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Tick-borne encephalitis (TBE) in children in Europe: Epidemiology, clinical outcome and comparison of vaccination recommendations

Robert Steffen[1]

Epidemiology, Biostatistics and Prevention Institute, World Health Organization Collaborating Centre for Travelers' Health, University of Zurich, Hirschengraben 84, CH-8001 Zurich, Switzerland

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ABSTRACT

Tick-borne encephalitis (TBE) vaccination recommendations for children residing in high-endemicity countries in Europe vary from universal recommendations to none at all. Such differences may result in uncertainty about the value of such prevention among public health authorities, healthcare professionals and parents. We conducted a systematic review of publications and data from the European Centres for Disease Prevention and Control focusing on the epidemiology, clinical characteristics, and outcomes of TBE in a pediatric population. TBE can affect children of any age, occasionally even before the first birthday. Overall, the clinical course of disease is milder compared to adults, and there are fewer neurologic sequelae persisting after the infection. However, recent follow-up surveys identified a substantial proportion of children with long-term cognitive impairment subsequent to TBE infection. Fortunately, two vaccines against western TBE are available, and both are effective and safe. It is an overly simplistic perception that TBE is severe in adults and mild in children, and to therefore conclude that vaccination is important mainly in older age groups. Even if TBE infection is less dramatic in pediatric populations, TBE often results in long-standing cognitive damage. Based on guidance from the World Health Organization, authorities in countries with high endemicity should either offer or recommend TBE vaccination to children at 1–3 years of age.

1. Introduction

Tick-borne encephalitis (TBE) is a serious health risk that is widespread in parts of Europe (ECDC, 2018), the Russian Federation (Tokarevich et al., 2017), and Northern Asia up to Japan (Sun et al., 2017; Yoshii et al., 2017). For a variety of reasons, a marked increase in incidence with respect to endemic regions has been observed over past decades (Süss, 2003). In Europe, the main vector is *Ixodes ricinus;* 0.1%–5% of these ticks harbor the TBE virus (Kaiser, 2008; Süss, 2003). Thus only a minority of individuals who experienced a tick bite will develop TBE. There is a broad range of the severity of clinically evident TBE virus infection, and it is also known that about 30% of those infected seroconvert without developing any symptoms, another 30% experience an abortive form ("fever form") of the infection (Bogovic and Strle, 2015; Borde and Zajkowska, 2017), whereas "only" the remaining persons develop central nervous system (CNS) disease. The pathogen, mode of transmission, clinical features, diagnostic results, and the limited means for treatment have often been described (Bogovic and Strle, 2015; Hombach et al., 2017; Kaiser, 2016, 2008; Rostasy, 2012). Traditionally the epidemiologic focus is on adults, as the outcome in pediatric patients is considered to be comparatively benign, and the prognosis becomes worse with the affected patient's age (Arnez and Avsic-Zupanc, 2009; Haglund and Günther, 2003; Hombach et al., 2017; Kaiser, 2016, 2008, 2000, 1999; Lesnicar et al., 2003; Lindquist and Vapalahti, 2008; Logar et al., 2006, 2000; Schmolck et al., 2005). This to some extent explains country-to-country differences in TBE vaccination guidelines for children and adults, which are based on differing risk perceptions and cost-benefit analyses among experts (Erber and Schmitt, 2018; Kunze and Haditsch, 2017). Such differences result in uncertainty among health professionals and parents.

The present review was based on the available data with the primary goal of comparing the outcome of symptomatic TBE virus infection in younger vs older children, or overall in a pediatric population vs adult patients. Additionally, the lower age limits for TBE immunization in the high risk countries will be listed based on current recommendations.

E-mail address: robert.steffen@uzh.ch.
[1] Personal office: Schiedhaldenstrasse 1, CH-8700 Kusnacht, Switzerland.

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2. Materials and methods

As suggested by systematic review guidelines (Moher et al., 2009), we conducted a search in PubMed using the string "tick-borne encephalitis" OR "TBE" AND "pediatric" OR "children" OR "age." Since more reliable diagnostic methods with specific immunoglobulins M and G antibodies against TBE by enzyme immunoassay were introduced in the 1980s (Holmgren and Forsgren, 1990; Roggendorf et al., 1981), only papers in English or German, which included at least part of the study population investigated later, have been included. Additionally, those published in various Eastern European languages were considered if they had an abstract in English with relevant data. Additional references were obtained from citations in relevant publications; some were book chapters or congress reports. The primary objective was to determine what proportion of patients in different age groups had a full recovery vs those left with sequelae or a fatal outcome of TBE infection. Besides older studies or those, which did not at least have an English abstract, we also excluded publications, which were limited to the territories of Russia and/or Asia. In a second step publications were excluded which essentially presented data previously published or which failed to provide any epidemiologic data on the outcome of infection in pediatric age groups.

Data from the European Surveillance System (TESSy), provided by Austria, Czech Republic, Estonia, Finland, France, Germany, Hungary, Italy, Latvia, Lithuania, Luxembourg, Norway, Poland, Romania, Slovakia, Slovenia, Sweden, United Kingdom and released by European Centres for Disease Prevention and Control (ECDC) were used to show the age of TBE infection in the years 2014 and 2015. Additional data were obtained from the Swiss Federal Office of Public Health.

To determine the vaccination recommendations against TBE in children, the plans issued by national authorities (or where such were missing, by national professional societies) were analyzed. Only those endemic countries with either an incidence of ≥ 1.0 per 100,000 or with > 100 cases in any year from 2012 to 2015 per ECDC data (ECDC, 2018) or the Swiss Federal Office of Public Health (Bundesamt für Gesundheit, 2016) were included. While the author was able to understand the recommendations in German texts, TBE experts in all other countries were invited to submit English translations. "Official" national data have also become available in a recently published online book (Dobler et al., 2017).

