Superior
Health Council

VACCINATION AGAINST TICK-BORNE ENCEPHALITIS (TBE)

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Federal Public Service Health, Food Chain Safety and Environment

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Superior Health Council

ADVISORY REPORT OF THE SUPERIOR HEALTH COUNCIL no. 9435

Vaccination against Tick-Borne Encephalitis (TBE)

In this scientific advisory report, which offers guidance to public health policy-makers, the Superior Health Council of Belgium provides recommendations on the prevention of TBE in the Belgian population.

This report aims at providing public authorities with specific recommendations on vaccination against TBE.

This version was validated by the Board on February 2019[1]

I INTRODUCTION

Tick-Borne Encephalitis Virus (TBEV) is a *Flavivirus* (such as Yellow fever virus, Dengue virus). TBEV occurs in large areas of Asia and Europe and circulates in between its principal vector which are ticks, usually of the genus *Ixodes*, and small mammals ('reservoir hosts'). Humans can acquire the infection by a bite of an infectious tick or, less frequently, following consumption of raw milk from infected animals (goats, sheep, cows). Occasional infections have been described through blood transfusions and breastfeeding (RIVM).

In Belgium, the virus has been shown to circulate in animals and wild life since several years, and in 2018, the first two (one possible and one probable) autochthonous infections in human were reported (Sciensano, 2018). In several European countries, such as Austria and Germany, TBEV is endemic.

The Superior Health Council (SHC) received 2 requests for an advisory report by letter, on May 12 2017 from the Risk Management Group (FPS Health, Food Chain Safety and Environment) and on November 14 2018 from the federal Minister of Health. Both requests are treated in this advisory report.

These requests asked to provide national recommendations for vaccination against TBE for the general population and risk groups for different scenarios of TBEV circulation:

- No human cases: low level circulation of the virus.
- Sporadic human cases (probable actual situation in Belgium).
- Endemic circulation.

[1] The Council reserves the right to make minor typographical amendments to this document at any time. On the other hand, amendments that alter its content are automatically included in an erratum. In this case, a new version of the advisory report is issued.

II RECOMMENDATIONS

The Superior Health Council formulated recommendations for vaccination against TBE for the following 3 situations: in case of no human cases, in case of sporadic human cases, in case of endemic disease.

2.1 In case of no human cases - low level circulation of the TBE virus:

a. Vaccination is not recommended for the general population.
b. No active surveillance.
c. Vaccination of risk groups:
   - Vaccination is recommended for travelers to endemic regions doing outdoor activities in forested areas (such as hiking, camping, mushroom picking, …) during tick season (spring, summer and autumn).
   - Vaccination is recommended for people handling TBEV in laboratory setting.
   - Vaccination is not recommended for professional (wood cutters, forest rangers, …) or recreational risk groups.

2.2 In case of sporadic human cases (occurring at irregular intervals or only in a few places; scattered geographically):

In case of 1 human case: active surveillance

a. Vaccination is not recommended for the general population.

b. Active surveillance
   - Collection of ticks and rodents from the region of the case.
   - Inform medical doctors (Belgium, not restricted to region of the case).
   - Sensibilisation of population on preventive measures.

c. Vaccination of risk groups:
   - Vaccination is recommended for travelers to endemic regions doing outdoor activities in forested areas (such as hiking, camping, …) during tick season (spring, summer and autumn).
   - Vaccination is recommended for people handling TBEV in laboratory setting.
   - Vaccination is not recommended for professional (wood cutters, forest rangers, …) or recreational risk groups.

In case of 2 or more human cases infected in the same region (natural park) during the same year

a. Vaccination is not recommended for the general population.

b. Active surveillance
   - Collection of ticks and rodents from the region of the case.
   - Inform medical doctors (Belgium, not restricted to region of the case).
   - Sensibilisation of population on preventive measures.

c. Vaccination of risk groups:

- Vaccination is recommended for travelers to endemic regions doing outdoor activities in forested areas (such as hiking, camping, …) during tick season (spring, summer and autumn).
- Vaccination is recommended for people handling TBEV in laboratory setting.
- Vaccination is not recommended for professional (wood cutters, forest rangers, green service…) or recreational risk groups. However, because the other preventive measures do not fully protect the individual (they reduce the risk of being bitten), and early removal of the tick does not protect against TBE and because there is no treatment, one can consider vaccination for some professionals and individuals with a high risk of tick bite. This recommendation can be reviewed when the seroprevalence study of TBE in Belgian forest rangers will be available (summer 2019).

