Chapter 14

Public health aspects of TBE

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Key Points

- The identification of TBE endemic areas is crucial to inform national and international TBE risk management programs. However, identification of TBE endemic areas remains incomplete.
- The risk of tick-borne disease is predicted to increase with climate change through several mechanisms, but the relationship between climate and tick-borne disease is complex and influenced by both environmental and human factors.
- Uptake and compliance with TBE vaccination in Europe vary greatly, with overall low rates.
- Disparities in TBE awareness and vaccine uptake exist between endemic and non-endemic countries. Targeted education, involvement of healthcare professionals, and accessible vaccination strategies are needed to address barriers and improve prevention for those living in or travelling to TBE endemic areas.
- Because children also suffer from long-term cognitive impairment and because TBE cases in children are likely to be underreported, TBE vaccination is important for this age group.
- Increasing vaccination rates across all age groups is the most effective and efficient strategy to reduce the burden of TBE and protect the overall population's health.
- To effectively manage and prevent the spread of TBE, a comprehensive One Health approach must consider the complex interactions between humans, animals, ticks, and the environment.

Introduction

Public health measures are a key strategy for reducing the transmission of pathogens with epidemic potential. These measures encompass vaccination programs and non-pharmaceutical interventions that can be implemented by individuals, institutions, communities, local and national governments, and international bodies to slow or stop the spread of an infectious disease. TBE requires significant public health attention due to its potential to harm individuals residing in or travelling to TBE endemic areas. The disease can lead to long-term disability and even death. It is important to inform the public about the risks associated with TBE and provide an appropriate public health response.

Reporting and surveillance

TBEV is found in natural foci, which are areas where the virus circulates among ticks and reservoir hosts. As a result, TBE is limited to specific geographical regions, resulting in TBE endemic areas.[1–3] More than 25 countries in Northern, Central, and Eastern Europe have one or more areas where TBE is endemic,[4] with the highest reporting rates in the Baltic States, Slovenia, and the Czech Republic.[5] Together with Russia and part of eastern Asia, these countries form what is known as the “TBE belt”.[6] The incidence of TBE has increased over the past 25 years,[7,8] with a northwestward spread in continental Europe, including to regions and altitudes previously believed to be free of the virus.[1,9–11] The number of reported TBE cases in Europe in 2020 was twice that of 2015;[9] nearly 30,000 cases were reported in the EU/EEA countries between 2012 and 2020[11]. However, annual case reporting fluctuates widely due to various factors.[1]

Since 2012, the European Centre for Disease Prevention and Control (ECDC) has required all European Union member states, as well as Iceland and Norway, to report their TBE data annually to the European Surveillance System (TESSy).[12] In 2022, 43% of European countries[13] used the latest diagnostic criteria introduced by the ECDC in 2018.[14] In some countries that do not use the ECDC criteria, such as Italy, national diagnostic criteria are largely similar to the ECDC criteria. Therefore, reported TBE case numbers may not differ significantly.[1,14] However, this may not be the case in countries that have key differences in requirements for the confirmation of a TBE case, such as in Germany, where clinical signs may be limited to non-specific symptoms (i.e., without CNS symptoms).[1,15–17] Country data on TBE prevalence is difficult to compare due to differences in case definitions between countries, resulting in varying degrees of accuracy.[1,9]

TBE is typically an acute disease, and progression may terminate after the first phase, which is called the “abortive” clinical pattern. This form of TBE may be asymptomatic or manifest as a mild febrile illness, including symptoms such as headache, fever, fatigue, myalgia, anorexia, nausea, and vomiting, without progression to any form of encephalitis.[18,19] However, only a few countries, namely Austria, Latvia, Germany, and Slovenia, collect data on nonspecific non-CNS symptoms.[1,15,20–23] Additionally, mild CNS symptoms may go unreported since they do not fulfill the ECDC criteria, leading to underreporting of TBE. This is particularly noteworthy in pediatric patients, where symptoms are often mild and can be misdiagnosed.[1] Cases of TBE in children are very likely to be underreported compared to adults, as up to two-thirds of pediatric TBE cases are missed.[9,24,25]

Clinicians who do not test for TBEV infection due to a lack of recognition of the possibility of CNS inflammation may impact the number of reported TBE cases. Furthermore, if they suspect CNS inflammation, they may be less inclined to perform a CSF examination that supports a TBE diagnosis.[1]

Access to diagnostic tests for TBE is limited, as is knowledge on their appropriate use.[1] Serological assays are the preferred method for TBE diagnosis.[26] However, interpreting serologic test results is challenging due to the high cross-reactivity of the antigenic structure among orthoflaviviruses, particularly in areas where other orthoflaviviruses co-circulate or where vaccination against other orthoflaviviruses is common.[27] Improved laboratory capacities and implementation of neutralization assays in these countries could improve identification of TBE by distinguishing it from other orthoflaviviral infections.[1,28] Due to strict biosafety regulations in a number of Western countries, the performance of neutralization assays is restricted to laboratories equipped with a biosafety level 3 facility (biosafety level 4 in the United States). Therefore, alternative assays not requiring the work with infectious viruses could also be of value.[29,30]

Accurately determining the tick populations infected with TBEV and the number of human TBE cases is crucial for defining TBE risk areas. Endemic areas, which are risk areas where recurrent transmission of TBEV to humans occurs over several seasonal cycles,[31] must be documented in most countries to make targeted vaccination recommendations.[1,32,33]

The geographic restriction of TBE allows for targeted surveillance in high-risk areas. However, incomplete surveillance can lead to a poor understanding of TBE endemic areas and potentially inadequate vaccine recommendations.[1] This was demonstrated in Poland, where numerous new endemic districts were identified, including foci far away from previously known endemic districts, during an enhanced surveillance project.[34] Restricted surveillance may hinder the early identification of new TBE endemic areas, thereby increasing the risk of TBEV infection for the public. Moreover, designating areas as endemic or high-risk may limit awareness and diagnosis of TBE in non-endemic areas, despite a national obligation to report TBE cases. This may lead to a decrease in the ability to detect cases of TBE in areas where the disease was not previously present, as well as in the diagnosis of imported cases of TBE.[1]

Overall, the identification of TBE endemic areas is crucial to inform national and international TBE risk management programs.[1] However, identification of TBE endemic areas remains incomplete, and TBE surveillance in Europe is generally sporadic rather than systematic.[9] TBE cases are likely to be underreported, and the true burden of TBE disease is significantly underestimated.[9]

Impact of climate change on tick-borne encephalitis

Infection transmission occurs when the activities of reservoirs, vectors, and humans overlap, with variations depending on the pathogen and location. Climate change has the potential to affect all of these stages and their interactions.[35] Climate change is expected to increase the risk of ticks and tick-borne diseases in a number of ways.[36–38] However, the relationship between tick-borne diseases and climate is not linear. Rather, it is influenced by other environmental and human factors.[36–41]

