as the duration of viraemia for all cases.
- The amount of virus uptake necessary for the infection through different routes (e.g. tick bites, alimentary route and blood transfusion) is unknown.
- The documented length of the various disease phases is variable across studies and remains uncertain for the Eu-sub-type.
- With regard to TBEV-FE and TBEV-Sib, and other sub-types, there are significant research gaps on the detailed clinical picture, viraemia, and precise geographical spread. Research gaps have also been identified for these sub-types in terms of natural and vaccination-induced immunity, and accuracy of available laboratory test methods. These research gaps have consequences for the diagnosis of the sub-types in the EU setting, where clinicians may only consider the Eu-sub-type.
- The effectiveness and overall benefit of TBEV-specific intravenous immunoglobulin in humans remains uncertain.
- There are still research gaps in the area of neutralisation titre correlation to immune protection and cutoffs.

Uncertainty and research gaps on the risk for SoHO

- The presence of TBEV during pregnancy and breast feeding and the risk of transmission through cord blood and breast milk as SoHOs is uncertain.
- The level of viraemia in the donor necessary for the infection of the recipient through blood transfusion is unknown.
- The risk of transmission through SoHO following alimentary exposure of the donor is unknown.
- The accuracy and the effectiveness of TBEV screening methods for SoHO donors, in particular as regards molecular testing, is uncertain.
- The effectiveness of pathogen reduction methods for TBEV specifically in different SoHO types is uncertain.
- There is still significant uncertainty as to the reasons that could explain the very low number of TBEV transmissions through SoHO in endemic regions.

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Annex 1. Case counts and notification rates of confirmed locally-acquired cases of TBE in EU/EEA countries, 2013–2022

Table A. Case counts and notification rates of confirmed, locally acquired cases of TBE in EU/EEA countries, by year, 2013–2022

	2013		2014		2015		2016		2017		2018		2019		2020		2021		2022	
Reporting country	**N**	**Rate**	**N**	**Rate**	**N**	**Rate**	**N**	**Rate**	**N**	**Rate**	**N**	**Rate**	**N**	**Rate**	**N**	**Rate**	**N**	**Rate**	**N**	**Rate**
Austria	98	1.16	76	0.89	66	0.77	89	1.02	118	1.35	167	1.89	103	1.16	238	2.67	132	1.48	203	2.26
Belgium	ND	NC	ND	NC	ND	NC	ND	NC	ND	NC	ND	NC	ND	NC	ND	NC	ND	NC	ND	NC
Bulgaria	ND	NC	ND	NC	ND	NC	ND	NC	ND	NC	ND	NC	ND	NC	ND	NC	ND	NC	ND	NC
Croatia	0	0.00	0	0.00	0	0.00	0	0.00	10	0.24	0	0.00	0	0.00	0	0.00	1	0.02	3	0.08
Cyprus	ND	NC	ND	NC	ND	NC	ND	NC	ND	NC	ND	NC	ND	NC	ND	NC	ND	NC	ND	NC
Czechia	622	5.91	408	3.88	346	3.28	559	5.30	684	6.47	706	6.65	770	7.23	849	7.94	592	5.64	703	6.68
Denmark	ND	NC	ND	NC	ND	NC	ND	NC	ND	NC	4	0.07	5	0.09	5	0.09	7	0.12	5	0.09
Estonia	114	8.64	82	6.23	113	8.59	80	6.08	83	6.31	83	6.29	82	6.19	69	5.19	82	6.17	140	10.51
Finland	0	0.00	0	0.00	0	0.00	0	0.00	63	1.14	63	1.14	62	1.12	71	1.28	11	0.20	0	0.00
France	1	0.00	7	0.01	7	0.01	12	0.02	1	0.00	20	0.03	2	0.00	43	0.06	23	0.03	32	0.05
Germany	401	0.50	228	0.28	200	0.25	312	0.38	453	0.55	533	0.64	371	0.45	648	0.78	358	0.43	470	0.56
Greece	0	0.00	1	0.01	1	0.01	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	4	0.04	1	0.01
Hungary	25	0.25	26	0.26	22	0.22	14	0.14	13	0.13	29	0.30	17	0.17	18	0.18	6	0.06	28	0.29
Iceland	ND	NC	ND	NC	ND	NC	ND	NC	ND	NC	ND	NC	ND	NC	ND	NC	ND	NC	ND	NC
Ireland	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Italy	0	0.00	0	0.00	5	0.01	40	0.07	23	0.04	39	0.06	36	0.06	37	0.06	18	0.03	102	0.17
Latvia	230	11.36	149	7.44	141	7.10	91	4.62	178	9.13	100	5.17	175	9.11	149	7.81	222	11.73	ND	NC
Liechtenstein	ND	NC	ND	NC	ND	NC	ND	NC	ND	NC	ND	NC	ND	NC	ND	NC	0	0.00	0	0.00
Lithuania	402	13.53	347	11.79	333	11.40	628	21.74	468	16.43	380	13.53	570	20.40	679	24.30	365	13.06	375	13.36
Luxembourg	ND	NC	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00