2.3 In case of endemic disease

Vaccination of the whole population is only recommended if the incidence is at least 5/100 000 (WHO, 2011).

For endemic circulation with a lower incidence, vaccination can be recommended for risk groups.
The recommendation will be updated according to the evolution of the epidemiology of TBE in Belgium.

Keywords and MeSH *descriptor terms*[2]

MeSH terms*	**Keywords**	**Sleutelwoorden**	**Mots clés**	**Schlüsselwörter**
Tick-Borne Encephalitis	Tick-Borne Encephalitis	'Tick-Borne'-encefalitis	Encéphalite à tiques	Tick-Borne'-Entzündungsherpes
Endemic Disease	Endemic disease	Endemische ziekte	Malade endémique	Endemische Krankheit
Vaccination	Vaccination	Vaccinatie	Vaccination	Impfung
Epidemiology	Epidemiology	Epidemiologie	Epidemiology	Seuchenbekämpfung
Prevention & Control	Prevention and control	Preventie en controle	Prevention et surveillance	Prävention & Kontrolle

MeSH (Medical Subject Headings) is the NLM (National Library of Medicine) controlled vocabulary thesaurus used for indexing articles for PubMed http://www.ncbi.nlm.nih.gov/mesh.

[2] The Council wishes to clarify that the MeSH terms and keywords are used for referencing purposes as well as to provide an easy definition of the scope of the advisory report. For more information, see the section entitled "methodology".

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III METHODOLOGY

After analysing the request, the Board and, when appropriate, the Chair of the area Vaccination identified the necessary fields of expertise. An *ad hoc* working group was set up which included experts in vaccinology, epidemiology, infectiology, occupational medicine, travel medicine and veterinary health. The experts of this working group provided a general and an *ad hoc* declaration of interests and the Committee on Deontology assessed the potential risk of conflicts of interest.

This advisory report is based on a review of the scientific literature published in both scientific journals and reports from national and international organisations competent in this field (peer-reviewed), as well as on the opinion of the experts.

Once the advisory report was endorsed by the working group and by the standing working group Vaccination, it was ultimately validated by the Board.

IV ELABORATION AND ARGUMENTATION

List of abbreviations used

CNS	Central Nervous System
EAN	European Academy of Neurology
ECDC	European Centers for Disease Control and Prevention
ELISA	Enzyme-linked immunosorbent assay
HCSP	Haut Conseil de la Santé Publique
PCR	Polymerase chain reaction
RIVM	*Rijksinstituut voor Volksgezondheid en Milieu*
RKI	Robert Koch Institute
SHC	Superior Health Council
TBE	Tick-Borne Encephalitis
TBEV	Tick-Borne Encephalitis Virus
WHO	World Health Organisation

1 Tick-Borne Encephalitis

1.1 Introduction

Tick-borne encephalitis (TBE) is a human viral infectious disease involving the central nervous system (CNS). TBE is caused by the tick-borne encephalitis virus (TBEV), a member of the family *Flaviviridae*, and was initially isolated in 1937. Three virus sub-types are described: European or Western TBEV, Siberian TBEV, and Far eastern TBEV (formerly known as Russian Spring Summer encephalitis virus) (CDC, Factsheet).

1.2 Transmission

TBE is mainly transmitted by hard ticks of the genus *Ixodes ricinus and Ixodes persulcatus* which act both as vector and as reservoir for TBEV. The main reservoir hosts are small rodents, with humans being accidental hosts. Large animals serve as feeding hosts for the ticks, but do not play a role in maintenance of the virus. The virus can chronically infect ticks and is transmitted both transstadially (from larva to nymph to adult ticks) and transovarially

(from adult female tick to eggs). Infection is also possible (but less frequently) by consumption of raw milk products from infected goats, sheep, or cows. Laboratory accidents through needle stick injuries and aerosols are reported. Person-to-person transmission is not possible, apart from the possibility of vertical transmission, blood transfusions and probably breast feeding. Transmission is probably also possible after slaughtering viremic animals.

1.3 Incubation time

The incubation period of TBE is usually between 7 and 14 days (range between 2 - 28 days). Shorter incubation times (3 - 4 days) have been reported after milk-borne exposure.