Ixodes ricinus, the primary vector of TBEV in Europe, is particularly sensitive to environmental conditions, as this tick species requires a microclimatic relative humidity of at least 80% during its extended non-parasitic periods to avoid lethal dehydration. While changes in climate and the duration of different seasons will affect tick survival, activity, and development, there is insufficient evidence to support the concept that an increase in temperatures will directly lead to a higher tick abundance simply by accelerating developmental rates. Instead, shifts in development rates will alter patterns of seasonal activity.[35,42]

Indirect effects of climate change will affect the number of infected ticks by affecting vegetation.[35] For example, there is a link between tree mast, rodent population dynamics, nymphal tick density, and the incidence of human TBE two years later.[43–46] While climate warming has increased seed production in certain trees, mast seeding events have decreased.[47] A warming climate in central Europe is expected to lead to shifts in dominant tree species, resulting in a favorable microclimate for the survival of the free-living tick stages.[35]

Climate change will indirectly affect the transmission of tick-borne pathogens by affecting the survival and abundance of tick maintenance hosts, such as deer, and pathogen reservoir hosts, such as rodents and birds.[35,48,49] Increasing temperatures will expand the distribution range of both reservoir and tick maintenance hosts[50,51] as well as their abundance and activity.[51,52]

Climate change may affect disease risk by influencing long-term land use (e.g., farming, tourism).[35] Human behavior is also expected to adapt as the climate changes. People may resume outdoor activities earlier in the spring and maintain them longer in the fall, thereby increasing the duration of annual tick contact for both animal hosts and humans. The risk of climate change to human exposure is more likely to be associated with shorter winters than with extreme summer heat.[36–38]

The influence of climatic factors on virus replication has not been elucidated. However, there is evidence that certain TBEV strains can adapt to different environmental temperatures within the tick.[53] The spread of TBEV infection locations is significantly more frequent where precipitation and temperature are high in summer and frost days are low in winter.[54] With projected climate change, the range of *I. ricinus* can expand to higher latitudes, particularly in northern and eastern Europe, and to higher altitudes.[10,55–58]

While *I. ricinus* is the primary vector of TBEV, the virus has also been isolated from other tick species. Therefore, changes in the range of these species may also affect the risk of contracting TBE. Statistical habitat models predict a further distribution and a potential long-term establishment of the tick species *Dermacentor reticulatus* and *Hyalomma marginatum.*[35,59]

Taken together, climate change can affect the transmission of tick-borne diseases by influencing the survival, abundance, and activity of ticks, as well as their hosts. The relationship between tick-borne diseases and climate is complex. Changes in temperature, precipitation, and vegetation are expected to shift the geographical distribution and incidence of diseases like TBE. This is due to factors such as changes in tick activity patterns and the expansion of tick habitats, which increase the risk of TBE in certain regions.

TBE and tick awareness and risk subjects and general protective measures

As there is currently no specific treatment available for TBE infection, prevention is strongly recommended. Vaccination is the most effective mechanism of protection against the development of TBE, in addition to the elimination of all possible exposures. General protective measures and behaviors are recommended as primary and secondary preventive measures, as summarized in Table 1.[60] The best way to reduce the risk of exposure is to avoid tick-infested areas, especially during the peak tick season in spring and late summer. However, it is not always possible to avoid exposure to ticks, especially for residents of endemic areas. Therefore, it is recommended to wear protective clothing with long sleeves and long trousers tucked into socks or boots, to use repellents on exposed skin, and to impregnate clothing with an acaricide (such as permethrin or pyrethroids). After a tick bite, TBEV is immediately transmitted to the host through the tick's saliva. It is recommended to remove the tick as soon as possible, even if it is already firmly attached to the skin, to prevent other potential infections. In the event of a tick bite, the tick should be removed using fine-tipped tweezers/forceps or a specially designed tick card/removal tool by pulling straight out without squeezing or twisting the tick. Unpasteurized dairy products in tick-infested areas may also contain TBE;[61–63] avoid eating or drinking unpasteurized milk and cheese from goats, sheep or cows from these areas.

The main individual-level risk factors for TBE can be divided into two categories: behavioral and occupational risks, and biological risks. Behavioral and occupational risks include factors that increase the likelihood of exposure to ticks and contracting TBE. Forestry workers, farmers and hunters are at higher risk of contracting TBE, due to the nature of their work. Additionally, leisure activities in the countryside also increase the risk of exposure to TBE, which are more common among older individuals with more leisure time. Studies of clinical TBE cases in Switzerland found that around 80-90% of patients with TBE or Lyme borreliosis contracted the disease during leisure activities.[64–66] Another related risk is the geographic region in which an individual lives, works, or spends leisure time.[64–68]

Biological risks for TBE disease include gender and age.[12,65,66,69,70] Cases are more common in men, but this may be due to an increased risk of exposure rather than a different immune response to TBE in men and women. Both the incidence and severity of the disease increase with age.[70,71] Existing comorbidities, immunosuppression and certain genetic predispositions also increase the risk of severe disease following exposure but not of the risk of exposure itself. Adults over the age of 50 not only have an increased incidence of TBE, but they also tend to experience more severe disease and have a higher risk of lasting neurological sequelae.[70–72] Immunocompromised individuals, such as immunosuppressed patients, organ or hematopoietic stem cell transplant recipients, and HIV-infected individuals, are particularly susceptible to TBE and often experience severe or fatal disease.[70,73–76]

Published research has identified several factors associated with awareness of TBE and uptake of TBE vaccines. A recent study assessed TBE awareness and vaccination rates in 2020 in 20 European countries.[67] Of these, 14 countries were identified as TBE endemic and 6 as non-endemic. The results showed that there was a difference in TBE awareness (74% vs. 30%) and TBE vaccine awareness (56%

Table 1: General primary and secondary preventive measures[60]