	2013		2014		2015		2016		2017		2018		2019		2020		2021		2022	
Reporting country	**N**	**Rate**	**N**	**Rate**	**N**	**Rate**	**N**	**Rate**	**N**	**Rate**	**N**	**Rate**	**N**	**Rate**	**N**	**Rate**	**N**	**Rate**	**N**	**Rate**
Malta	ND	NC	ND	NC	ND	NC	ND	NC	ND	NC	ND	NC	ND	NC	ND	NC	ND	NC	0	0.00
Netherlands	ND	NC	ND	NC	ND	NC	2	0.01	1	0.01	2	0.01	2	0.01	5	0.03	2	0.01	2	0.01
Norway	4	0.08	9	0.18	9	0.17	9	0.17	11	0.21	22	0.42	28	0.53	36	0.67	64	1.19	63	1.16
Poland	135	0.35	129	0.34	114	0.30	209	0.55	196	0.52	148	0.39	197	0.52	114	0.30	179	0.47	365	0.97
Portugal	ND	NC	ND	NC	ND	NC	ND	NC	ND	NC	ND	NC	ND	NC	0	0.00	0	0.00	0	0.00
Romania	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	2	0.01	0	0.00	0	0.00	1	0.01	0	0.00
Slovakia	161	2.98	115	2.12	79	1.46	167	3.08	75	1.38	154	2.83	162	2.97	183	3.35	70	1.28	154	2.83
Slovenia	307	14.91	100	4.85	62	3.01	83	4.02	102	4.94	153	7.40	111	5.33	187	8.92	62	2.94	125	5.93
Spain	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Sweden	203	2.12	177	1.84	257	2.64	234	2.38	0*	0.00	353	3.49	349	3.41	263	2.55	512	4.93	427	4.09

** In 2017, Sweden did not report confirmed cases of tick-borne encephalitis.*

ND: no data reported
NC: not calculated.

Annex 2. Notification rates map specifications

- Only countries that reported data for five or more years between 2013 and 2022 are included.
- Only confirmed and locally-acquired cases are included.
- Only cases reported by EU/EEA countries are included.
- The NUTS level corresponds to the level for which at least 80% of the cases are reported.
- The years considered in the notification rate denominator (population) are only the years for which the country reported data.

Reporting Country	NUTS level	Population years considered in the notification rate denominator
CZ	NUTS3	ALL
DE	NUTS3	ALL
DK	NUTS3	2018, 2019, 2020, 2021, 2022
EL	NUTS3	ALL
FI	NUTS3	ALL
HU	NUTS3	ALL
LT	NUTS3	ALL
RO	NUTS3	ALL
SE	NUTS3	ALL
SK	NUTS3	ALL
AT	NUTS2	ALL
FR	NUTS2	ALL
EE	NUTS0	ALL
HR	NUTS0	ALL
IT	NUTS0	ALL
LV	NUTS0	2013, 2014, 2015, 2016, 2017, 2018, 2019, 2020, 2021
NL	NUTS0	2016, 2017, 2018, 2019, 2020, 2021, 2022
NO	NUTS0	ALL
PL	NUTS0	ALL
SI	NUTS0	ALL
LU	NUTS0	ALL
IE	NUTS0	ALL
ES	NUTS0	ALL
PT	Not included	
MT	Not included	
IS	Not included	
BG	Not included	
BE	Not included	
CY	Not included	
LI	Not included	

European Centre for Disease Prevention and Control (ECDC)

Gustav III:s Boulevard 40
16973 Solna, Sweden

Tel. +46 858601000
ECDC.info@ecdc.europa.eu

www.ecdc.europa.eu

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