1.4 Pathogenesis of TBE in humans

The virus is transmitted by saliva from the salivary glands of the tick during the early feeding process. Analysis of tick-feeding sites suggest that skin-resident dendritic cells are likely to serve as a vehicle for transport of the virus to draining lymph nodes.
TBEV is a neurotropic virus and neuropathogenesis depends on the ability of the virus to enter the Central Nervous System (CNS). So far, it is not known how TBEV reaches the CNS.

1.5 Clinical disease (CDC, yellow book 2018)

Approximately two-thirds of infections are asymptomatic. The disease can be mild, but acute neuroinvasive disease is the most commonly recognized clinical manifestation. Disease severity tends to be less severe in children and increases with age. TBE infection often has a biphasic course:

- First phase: nonspecific febrile illness with headache, myalgia, and fatigue. Usually lasts for several days and may be followed by an afebrile and relatively asymptomatic period. Up to two-thirds of patients recover without any further illness.
- Second phase: central nervous system involvement resulting in aseptic meningitis, encephalitis, or myelitis. Findings include meningeal signs, altered mental status, cognitive dysfunction, ataxia, rigidity, seizures, tremors, cranial nerve palsies, and limb paresis.

Clinical course and long-term outcome vary by TBE virus subtype. Residual neurologic deficits have been described.

- The European subtype is associated with milder disease: 20 – 30 % experience a second phase with a case-fatality ratio of < 2 %, and neurologic sequelae in up to 10 % of patients (ECDC).
- The Far Eastern subtype is often associated with a more severe and monophasic disease course, including a case-fatality ratio of 20 % – 40 % and higher rates of severe neurologic sequelae.
- The Siberian subtype is more frequently associated with chronic or progressive disease and has a case-fatality ratio of 2 % – 3 %.

1.6 Diagnosis

The diagnosis of TBE is usually made by specific antibody detection on serum and/or CSF. The method of choice is the demonstration of specific IgM- and IgG-serum antibodies by enzyme-linked immuno-sorbent assay (ELISA), since these antibodies are detectable in practically every case at the time of hospitalization. However, serology (including virus neutralization tests) does not allow to differentiate between infection and vaccination.

Early after onset of disease in the cerebrospinal fluid specific antibodies can only be found in 50 % of the patients, but by the 10th day of illness they almost invariably become detectable. The value of RNA detection in CSF and serum is limited, since the virus has already been cleared from these fluids when neurological symptoms appear (Holzmann et al., 2003). PCR on urine may be a better option and may be positive up till 14 days post symptom onset.

1.7 Treatment (CDC, 2018)

There is no specific antiviral treatment for TBE. Therapy consists of supportive care and management of complications.

The administration of immunoglobulins with high concentrations of antibodies have had no beneficial effect in western Europe, and this practice is no longer recommended. Nevertheless it seems that in the Russian federation, there could be a beneficial effect of early administration using Russian immunoglobulin preparations.

1.8 Prevention (ECDC, factsheet)

One can try to prevent TBE virus infection by:

- Reducing the likelihood of being bitten by ticks:
  - stay on trails and walk in the centre;
  - wear protective clothing with long sleeves and long trousers tucked into socks;
  - wear clothes treated with insecticides. The use of impregnated clothes for a shorter period (weeks or months) is safe (Sullivan et al., 2019), and probably safe for long-term use (Rossbach et al., 2010);
  - application of insect repellents to exposed skin.

Inspecting the body for ticks after outdoor activities and removing ticks with tweezers or forceps does not protect against TBE, but is important because ticks can harbour other pathogens.

- Avoiding consumption of unpasteurised milk and dairy products in risk areas.
- Vaccination (see further): is considered to be the most efficient mean to prevent TBE in endemic settings.

1.9 PEP

Post exposure vaccination is not recommended after a tick bite in non-vaccinated persons because it is very unlikely that immune response will have developed before the first symptoms start and because of a theoretical risk of antibody enhancement (WHO, WER 2016).

1.10 Epidemiology

1.10.1 World wide

Tick-borne encephalitis occurs in a large geographical area from Europe to the Far East. Approximately 10 to 12 000 cases are reported each year, the vast majority of which are in Russia, but this number is probably significantly underestimated. Changes in leisure activities and possibly also in climate and habitat have changed the epidemiology of tick-borne encephalitis in recent years, affecting previously TBE-free areas and extending endemic areas to higher altitudes (from < 800 m above sea level to about 1500 m) and in more northern regions. It could be expected that warmer winters could extend the season in which ticks

survive. However, even in the most severely affected areas, the disease is usually limited to particular sylvatic foci (WHO, 2011; Alkishe et al., 2017)).