	Measure	Comment
Behavior	Avoid tick-infested areas Avoid unpasteurized dairy products Adhere to personal protection measures when working with viable TBEV	Whenever possible
Clothing	Light-colored clothing that covers arm and legs (long-sleeved shirts – tight at the wrists, long pants – tight at the ankles and tucked into the socks); shoes covering the entire foot	Dark clothing is proven to be more attractive for ticks (which in addition are more difficult to identify on a dark background)
Use of repellents	Apply adequate repellent (with proven action against ticks) to clothing and skin	e.g. DEET in higher concentrations, (p)icaridine as well as permethrin / pyrethroids are proven to act against ticks; allow clothing to dry up before wearing
Early detection	Adults should be checked daily; children should be checked more frequently, i.e. after some hours of exposure (could result in 2 to 3 checks per day)	The checks should especially focus on waist bands, sock tops, under arms, other moist areas (for children: head and especially behind the ears); even adults may need the assistance of a second person to check the whole body
Early removal of ticks	Remove tick as soon as possible using fine-tipped tweezers or special cards (resembling carved credit cards); grasp the tick firmly as close to the skin as possible and simply tear it out without squeezing or rotating the tick	Don´t suffocate the tick (oil, cream, nail polish, water); don’t burn the tick; don´t apply “home remedies”; don´t wait for medical services if not promptly available

vs. 12%) between endemic and non-endemic countries.[67] Motivating predictors of TBE vaccination include recommendation from a physician (in both endemic and non-endemic countries), personal or occupational risk exposure, fear of TBE, dog ownership, experience with tick-related health problems, desire to avoid contracting the disease, trust in vaccine recommendations, frequent outdoor activities, gardening and travel to an endemic area.[67,68,77–80] While those who were vaccinated against TBE were better informed about TBE disease than non-vaccinated individuals in a non-endemic TBE area, getting a TBE vaccination was not associated with a reduced uptake of general protective measures.[81] Barriers to TBE vaccination include not living in or visiting risk areas, low risk perception, fear of adverse events following vaccination, lack of information about TBE and the vaccine, unavailability of the TBE vaccine, and the belief that vaccination is unnecessary.[67,68,78,79]

Individual-level risk factors for TBE include higher exposure risks for forestry workers and individuals engaging in outdoor activities in endemic areas. Additionally, age, gender and comorbidities can contribute to the degree of susceptibility to TBE. The recognition of differences in TBE awareness and vaccine uptake between endemic and non-endemic countries underlines the need for targeted education, involvement of health professionals, and accessible vaccination strategies to eliminate barriers and enhance prevention.

Vaccination schedules and recommendations

There are six licensed vaccines available, all of which use inactivated whole virus strains. These vaccines can be grouped into European, Russian, and Chinese vaccines.[82] Currently, two European vaccines are available in many European countries and Canada, and one is available in the United States. They are based on the Austrian isolate Neudoerfl (FSME-IMMUN) and the German isolate K23 (Encepur), both TBEV-Eu strains. Additionally, licensed vaccines in Russia and some neighboring countries are based on the Russian TBEV-FE isolate Sofjin (TBE vaccine Moscow and Tick-E-Vac/Klesch-E-Vac) and TBEV-FE strain 205 (EnceVir). In China, SenTaiBao, which is based on the Chinese TBEV-FE strain Sen-Zhang, has been approved as a TBEV vaccine (reviewed in[17,19,82–85]). Pediatric formulations are available for FSME-IMMUN, Encepur, TBE vaccine Moscow, Tick-E-Vac, and EnceVir vaccines.[19] The standard immunization schedule for all vaccines, except for Sen Tai Bao which has only two doses, consists of three doses. The initial vaccination is followed by a second injection 4-12 weeks later, and a third injection is given 5-12 months later, with variations in the specific intervals between vaccine brands. Vaccine manufacturers prescribe booster doses to maintain protection: the first three years after primary

Table 2: Booster dosing schedules in adults in Switzerland, Finland, and Belgium. Adapted from Schelling et al, 2024[91]

Country	First booster	Subsequent boosters
Switzerland[86] (64)	after 10 years	every 10 years
Finland[87] (65)	after 3 years	age <50: every 10 years age 50-60: every 5 years age >60: every 3 years
Belgium[88] (66)	after 3 years	age <60: every 5-10 years age ≥60: every 3 years
Latvia[89,90] (ref)	after 3 years	every 10 years

immunization and subsequent boosters every three to five years. Sen Tai Bao is an exception, requiring an annual booster dose.[17,19,85] In addition to conventional schemes, rapid vaccination schedules are available for most of these vaccines. If necessary, European vaccines can be used interchangeably.[19]

Although TBE vaccination is common in Europe, recommendations for TBE vaccination vary even among countries where TBE is endemic.[1,9,67] At present, only Austria and Switzerland have national universal vaccination programs.[1] In the Czech Republic, Estonia, Germany, Hungary, Latvia, Lithuania, and Slovenia, vaccination is generally recommended. Other European countries link their vaccine recommendations to specific factors, such as predefined risk areas. For example, in Croatia, Poland, and Serbia, vaccination is recommended for people living in or travelling to endemic areas. In Belarus, Italy, Kazakhstan, Mongolia, Slovakia, Sweden, Russia, and Ukraine, vaccination is recommended for those with possible occupational exposure. Several countries, including Belgium, Bulgaria, Finland, France, Greece, Ireland, Israel, Netherlands, Spain, UK, and Turkey, provide recommendations for individuals travelling to endemic regions[9]. Simplifying vaccine recommendations could aid the public in understanding local guidelines.[1]

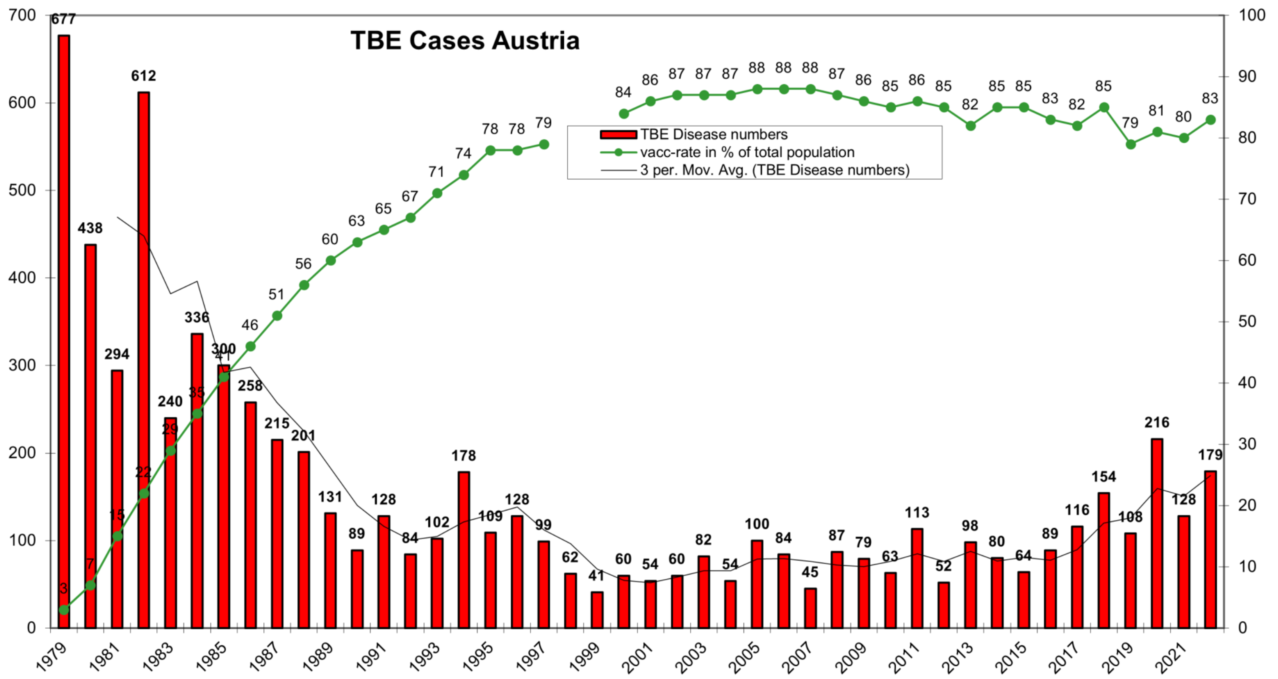
Although most countries require documentation of TBE-endemic areas in order to make targeted vaccination recommendations,[1,32,33] it is unclear how national vaccination recommendations relate to observed TBE incidence, as incidence surveillance systems may underreport cases.[9] The unpredictability of TBEV microfoci and the difficulty in identifying TBE-endemic areas raise questions about the suitability of vaccine recommendations that focus solely on these areas. Therefore, it may be advisable to expand TBE vaccine recommendations to cover the entire population, rather than just those residing in or travelling to currently identified endemic areas.[1]