1.10.2 Europe

TBE with neurological symptoms is a notifiable disease on EU level since 2012. However, not in all European countries, it is notifiable at country level. Most countries use the EU case definition, but some countries use different case definitions (Beauté et al., 2018).
When looking at the number of recorded numbers, one has to take in account that

- many infections are asymptomatic/ give aspecific symptoms, so many cases are unrecognized and therefore do not appear in the statistics;
- TBE can occur in local microfoci;
- many different factors influence the epidemiology of TBE, including the animal reservoir, vector abundance, human behavior, vaccination coverage;
- in regions with a vaccination strategy/ high vaccination coverage, the numbers of reported cases do not always reflect the real risk for an unvaccinated traveler entering the region;
- increase of medical awareness can influence reported numbers.

Nevertheless it is useful to have an idea of the numbers reported and look at the evolution. During the last 5 years (between 2012 and 2016) most of the cases in the EU were reported in Lithuania, Czech Republic, Germany, Sweden, Poland and mainly among males over 45 y. In most countries, the number of reported cases seems to be stable, except for a few countries where new foci with TBE were discovered (France and Finland). In Switzerland, the number of cases was much higher in 2017 than in former years.

Most cases were reported between May and October, with a peak in July and August (ECDC).

Evolution in neighboring countries:

France:

The first human case of TBE in France was recorded in 1968 in Alsace (Dobler et al., 2018). In total, 171 cases were reported between 1968 and 2016 with the majority (90 %) in Alsace. Ten cases were considered as imported.
Between 2013 and 2016 +/- 10 confirmed cases/ year were reported with an annual incidence of about < 1/100 000 (ECDC 2015, Dobler et al., 2018; Velay et al., 2017).
The autochthonous cases occurred mainly in Alsace (annual incidence estimated at 0.5 cases/100000) and Alpine region (Annecy), accounting for 5 cases between 2014 and 2016. In 2016 a significant increase of 29 confirmed cases was recorded (corresponding to an incidence of 1.33/100 000 inhabitants in Alsace) (Velay et al., 2017). The seroprevalence of TBE among professionally exposed people in Alsace in 2003 was 5.5 % (Thorin et al., 2008).

Germany

In Germany, TBE is mainly found in southern parts of the country: Bavaria and Baden-Württemberg, Hesse, Rhineland-Palatinate, Saxony, Thuringia (STIKO 2017/2018). Yearly, 200 - 500 cases are confirmed. In 2016, a small outbreak linked to unpasteurized dairy products was described (Brockmann et al., 2016). In 2011 - 2013, the seroprevalence of TBE

among professionally exposed people (forestry workers) was 3.4 % in North Rhine-Westphalia (a low endemic region) (Jurke et al., 2015).

Luxembourg

In Luxembourg no human TBE cases were reported so far.

Netherlands

Until now (10/2018) five autochthonous TBE case were confirmed in the Netherlands: in Sallandse Heuvelrug and at Utrechtse Heuvelrug (Dobler et al., 2018, de Graaf et al., 2016).

1.10.3 Belgium

In total, 10 cases have been reported from 2012 until November 2018 at the Belgian TBE National Reference Centre (NRC) (Sciensano and ITM).
Eight of them were imported cases, and the remaining 2 were probably and possibly autochthonous cases in 2018.
Seropositive cattle, roe deer and wild boar have been found which indirectly suggest that the virus circulates in Belgium for at least several years (see further). TBEV can indeed remain unnoticed during its enzootic cycles within vectors and animal species. The presence of the virus in nature and the incidence of TBE in humans are poorly related (Bormane *et al*., 2004; Brinkley *et al*., 2008; Broker, 2002; Makowka *et al*., 2009; Süss *et al*., 2006; Takashima, 1998).

1.11 Prevalence in ticks and animals in Belgium

1.11.1 Ticks

No data on prevalence of TBEV in ticks are available. In general, these data are less useful because testing large numbers of ticks does not guarantee virus detection even in endemic areas and because the prevalence of TBEV in ticks does not seem to be directly related to the incidence of TBE in humans (Stefanoff et al., 2013).

1.11.2 Animals

Different studies have been undertaken to look for the presence of TBEV in Belgian domestic and wild animals. All five Belgian veterinary studies demonstrated the presence of TBEV-reactive antibodies in Belgian sentinel animals, but none of them could demonstrate the presence of TBEV RNA. Although the virus(es) that caused seroconversion in these animals is (are) clearly antigenically closely related or similar to the European reference strain of TBEV, it is unsure whether this (these) virus(es) is (are) also pathogenic for humans.
In 2014 - 2015, a study was undertaken by investigators from Sciensano (Suin *et al.*, unpublished results) to look for the presence of TBEV in wild rodents, captured at sites were previously seropositive cattle was detected by the same researchers (Roelandt *et al*., 2014). Although 4 – 8 % of *M. glareolus* and 1.9 % of *A. sylvaticus* tested positive for TBEV antibodies, no TBEV RNA could be detected in any of the rodents. Further studies in animals and/or ticks are therefore necessary to attempt the isolation and characterisation of TBEV in Belgium.

2 Recommendations for vaccination in Europe

In line with the WHO position paper on vaccines against tick-borne encephalitis from 2011, the European Academy of Neurology (EAN) recommends vaccination against TBE for all age groups above 1 year in highly endemic areas (≥ 5 cases/100 000/year), but also for individuals at risk in areas with a lower incidence (WHO; TABA et al). Incidence could be relevant on a regional, rather than a national scale, and cost-effectiveness could be considered based on age groups, rather than the whole population. Travellers to endemic areas should be vaccinated if their visits will include extensive outdoor activities.

At country level, different immunization strategies for TBE vaccination exist in Europe, according to the local epidemiological situation and risk assessment on regional/country level. Some countries, like Portugal, Denmark and Norway have no recommendation for vaccination (source: Pfizer, as of March 2017). Western European countries (Spain, France, Netherlands, UK, Ireland and Belgium) recommend vaccination only for travellers to endemic areas during tick season and when exposure to ticks is expected (risk activities). The northern part of Italy, Sweden and some East-European countries (Poland, Slovakia, Ukraine…) recommend vaccination for (high) risk groups. In addition to risk groups, vaccination is recommended for some age groups or the whole population in the South of Germany, Czech Republic, Austria, Slovenia, Hungary, Estonia, Latvia, and some parts of Switzerland, though the Suisse government is considering to expand vaccination to the whole population (Swissinfo, 2018).

2.1 Neighbouring countries

Despite the occurrence of some autochthonous cases of TBE in the Netherlands in the last two years, the recommendation is still to consider vaccination only in case of possible exposure to tick bites when staying in or travelling through endemic areas (RIVM). According to the travel medicine guidelines, vaccination is recommended for campers and hikers who are staying for at least four weeks (cumulative) in an endemic area in Europe (LCR).

In France, vaccination is recommended only for travellers staying in endemic rural or forest areas in Central, Eastern and Northern Europe, from spring to autumn (HCSP, 2009). Based on the epidemiological situation, the Haut Conseil de la Santé Publique (HCSP) stated in 2004 that vaccination was not needed for persons residing in France. There has not been a recent review of the recommendations.

In Luxemburg, vaccination is recommended for all adults and children over six years of age who stay during the tick season (early summer and autumn) in the forests of endemic territories for leisure or professional activities (mainly in Central and Northern Europe) (CSH).

Germany counts some endemic areas for TBE in the southern part of the country, in particular in Bavaria and Baden-Wuttemburg. Risk areas are well defined by the Robert Koch Institute (RKI). The Standing Committee on Vaccination (STIKO) recommends that all residents in and people who travel to these risk areas and are exposed to ticks, get vaccinated against TBE. For residents in risk areas and travellers within Germany, the costs of TBE vaccination are covered by the statutory health insurers.

3 Vaccines in Belgium: FSME-IMMUN® and FSME-IMMUN®Junior (BCFI, Leaflet)

The vaccine can be administered from the age of 1 year. For children under 16 years of age, a pediatric TBE vaccine (FSME-IMMUN junior) is recommended which contains half of the adult vaccine.

3.1 Composition

The vaccine contains TBE virus (Neudorflstam) 1.2 microgram produced on chicken embryofibroblastcells and adsorbed on hydrated aluminiumhydroxide (0.17 milligram Al^{3+}) and:

- human albumine
- natriumchloride
- dinatriumfosfaatdihydraat
- kaliumdiwaterstoffosfaat
- water for injections
- sucrose

3.2 Storage

Store in a refrigerator (2 °C – 8 °C). Keep the syringe in the outer carton, in order to protect from light. Do not freeze. Do not use this vaccine if you notice any visible signs of foreign particulate matter or leakage.