Regarding booster vaccinations, some countries, such as Switzerland, Finland, Belgium, and Latvia, have extended the recommended interval from every 3-5 years to up to 10 years, as approved locally (Table 2).[86–90]

In 2006, the Federal Office for Public Health in Switzerland recommended extending the booster intervals for TBE vaccine from 3 to 10 years. TBE vaccine reluctance was associated with the need for frequent boosters.[92] After adjusting the vaccination schedule, the sales of the annual TBE vaccine increased more than four times,[93] and vaccination coverage (1 dose) among children aged 16 increased from 10% (95% CI: 8.8-11.2%) in 2005-07 to 55% (95% CI: 53.0-56.6%) in 2020-22.[94] In adults, the vaccination coverage reached 42% in 2018 (up to 50% in endemic regions).[68] The Swiss strategy has not only been more cost-effective but has also led to a significant increase in the number of people accepting TBE vaccination without an increased rate of vaccine breakthrough infections in any age group, which is a substantial benefit for public health.[95]

TBE vaccination is fully or partially reimbursed in only a few countries. Typically, reimbursement is linked to specific factors.[1,9] For example, Switzerland and Germany provide reimbursement for individuals who are traveling to, living in, or working in risk areas. Hungary provides reimbursement for residents of highly endemic areas, and Latvia provides partial reimbursement for children and adolescents living in endemic areas. In Austria, designated risk groups receive full coverage for vaccination costs. In Estonia, Latvia, and Poland, employers fully reimburse vaccination expenses for their employees falling into high-risk categories. In Slovenia, compulsory insurance schemes facilitate reimbursement for high-risk workers. In the Czech Republic, there are contributions from preventive funds from health insurance companies. TBE endemic countries that do not offer reimbursement for the TBE vaccine include

Figure 1: TBE – annual disease numbers and vaccination rate in Austria[60]



TBE vaccination status data were collected annually by surveys conducted by GfK Austria Health Care (Vienna, Austria). TBE case data are collected by the Center for Virology, Medical University of Vienna, Austria, serving as a national reference laboratory for TBEV

Sweden and Romania.[9] The absence of a broad reimbursement policy may be a significant factor in low vaccine uptake,[96] as discussed below.

Vaccine effectiveness and vaccine uptake

TBE vaccines are highly effective in preventing infection, disease, and other outcomes, including serious outcomes, regardless of age.[20,21,68,79,96–104] Vaccine effectiveness ranges from at least 91.5% for receipt of three or more doses[68] to at least 95.4%[20] for receipt of four or more doses.[96] Studies have reported minimal differences in vaccine effectiveness estimates between individuals who received their last dose ≤10 years ago and those who received it more than 10 years ago.[79,96,102,104]

The impact of vaccination on disease incidence was well-documented in Austria. Austria is unique among European countries in having implemented an annual, nationwide TBE awareness and vaccination campaign as early as 1981, targeting the entire population. The implementation of vaccination programs has led to a substantial reduction in the incidence of TBE cases. In Austria, the number of TBE cases has decreased by approximately 90% compared to the time before vaccination programs were introduced and when vaccination coverage was low[98] (Figure 1).

Between 2000 and 2011, TBE vaccination in Austria prevented approximately 333 cases annually within a population of 8.2 million.[97] In Switzerland, TBE vaccination of adults was estimated to prevent 112-162 cases in 2018 among a population of 6.6 million adults.[68] During the three -year study period in Latvia, vaccination was estimated to have prevented 897 hospitalizations, 26 intensive care admissions, 34 patients discharged from the hospital with paresis, and 20 deaths. Additionally, in the Czech Republic, TBE vaccination was estimated to prevent approximately 204 cases per year from 2018 to 2022 among a population of 10.4 million.[105] Vaccination prevented over 1,000 cases of TBE and hundreds of hospitalizations annually in the four countries studied, highlighting the significant public health impact of TBE vaccines. These vaccines are widely used in over 25 European countries with TBE-endemic areas, suggesting that thousands of TBE cases are likely prevented each year through vaccination. However, even though TBE vaccines are effective, the incidence of TBE remains high in the endemic areas of many countries due to the high number of unvaccinated individuals.[96]

Uptake and compliance with TBE vaccination in Europe vary greatly, with overall low rates.[1,67,106] The average TBE vaccine uptake in European countries was only 22% in endemic countries and 5% in non-endemic countries in 2020.[67] At the country level, TBE vaccine coverage varies widely in endemic countries. Austria has the highest coverage at 81%, followed by Latvia at 62%. In contrast, Finland and Hungary have coverage of just under one-third of the population, while Slovakia, Poland, and Romania have the lowest coverage at 12%, 11%, and 7%, respectively (Table 3). In non-endemic countries, TBE vaccine coverage is

Table 3: Vaccine uptake in endemic European countries[67]. "Vaccine uptake" was defined as the percentage of subjects with at least 1 TBE vaccination at any time. "Dose 3 compliance" measured the percentage of subjects who completed the primary series on time according to the licensed vaccine regimen after receiving their first dose of vaccine. "Protection share" measured the percentage of subjects who were within the licensed vaccination regimen after receiving at least 3 prior TBE vaccinations.