3.3 Method of administration

This vaccine should be injected intramuscular.

<u>First course of injections</u>

The first course of injections consists of three doses of FSME-IMMUN 0.5 ml (or FSME-IMMUN junior):

- The second injection will be given 1 to 3 months after the first injection. It can be given two weeks after the first dose if you need urgent protection.
- The third injection will be given 5 to 12 months after the second injection.
- It is best to have the first and second doses in the winter. This is because the tick starts being active in spring. This allows you to develop enough protection before the tick season starts.
- The third dose completes the primary course of injections. The vaccination schedule should ideally be completed with the third vaccination within the same tick season or at the least before the start of the following tick season.
- It gives protection for up to three years.

Basic Immunization	**Dose**	**Conventional Schedule**	**Rapid Immunization Schedule**
1st dose	0.5 ml (or 0.25 ml junior dose)	Elected date	Elected date
2nd dose	0.5 ml (or 0.25 ml junior dose)	1 to 3 months after the 1st vaccination	14 days after the 1st vaccination
3rd dose	0.5 ml (or 0.25 ml junior dose)	5 to 12 months after the 2nd vaccination	5 to 12 months after the 2nd vaccination

Booster vaccinations

For persons younger than 60 years
The first booster dose is given 3 years after the third dose. Further booster doses should be given every 5 to 10 years.

Persons above 60 years of age (elderly persons)
The first and all further booster doses should be given at three years' intervals.

Booster dose ≥ 16 to < 60 years	**Dose**	**Timing**
1st booster	0.5 ml	3 years after the 3rd vaccination
Sequential booster doses	0.5 ml	every 5 to 10 years
Booster dose ≥ 60 years	**Dose**	**Timing**
All booster doses	0.5 ml	every 3 years

Extending the interval between any of the doses (primary vaccination schedule and booster doses) may leave subjects with inadequate protection against infection (see section 5.1).

However, in the case of an interrupted vaccination schedule of at least two previous vaccinations, a single catch-up dose is sufficient to continue the vaccination schedule.

3.4 Concomitant administration

No interaction studies with other vaccines or medicinal products have been performed. The administration of other vaccines at the same time as FSME-IMMUN (and FSME-IMMUN Junior) should be performed in accordance with official recommendations. If other injectable vaccines are to be given at the same time, administrations should be into separate sites and, preferably, into separate limbs.

3.5 Vaccine efficacy

No clinical studies with efficacy endpoints have been conducted on any of the licensed TBE vaccines. These vaccines have been registered on the basis of immunogenicity and safety studies, which consistently show strong immune responses after primary vaccination with the vaccine. A Cochrane Collaboration review published in 2009 summarized 11 randomized clinical trials (10 publications), conducted with 3 different TBE vaccines (IPVE, FSME-IMMUN, and Encepur) and involving 8 184 subjects (6 586 adults and 1 598 children). Overall seroconversion rates exceeding 87 % were observed. Studies conducted by the respective manufacturers report seroconversion rates in the range of 92 % – 100 % for Encepur and FSME-IMMUN, as measured by a commercial enzyme-linked immunosorbent assay (ELISA) or neutralization test (NT), with seroconversion being defined as NT ≥ 1:10, or according to the recommendations of the ELISA manufacturer (Loew-Baselli et al., 2011; Ehrlich et al., 2003; Loew-Baselli et al., 2006; Schöndorf et al., 2007).

3.6 Immunogenicity

The clinical development program for FSME-IMMUN included 13 studies that investigated the immunogenicity and safety of the vaccine in approximately 5 180 adults and 6 430 children. An additional 4 studies on FSME-IMMUN were identified after review and analysis of published literature (Loew-Baselli et al., 2011). The seroconversion rate in adults 16 to 65 years of age,

vaccinated according to the conventional schedule, was 97 % after the second dose and ranged between 99.5 % and 100 % after the third dose, as measured by ELISA and/or NT. When the rapid immunization schedule was used, seroconversion rates in NT after the second vaccination were 98.0 % and 89.9 % in adults younger or older than age 50, respectively, and 100 % and 99.3 % in those 2 age groups after the third vaccination, respectively.

Two pediatric studies (a dose-finding study with more than 400 children who received the later licensed pediatric dose and a large safety study with an immunogenicity subset that included approximately 370 children, all between the ages of 1 and 15 years) found seroconversion rates (ELISA) of 96 % to 100 % (depending on the age subgroup) after the second vaccination and almost 100 % in all age subgroups after the third vaccination (Pöllabauer et al., 2010).