Country	Vaccine uptake (%)	Dose 3 compliance (%)	Protection share (%)
All endemic	36	46	26
Austria	81	74	47
Latvia	62	70	44
Germany	48	43	25
Sweden	47	57	41
Estonia	45	59	41
Switzerland	43	40	24
Slovenia	39	63	41
Lithuania	37	67	43
Czech Republic	33	48	31
Hungary	30	29	15
Finland	26	41	26
Slovakia	12	35	16
Poland	11	28	12
Romania	7	no data	no data

very low, with only 1% in France, 5% in Belgium, 6% in the Netherlands, 7% in Norway, and 8% in Denmark and the United Kingdom.[67]

In Russia, vaccination coverage varies greatly between regions, as reviewed in.[19] The Rospotrebnadzor regulations prescribe mandatory vaccination of adolescents (at school) and high-risk groups in endemic territories, which is funded from the regional budget. In certain endemic areas, vaccination coverage can be high (e.g., 88% in the Sverdlovsk region). However, in other endemic regions, less than 10% of the population is vaccinated. The differences arise because vaccination is administered in endemic districts, while the level of vaccine coverage is calculated for the entire region. In non-endemic areas, vaccination is not compulsory, making it challenging to assess the impact of vaccination.[19]

In certain countries, high levels of disease and vaccine awareness may result in high vaccination rates, as seen in Austria. However, in other countries like the Czech Republic, despite high levels of awareness, vaccination rates remain low.[67] In fact, vaccine uptake is a multifaceted issue that does not always correspond with vaccine awareness.[1,67] The low vaccination rates across most of Europe can be attributed to various factors, including the complexity of the TBE vaccination schedule, low awareness of the potential consequences of TBE, and limited vaccine accessibility and reimbursement.[106]

The limited reimbursement of vaccine costs may reduce vaccine uptake due to economic constraints. For example, in Slovakia and Poland, the proportion of individuals who receive the vaccine is approximately five times smaller than the proportion of individuals who are aware of the availability of a TBE vaccine (12% vs. 63% in Slovakia, and 11% vs. 47% in Poland, respectively).[67] In these countries, vaccination is (partially) reimbursed for high-risk occupational groups only.[9] In contrast, in countries like Switzerland and Germany where the TBE vaccine is fully reimbursed for individuals staying in endemic areas, a high proportion of people who are aware of the vaccine's availability actually get vaccinated[9] (43% vs 59% in Switzerland, and 48% vs. 55% in Germany, respectively).[67] Reimbursement can therefore be an important motivator for individuals to be vaccinated, and the introduction of a broad reimbursement policy can support better vaccine uptake. It is noteworthy, however, that despite the availability of low-cost TBE vaccines, their uptake remains low in some endemic countries due to limited awareness of the burden of the disease and the risk it poses.[96] Thus, the relationship between vaccine uptake and reimbursement is not linear. It is influenced by other factors, as described above.

Necessity of pediatric vaccination

TBE vaccination is safe and effective and is currently recommended by the WHO for children one year of age and older.[20,96,107–109] Seroconversion rates in children (up to 15 years of age based on data from clinical development programs) are similar to those in adults, approaching 100% even in children as young as 1 year of age.[110–112] Studies have also shown high levels of protection and antibody persistence (94-100% seropositivity), with protection lasting up to 5 years following primary vaccination with three doses.[113,114] A recent case-control study showed that TBE vaccination is highly effective (>90%) in fully vaccinated children 0-17 years in Switzerland and remains high for up to 10+ years post completion of primary vaccination.[107]

Despite evidence that the TBE vaccines used in Europe are both effective and safe, they are administered conservatively in children. Disease incidence is lower in children than in adults.[14,24,70,71,115] However, infection in children may be underreported because symptoms are non-specific and vague, and children may not be able to describe their symptoms.[25,72] About 40-80% of the children can recall tick-bites.[25,116–118] In a study of asymptomatic TBE infections in a highly endemic area of northern Poland, only 2% of 180 unvaccinated children were seropositive for TBE, compared with 5% of adults, suggesting that TBE infections may be undiagnosed.[119]

The clinical course of TBE infection in children is similar to that in adults, albeit less severe. Although the frequency of occurrence varies, non-specific symptoms usually include fever, fatigue/malaise, behavioral changes, photophobia, myalgias.[120] The most common clinical manifestation of the disease in children is meningitis in 60-80% of the cases, followed by 20-40% meningoencephalitis and 0-4% meningoencephalomyelitis.[121,122] Disease severity is lower in children than in adults, but this discrepancy varies across the different age groups (0-5, 6-11 and 12-17 years).[107] The biphasic clinical course typical of TBE infection is less common in pre-school children than in older children and adults.[25] Consistent with the reduced overall incidence and severity of disease, permanent neurological sequelae of TBE infection are less common in children (0-2%)[115,123–126] than in adults (30-50%).[127–132] In a study of 523 TBE patients in Germany, overall 95% of 59 children and 64% of 464 adults recovered completely; compared with adults aged 18-39 years, the recovery rate in children was 79% higher.[72] Post-encephalitic syndrome is reported 3-10 times more frequently in adults than in children, regardless of the severity of TBE and the time point during the 18-month follow-up.[72]

A comprehensive systematic review focusing on the epidemiology, clinical characteristics, and outcomes of TBE in the pediatric population confirmed that the disease is less severe in children. However, recent follow-up cases have shown that a significant proportion of children suffered from long-term cognitive impairment.[24] These recent studies evaluating cognitive function in recovered pediatric TBE patients found abnormal EEG and MRI findings, a higher incidence of headache, fatigue, cognitive impairment, and reduced motor function compared to controls.[118,125,133–135] Thus, although mild in the early stages, infections can lead to long-term neurological sequelae and increased morbidity in children, which can affect their performances in school and everyday life.[72,118,122]

A recent study in Switzerland evaluated 463 TBE cases in children aged 0-17 years.[107] The study found that diagnoses of disease severity in young children aged 0-6 years are not different from those in older children. More severe disease, such as meningoencephalomyelitis, encephalomyelitis, and radiculitis, occurred in 1-5% of children across all three age groups (0-5, 6-11 and 12-17 years). The study also found that unvaccinated children were 6.7 times more likely than vaccinated children (1 or more doses) to develop neurological disease symptoms. Incompletely vaccinated children (2 doses or less) and completely vaccinated children (3 or more doses) were less likely to experience mild neurological disease compared to unvaccinated children.

Given the recent increase in incidence and severity of TBE, it is important to improve vaccination rates among children and adolescents. As they are more likely to engage in outdoor activities, children are at high risk, particularly those between 5 and 14 years.[12,64,66] Among the factors associated with uptake of TBE vaccination, having had a recent tick bite was the only predictor of having had a child vaccinated against TBE.[119] As TBE cases in children may be underreported, and mild symptoms may develop into long-term cognitive impairment, vaccination should be encouraged for children, especially those living in or travelling to TBE-endemic area.

TBE vaccination and travel

Global incidence estimates of TBE range from 10,000 to 12,000 cases per year,[109] with many cases remaining unreported or misdiagnosed.[1] According to the United Nations World Tourism Organization, there were almost 1.3 billion international tourist arrivals in 2023, which represents an increase of 34% from 2022.[136] More than half of these arrivals occurred in Europe.[136] The increase in international tourism, particularly in Europe, increases the risk of individuals travelling from non-endemic to endemic TBE areas.[137,138]

While the risk of mortality due to TBE is relatively low (ranging from 1% in central Europe up to 40% in the Far East),[139] the burden of long-term morbidity can be significant, lasting from months to years and ranging from post-encephalitic syndrome to permanent paralysis and seizures.[140] As there is currently no specific treatment for TBE, prevention is recommended. This includes preventing tick-bites, as described earlier, and vaccination. TBE vaccines may be administered in an accelerated schedule shortly before travel.[96,108] Vaccination is recommended for travellers from non-endemic countries with a high risk of tick exposure during travel between April and November.[138,141] Therefore, it is important to assess the risk of acquiring TBE for travellers from non-endemic countries visiting endemic countries before deciding whether to get vaccinated. This assessment should consider both environmental and personal factors. Environmental concerns relate to the choice of destination, including whether the area is endemic for TBE, the season, and altitude. Surveillance data have shown that tick activity is highest between April and November in endemic areas,[12,142] and TBEV foci have been found in places as high as 2100 meters above sea level.[143] When assessing the risk of exposure, it is important to consider individual behavior, the type of outdoor activity, duration of stay, and demographic variables such as age, gender, and personal health status.[140]

Several studies have assessed awareness of TBE and the TBE vaccine among travellers.[78,144,145] One study assessed perceptions of TBE risks among travellers from Canada, Germany, Sweden and the United Kingdom who were travelling to a TBE-endemic country.[144] The study found that 69% of travellers were aware of the disease, and 26% prepared for their trip by searching for information online. While 14% were aware that TBE vaccines were offered by travel clinics, 52% were not aware of the existence of travel clinics. Furthermore, while 14% of participants reported feeling at high risk when travelling to an endemic region, 26% never felt at risk. Among those who engaged in pre-defined at-risk activities, such as camping or hiking in the forests, 79% were aware of at least one correct TBE prevention measure. However, only 15% had been vaccinated within the last 3 years and 11% had been vaccinated following a clinic recommendation. Only 35% of the participants had heard of a TBE vaccine. Health professionals working in travel clinics recommended TBE vaccination to 61% of their travellers going to endemic areas.[144] Another study that surveyed international travellers residing in the United States found that the likelihood of travellers choosing the TBE vaccine depends on the level of endemic risk in the destination country, provided that the vaccine is available at no cost.[145] Almost all travellers (94%) would choose to be vaccinated should the risk be at the highest level, whereas 6% would remain unvaccinated regardless of the risk level. Respondents who participated in outdoor activities were more likely to choose vaccination than the average respondent.

While TBE awareness may have increased among travellers and travel clinics, vaccination may not be available in the country of origin where TBE is not endemic. Additionally, the subsequent costs of vaccination, diagnosis, and medical care may not be covered. If symptoms of infection occur upon returning home, they may not be recognized, leading to a misdiagnosis or no diagnosis at all, especially if adequate diagnostic testing tools are not available.[146]

In conclusion, it is important for both travellers and health professionals in travel clinics to be well-informed about the risks, preventive measures and symptoms of TBE when travelling from a TBE non-endemic country to an endemic destination. Lack of awareness or failure to take the necessary precautions could increase the likelihood of infection. These concerns highlight the need for international guidelines on TBE for travellers.

Economic impact

Health economic evaluations inform medical procurement and reimbursement decisions by public and private healthcare providers. The most common form of health economic evaluation is cost-effectiveness analysis, which presents the ratio of the incremental cost of an intervention to the incremental health benefits of an intervention.[147] However, there are only a few cost-effectiveness evaluations of the TBE vaccine.

In 1981, Austria introduced an overall TBE vaccination campaign[97] that led to a significant reduction in TBE cases.[99] The economic benefit of the campaign, which included reducing costs for inpatient care, loss of productivity, and premature retirement, was evaluated to be EUR 24 million for the years 1981 to 1990[148] and EUR 60 million between 1991 and 2000.

A study conducted in Slovenia found that TBE vaccination is cost-effective from a healthcare payer's perspective when vaccination begins at 18 years of age and continues until the age of 80.[149]

In 1996, a cost-effectiveness estimation of TBE vaccination in the Stockholm area was performed and it was calculated that, based on the TBE incidence at that time and the cost of vaccination, mass vaccination would be an unrealistic alternative.[150] However, more than 20 years later, much higher incidences in the unvaccinated population were reported. A health economic analysis was conducted in Sörmland County, which is a highly TBE-endemic area adjacent to Stockholm County. The analysis calculated that the costs per QALY (quality adjusted life year) for a fully free of charge vaccination program would come much closer to the generally acceptable cost-effectiveness threshold in Sweden. The authors concluded that introducing a structured vaccination program would be cost-effective at all ages. However, it would be particularly cost-effective if implemented in childhood.[77]

Estimating the economic impact of a disease requires an assessment of its disease burden, in addition to cost-benefit analyses. The Burden of Communicable Diseases in Europe study computed disability-adjusted life years (DALYs) for 31 selected diseases, including tick-borne encephalitis, in the European Union and European Economic Area.[151] DALYs represent the equivalent of a year of full health lost and are the sum of the years of life lost due to premature mortality and the years lived with a disability. The calculation of DALYs relies on the incidence of acute, symptomatic disease as a crucial input variable. Furthermore, it requires several age-group and sex-specific variables, such as the risk of developing short- and long-term complications, their duration, and weights reflecting their severity. The study found that the median annual burden of TBE was 0.69 (0.65 -0.74) DALYs per 100,000 population[151]. It is worth noting that a Slovenian study found a much higher disease burden on the country level (11.0 (10.2-11.7) per 100,000).[152] Thus, differences in underlying assumptions and disease modelling approaches heavily influence the outcomes of such analyses. Although DALYs provide useful information for prioritization and planning in public health, they do not fully encompass all unknowns, uncertainties, variability and other “softer” criteria such as public perception.[153]

A TBE vaccination program must be evaluated against other healthcare resources. To determine if funding a TBE vaccination program yields better health outcomes at a reasonable cost, it is important to establish the long-term costs and health outcomes of a local TBE vaccination strategy.[154] Furthermore, TBE can result in high productivity loss beyond the healthcare sector. Increasing vaccination rates across all age groups is the most effective and efficient strategy to reduce the burden of TBE and protect the overall population's health.[155] Therefore, a vaccination program or at least a vaccination recommendation should be considered. It is important to note that out-of-pocket costs may have a positive impact on an individual's private consumption, which is not included in the health care analysis.