Another pediatric study investigated immune response in 149 and 152 children 1 – 11 years of age, who were vaccinated with FSME-IMMUN Junior and Encepur Children, respectively, in the context of a primary immunization schedule. According to the NT based on the Neudörfl strain, seropositivity rates after the second vaccination in the combined age groups was 100.0 % in children who received FSME-IMMUN Junior and 97.8 % in those who received 2 vaccinations with Encepur Children (Pöllabauer et al., 2010). A third vaccination with FSME-IMMUN Junior induced 100 % seropositivity in both study groups (Prymula et al., 2012).

An earlier pediatric study, which investigated the immune response in 334 children to both FSME-IMMUN Junior and Encepur Children for the first 2 vaccinations, using the conventional as well as the rapid immunization schedule, found higher seropositivity rates (NT ≥ 10) in the Encepur-immunized group versus the group that received FSME-IMMUN Junior, using either vaccination schedule. Upon completion of the primary vaccination course, and after the third dose (given with Encepur Children), > 95 % of all children achieved an NT ≥ 10 (Wittermann et al., 2009). Both studies confirmed the interchangeability of the 2 TBE vaccines when given as a third dose in the context of a conventional or rapid primary immunization schedule.

3.7 Immunocompromised people

The vaccine is probably less immunogenic in at least some sorts of immunosuppression. One can decide to add an extra priming dose (M0-M1-M2-M 5 to12) in case of immunosuppression, as is recommended in some endemic regions (Austria and some parts of Sweden). However, evidence is limited (Hertzell et al., 2016).

3.8 Elderly patients

The vaccine is probably less immunogenic in at least some sorts in the elderly (> 60 y) (Lindblom et al., 2014).

3.9 Vaccine Safety

The most frequent reported reactions within adults to the TBE vaccination are local pain (≥ 1/10), headache, fatigue, malaise, myalgia, arthralgia and fever (≥ 1/1 000). The adverse reactions seen in children are similar to those observed in adults. However, children more frequently experience fever.

3.10 Contraindications

Hypersensitivity can occur to the active substance, any of the excipients or production residues (formaldehyde, neomycin, gentamycin, protamine sulfate). Cross allergies with aminoglycosides other than neomycin and gentamycin should be considered. Severe hypersensitivity to egg and chick proteins (anaphylactic reaction after oral ingestion of egg protein) may cause severe allergic reactions in sensitized individuals. TBE vaccination should

be postponed if the person is suffering from a moderate or severe acute illness (with or without fever).

4. Conclusion and Recommendations

The Superior Health Council formulated recommendations for vaccination against TBE for the following 3 situations: in case of no human cases, in case of sporadic human cases, in case of endemic disease.

4.1 In case of no human cases - low level circulation of the TBE virus:

a. Vaccination is not recommended for the general population.
b. No active surveillance.
c. Vaccination of risk groups:
   - Vaccination is recommended for travelers to endemic regions doing outdoor activities in forested areas (such as hiking, camping, mushroom picking, …) during tick season (spring, summer and autumn).
   - Vaccination is recommended for people handling TBEV in laboratory setting.
   - Vaccination is not recommended for professional (wood cutters, forest rangers, …) or recreational risk groups.

4.2 In case of sporadic human cases (occurring at irregular intervals or only in a few places; scattered geographically):

In case of 1 human case: active surveillance

a. Vaccination is not recommended for the general population.

b. Active surveillance
   - Collection of ticks and rodents from the region of the case.
   - Inform medical doctors (Belgium, not restricted to region of the case).
   - Sensibilisation of population on preventive measures.

c. Vaccination of risk groups:
   - Vaccination is recommended for travelers to endemic regions doing outdoor activities in forested areas (such as hiking, camping, …) during tick season (spring, summer and autumn).
   - Vaccination is recommended for people handling TBEV in laboratory setting.
   - Vaccination is not recommended for professional (wood cutters, forest rangers, …) or recreational risk groups.

In case of 2 or more human cases infected in the same region (natural park) during the same year

a. Vaccination is not recommended for the general population.

b. Active surveillance
   - Collection of ticks and rodents from the region of the case.
   - Inform medical doctors (Belgium, not restricted to region of the case).
   - Sensibilisation of population about preventive measures.

c. Vaccination of risk groups:

- Vaccination is recommended for travelers to endemic regions doing outdoor activities in forested areas (such as hiking, camping, …) during tick season (spring, summer and autumn).
- Vaccination is recommended for people handling TBEV in laboratory setting.
- Vaccination is not recommended for professional (wood cutters, forest rangers, green service, …) or recreational risk groups. However, because the other preventive measures do not fully protect the individual (they reduce the risk of being bitten), and early removal of the tick does not protect against TBE and because there is no treatment, one can consider vaccination for some professionals and individuals with a high risk of tick bite. This recommendation can be reviewed when the seroprevalence study of TBE in Belgian forest rangers will be available (summer 2019).

4.3 In case of endemic disease

Vaccination of the whole population is only recommended if the incidence is at least 5/100 000 (WHO, 2011).

For endemic circulation with a lower incidence, vaccination can be recommended for risk groups.
The recommendation will be updated according to the evolution of the epidemiology of TBE in Belgium.

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IV. COMPOSITION OF THE WORKING GROUP

The composition of the Committee and that of the Board as well as the list of experts appointed by Royal Decree are available on the following website: About us.

All experts joined the working group ***in a private capacity***. Their general declarations of interests as well as those of the members of the Committee and the Board can be viewed on the SHC website (site: conflicts of interest).

The following experts were involved in drawing up and endorsing this advisory report. The working group was chaired by **Ula MANIEWSKI**; the scientific secretary was Veerle MERTENS.

DELAERE Bénédicte	Infectious Diseases	*UCLouvain*
LEONARD Philippe	Internal and tropical medicine, Travel Clinic	ULG
LERNOUT Tinne	Epidemiology of infectious diseases	Sciensano
MANIEWSKI Ula	Internal medicine, Tropical Medicine, Vaccination	ITG
REZETTE Jean-Pierre	Occupational Medicine	*C.H.U. de Charleroi*
SUIN Vanessa	Epidemiology of infectious diseases	Sciensano
VAN GUCHT Steven	Epidemiology of infectious diseases	Sciensano
VAN LAETHEM Yves	Infectiology, Vaccination, Travel Clinic	*CHU Saint-Pierre*

The following administrations and/or ministerial cabinets were heard:

TOP Geert	Zorg en Gezondheid

The standing working group Vaccination has endorsed the advisory report. The standing working group was chaired by Yves VAN LAETHEM; the scientific secretary was Veerle MERTENS.

About the Superior Health Council (SHC)

The Superior Health Council is a federal advisory body. Its secretariat is provided by the Federal Public Service Health, Food Chain Safety and Environment. It was founded in 1849 and provides scientific advisory reports on public health issues to the Ministers of Public Health and the Environment, their administration, and a few agencies. These advisory reports are drawn up on request or on the SHC's own initiative. The SHC aims at giving guidance to political decision-makers on public health matters. It does this on the basis of the most recent scientific knowledge.

Apart from its 25-member internal secretariat, the Council draws upon a vast network of over 500 experts (university professors, staff members of scientific institutions, stakeholders in the field, etc.), 300 of whom are appointed experts of the Council by Royal Decree. These experts meet in multidisciplinary working groups in order to write the advisory reports.

As an official body, the Superior Health Council takes the view that it is of key importance to guarantee that the scientific advisory reports it issues are neutral and impartial. In order to do so, it has provided itself with a structure, rules and procedures with which these requirements can be met efficiently at each stage of the coming into being of the advisory reports. The key stages in the latter process are: 1) the preliminary analysis of the request, 2) the appointing of the experts within the working groups, 3) the implementation of the procedures for managing potential conflicts of interest (based on the declaration of interest, the analysis of possible conflicts of interest, and a Committee on Professional Conduct) as well as the final endorsement of the advisory reports by the Board (ultimate decision-making body of the SHC, which consists of 30 members from the pool of appointed experts). This coherent set of procedures aims at allowing the SHC to issue advisory reports that are based on the highest level of scientific expertise available whilst maintaining all possible impartiality.

Once they have been endorsed by the Board, the advisory reports are sent to those who requested them as well as to the Minister of Public Health and are subsequently published on the SHC website (www.hgr-css.be). Some of them are also communicated to the press and to specific target groups (healthcare professionals, universities, politicians, consumer organisations, etc.).

In order to receive notification about the activities and publications of the SHC, please contact: info.hgr-css@health.belgium.be.

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