Health economic evaluations play a crucial role in informing decisions regarding the implementation of TBE vaccination programs. While the cost-effectiveness of such programs varies depending on factors such as incidence rates and population demographics, evidence suggests that TBE vaccination can yield significant economic benefits by reducing healthcare costs and productivity losses. Despite challenges in estimating disease burden and modelling economic impacts, prioritizing TBE vaccination efforts across age groups remains a cost-effective strategy for mitigating the overall burden of the disease and safeguarding public health.

The One Health approach

The One Health approach is a collaborative and holistic strategy that recognizes the interconnectedness of human, animal, and environmental health.[156] TBE involves a complex ecosystem in which the virus circulates between ticks, animals (such as small mammals and deer), and humans.[157–159] The One Health approach considers the interdependence of these systems with the environment and seeks to understand how changes in one component can affect the entire ecosystem.

As discussed earlier in this chapter, the tick species *Ixodes ricinus* is the predominant TBEV vector in Europe, while *Ixodes persulcatus* and *Haemaphysalis concinna* are found in Russia and Asia.[158,160] The main reservoir hosts for ticks are small mammals or insectivores such as rodents, hedgehogs, shrews and hares. While their small size makes them easy targets for ticks, especially nymphs, their biological characteristics allow TBEV to circulate in the bloodstream at levels that allow the virus to be transmitted to feeding ticks without killing them. As these hosts have a high reproductive rate and short lifespan, there are always enough animals naive to the virus for it to spread.[158] Larger animals, such as deer, serve as hosts for adult ticks.[161] With a lag time of one year, a study in Sweden showed that the number of roe deer and hares was positively correlated with the number of TBE cases in the region.[162]

Tick populations are also strongly influenced by environmental factors such as climate, vegetation, habitat and human activity.[157] As discussed earlier, climate change can influence the survival, abundance and activity of ticks and their hosts by affecting the vegetation and their habitat through prolonged higher temperatures and relative humidity.[35–38] Human activity has also changed over the years, which has contributed to the increase in TBE cases. In addition to heightened awareness of the diagnosis of the disease, the number of TBE cases could be affected by farming and global tourism (both recreational and business). This increases the possibility of human and tick contact when individuals travel from a non-TBE endemic region to a TBE endemic region.[1,35–38,137,138,157] Surveillance of tick, animal, and human activities can aid in tracking the prevalence of TBEV, identifying potential hotspots, assessing the risk of human exposure, and exploring the dynamics of cross-species transmission to reduce the risk of spillover events.

A model incorporating data on climate, forest cover, water, tick abundance, and sheep (as an indicator species) identified an increase in TBE incidence in the Örebro region of Sweden during the study period.[163] They found a variation in hotspots across the region. The risk of acquiring TBE increased by 12.5% for every 1% increase in relative humidity and by 72.3% for every 1% increase in the proportion of wetland forest. However, as the model had a low goodness of fit, other variables, such as human behavior could help create a stronger model for understanding the spatial distribution of ticks. Historical data on TBE cases, human population demographics and migration, climate teleconnection, beech fructification (used as a proxy for rodent density, which acts as a host for the TBE virus vector), and annual sunshine duration were used to forecast TBE incidences for Austria, Germany, and Switzerland from 2019 to 2021.[45] The first verified forecasting results for 2019 were highly reliable, but could be improved for better accuracy.[164]

The most common way to contract TBE is through a tick bite. However, it is also possible to acquire TBE through the consumption of unpasteurized TBEV-contaminated dairy products from goats, cows and sheep.[61] The largest outbreak of TBE occurred in 1951 in the former Czechoslovakia, where over 600 cases were reported due to the consumption of contaminated, unpasteurized cow and goat milk.[61,165] An analysis of TBE outbreaks in Slovakia from 2007 to2016 revealed that 17% of all TBE cases were due to consumption of dairy products.[166] This percentage showed an increasing linear trend throughout the study period. Notably, none of these cases reported a tick bite, nor were they vaccinated against TBE.[166] A systematic review and meta-analysis of 410 cases of foodborne-TBE (FB-TBE) between 1980 and 2021 confirmed that the majority of cases were located in Central and Eastern Europe (the so-called FB-TBE triangle) and Russia.[63] The clinical presentation is similar to non FB-TBE infections, and neuroinvasive disease is common in 39% of cases. However, the median incubation time is shorter at 3.5 days. None of the cases were vaccinated, except for one whose last booster was more than 15 years ago. The clinical attack rate was 14% in outbreaks with 10 or more cases, with significant heterogeneity.[63] These FB-TBE outbreaks have the potential to cause a significant public health issue, despite their infrequency. However, unlike non FB-TBE cases, patients with mild and nonspecific symptoms can be actively contacted during an epidemiological investigation to locate the source of the outbreak. FB-TBE cases can be prevented by vaccination and avoidance of unpasteurized dairy products in TBE-endemic areas.[100]

In April 2020, the first FB-TBE outbreak occurred in France where the virus had never been detected before.[167] The research team utilized the One Health approach to investigate the outbreak.[159] Forty-two out of 43 cases of FB-TBE were linked to the consumption of unpasteurized raw goat cheese from a local producer. The methodology of investigation included screening for TBEV in cheese and milk products to identify the source of infection, serological testing of all animals on the suspected farm and surrounding farms, landscape analysis and localization of the wooded area, ticks, and small animal surveys for virus detection and virus isolation and genome sequencing. Information gained from this thorough and integrative approach should help the farmers and health authorities assess the risk of infection and develop control strategies. This outbreak underscored the need to improve surveillance, detection and prevention of FB-TBE in France, particularly given the increasing global trend toward the consumption of local and traditional delicacies.[168]

In summary, the One Health approach provides a robust framework for understanding and addressing the complexity of TBE. By acknowledging the interdependence of human, animal, and environmental health and involving health authorities and local communities, this collaborative strategy enables comprehensive surveillance, targeted interventions and effective control measures. Interdisciplinary collaboration and integrated surveillance systems are essential steps in reducing the burden of TBE and protecting public health.

Recommendations

TBE is considered an emerging disease and a growing public health concern. A One Health approach should be considered to combat this complex problem, as it emphasizes the importance of interdisciplinary collaboration in addressing complex health challenges by highlighting the interconnectedness of tick, human, animal, and environmental health.

Although there is considerable variation in national reporting of annual cases, the cumulative number of reported TBE cases across Europe increases, highlighting the need for improved TBE risk management.[1,9,10] Surveillance methods for TBE vary across Europe, with countries using different diagnostic criteria, access to diagnostic tests and knowledge on their appropriate, and approaches to national and regional surveillance.[1,9,13] Surveillance of TBE in Europe is currently incomplete, which means that reported cases are likely to only partially reflect the true risk, and that the true burden of TBE is significantly underestimated.[1,9,67,106] Experts on TBE have suggested the following measures to improve the surveillance of TBE throughout Europe:[1]

- Use of a single TBE case definition across Europe to ensure comparability of data;
- Testing all cases of aseptic meningitis/encephalitis of unknown etiology for TBEV infection;
- Rapidly extend testing to all patients with either a fever of unknown origin or CNS symptoms who live in or have visited an endemic, probable, or potential endemic area or who have received a tick bite;
- Improved funding for and access to diagnostic tests and testing facilities;
- Establishment of nationwide surveillance systems in countries that do not have them by implementing active surveillance systems with interactive maps of Ixodid tick activity across Europe; and
- Implementing active surveillance systems throughout Europe.

The national TBE disease burden and funding constraints will largely determine the extent to which these measures are implemented.[1]

Other recommendations to address the challenges as outlined in this chapter include:

- Climate change: The influence of climate change on the transmission of tick-borne diseases includes its impact on the survival, abundance, and activity of ticks, as well as their hosts. Changes in temperature, precipitation, and vegetation are expected to alter the geographic distribution and prevalence of diseases like TBE.[35–38] The spread of TBE to new regions in Europe presents a significant public health challenge. This challenge involves implementing measures to prevent TBE in regions not previously affected by the disease and where awareness of the disease is low. Such measures include establishing a surveillance system, recommending vaccination, and conducting awareness-raising campaigns.

- TBE vaccination recommendation: Vaccination remains the most effective method of protection against TBE. However, National Immunization Technical Advisory Groups in some European countries with TBE-endemic areas do not recommend TBE vaccines,[96] and only a few European countries have universal vaccination recommendations.[1,9] The unpredictability of TBEV microfoci and the difficulty in identifying TBE-endemic areas raise questions about the suitability of vaccine recommendations that focus solely on these areas. It may be advisable to expand TBE vaccine recommendations to cover the entire population, rather than just those residing in or travelling to currently identified endemic areas.[1] Alternatively, if TBE risk is limited to specific areas or if vaccination poses a significant burden on national or local healthcare services, vaccine recommendations should be simplified and standardized for healthcare practitioners and the public. TBE experts believe that this will aid the public in comprehending the recommendations and minimizing confusion.[1] In order for TBE vaccine recommendations to be effective, it is crucial that the public trusts the recommendations, understands the health risks associated with tick bites, has knowledge of TBE, and has easy access to vaccination services.[1,67,169]

- TBE vaccination rates: Uptake and compliance with TBE vaccination in Europe vary greatly, with overall low rates.[1,67,106] The uptake of the TBE vaccine is influenced by various factors, including specific recommendations, public awareness programs, vaccine awareness, perceptions of vaccine safety and reimbursement.[67] In many countries where TBE vaccines are recommended, vaccine uptake is low due to limited reimbursement of vaccine costs.[96] Although some countries have achieved good levels of vaccine uptake without a comprehensive national program,[67,106] vaccine reimbursement could lead to improved vaccine uptake, especially in low-income households.[169] However, in some countries, TBE vaccines are recommended and available at low cost, but vaccine uptake remains inadequate due to limited awareness of the disease burden and understanding of the risk.[96] Therefore, in countries where high awareness of the disease and vaccine does not directly translate into high vaccine uptake, motivators and barriers to vaccination must be analyzed to increase vaccine uptake. In countries where low vaccine awareness is associated with limited vaccine uptake, it is necessary to improve public awareness of TBE vaccines. In countries with low vaccine compliance, it is important to emphasize the need for booster shots.[67]

- TBE awareness and risk exposure: The incidence of TBE has increased over the past 25 years, posing a risk to individuals living in both TBE endemic and non-endemic countries, especially with the growth in international tourism.[137,138,157] Although TBE mortality rates are low, long-term morbidity underscores the importance of prevention. Therefore, safe and effective TBE vaccination is strongly recommended for travellers from non-endemic areas with a high risk of tick exposure. Studies show that awareness of TBE varies among individuals.[1,67,138,170] Therefore, comprehensive risk assessments that include environmental and personal factors are necessary. Targeted awareness campaigns and the involvement of health professionals are essential to promote preventive measures. These campaigns should focus on risk areas, risk perception, and the benefits of vaccination to address barriers and misconceptions. These campaigns should improve access to vaccination while tailoring interventions to specific populations, such as the elderly, immunocompromised individuals, individuals with comorbidities and behavioral and occupational risks, and travellers.

- TBE vaccination for children: Evidence strongly supports the safety and efficacy of TBE vaccination in children, with seropositivity comparable to adults and high long-term protection rates.[24,107,108,110,111,113] However, despite its proven benefits, vaccination rates remain conservative, possibly due to lower disease incidence in children and underreporting of TBE cases. In recent years, there has also been an increase in cases of neurological sequelae and long-term cognitive impairment in children diagnosed with TBE.[24,72,118,133] To address this, there should be a concerted effort to increase vaccination uptake among children and adolescents, particularly in endemic areas. Given the potential underreporting or missed diagnoses of TBE, particularly in preschool children, pediatricians in TBE-endemic regions should remain vigilant for TBEV infection in children presenting with non-specific central nervous system symptoms. It is imperative for them to ensure comprehensive clinical follow-up for children diagnosed with TBE to address potential long-term morbidity.

- Economic impact: Health economic evaluations are essential to guide decisions about the implementation of TBE vaccination programs. Despite the limited number of cost-effectiveness analyses of the TBE vaccine, studies have demonstrated its economic benefits, particularly in reducing healthcare costs and productivity losses. Evaluating the long-term costs and health outcomes of local vaccination strategies is essential to determine their effectiveness and prioritize resource allocation. Increasing vaccination coverage across all age groups has been identified as the most effective strategy for reducing the burden of TBE and protecting public health. Despite challenges in estimating disease burden and economic impact, prioritizing TBE vaccination efforts is considered cost-effective and essential to reduce the overall burden of the disease.

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