3. Results

3.1. Literature search

From a total of 708 articles retrieved from PubMed (Fig. 1), 123 were excluded as they had been published before 1980 and another 66 as they had neither an English nor a German abstract. The remaining 519 publications underwent title review; 355 were excluded for being unrelated to the defined focus. Among the 164 publications, which underwent abstract review, 85 were excluded, because there were insufficient data on the outcome of TBE in children, leaving 79 publications. Another 21 publications were added from their bibliographies and 3 websites were finally included.

3.2. Incidence of TBE

3.2.1. All ages average

During the period 2012–2015, overall rates (all ages) exceeding 10 per 100,000 were recorded in Estonia (13.4, 2012), Latvia (11.4, 2013), Lithuania (11.7, 2012; 16.4, 2013; 12.0, 2014; 11.5, 2015), and Slovenia (14.9, 2013) (ECDC, 2018).

3.2.2. Comparison between pediatric and adult populations

Recent ECDC data illustrate how the average incidence of reported TBE cases increased from the 0- to 4-year-olds to a maximum of 0.5 per 100,000 among those aged 45–64 years. Subsequently, there is a decrease in those aged ≥ 65 years. For females, the same trend is observed, but there is a male-to-female ratio of 1.4:1 (Fig. 2). The Swiss data (which were not included in the ECDC data) for the 2002-to-2015 period in all age groups similarly show more cases among males. The average rates per 100,000 for this period among those aged < 6 years were 1.0 for boys and 0.4 for girls; there were higher rates in older age groups (Bundesamt für Gesundheit, 2016; Stahelin-Massik et al., 2008).

A review of the literature offers additional insight on the incidence in children vs adults. According to a survey conducted in Baden-Wuerttemberg (Southern Germany) 95 of 850 patients (11%) were aged ≤ 14 years (Kaiser, 2002); the same proportion in the same age group has been recorded in Lithuania (Vaisviliene et al., 2002). In Slovenia, 371 in 1578 cases (24%) were children aged 0–15 years (Lesnicar et al., 2003). Among 476 hospitalized TBE cases in Stockholm, 29 (6%) were aged ≤ 10 years (Holmgren and Forsgren, 1990).

Somewhat in contrast to rather low TBE incidence proportions in pediatric populations, another Swedish group demonstrated that pediatric cases are not as rare as evidenced by surveillance data. On the basis of serologic assessment, it is shown that, in addition to subclinical infection, TBE diagnosis in preschool children is often missed, as symptoms may be vague and less specific; often there is no biphasic course (Hansson et al., 2011).

3.2.3. Details on the incidence within the pediatric population

Based on 3953 cases reported to the ECDC in 2014 and 2015, there were 5 cases in children aged < 1 year, 5 cases aged 1 year, 10 cases aged 2 years, and 16–28 cases in each single age group of children aged 3–10 years. The 81 cases aged < 6 years represent 2.0% of all cases. Similar to the ECDC data, a Swedish study recorded a proportion of 1.6% of all cases in those < 5 years of age (Holmgren and Forsgren, 1990).

In addition to the 5 infants listed above, the youngest patients with published details on their TBE infection were 17 days (Austria), 6 weeks (Switzerland), 3 months (one each in Austria and Czechia) and 4.5 months old (Germany) (Fritsch et al., 2008; Grubbauer et al., 1992; Iff et al., 2005; Jones et al., 2007; Kosina et al., 2008; Leistner and Dahlem, 2011; Stahelin-Massik et al., 2008); one aged 10 months was infected on Aland Island (Wahlberg et al., 1989).

The paucity of cases in the very young has been confirmed in Styria (Austria), where among 116 pediatric patients 9% were aged less than 4 years, whereas approximately 30% each were 4–7, 8–11, and 12–15 years old (Fritsch et al., 2008). In Slovenia 8% were aged less than 6 years in a total population of 371 with an upper age limit of 15 years (Lesnicar et al., 2003). In the German study population of 124 aged ≤16 years, just 4% had not reached their fourth birthday (Kaiser, 2006). The proportion of young children affected by TBE was a bit higher in Switzerland, as 16% were up to 5 years old among 55 patients aged 15 years or less (Stahelin-Massik et al., 2008). In Czechia, the incidence per 100,000 was < 1 in the age group 0–4 years, but > 3 for any other male and ≥ 2 for any other female age group except senior citizens (Pazdiora et al., 2008). Several studies summarized in Table 1 demonstrate that only a small proportion of all symptomatic TBE infections occur in children. According to all larger studies (≥ 20 patients), about two thirds of the children diagnosed with TBE are boys. Boys also tended to have a higher degree of morbidity (Sundin, 2017).

In Slovenia, the majority of pediatric TBE-related admissions to hospitals were recorded between June and August, but some occurred from February to December (Lesnicar et al., 2003; Tomažič et al., 1996). Further north in Sweden and Finland, the first diagnoses were made in May and June, respectively (Lindquist, 2014; Sundin et al., 2012; Wahlberg et al., 1989). A second peak has been recorded in Central Europe in September and October (Bundesamt für Gesundheit, 2016; Lindquist, 2014). In contrast to all school-age groups with rates ≥ 56%, only 19% of the infections in children aged 0–4 years occurred in July or August in Bohemia (Pazdiora et al., 2012). There, it

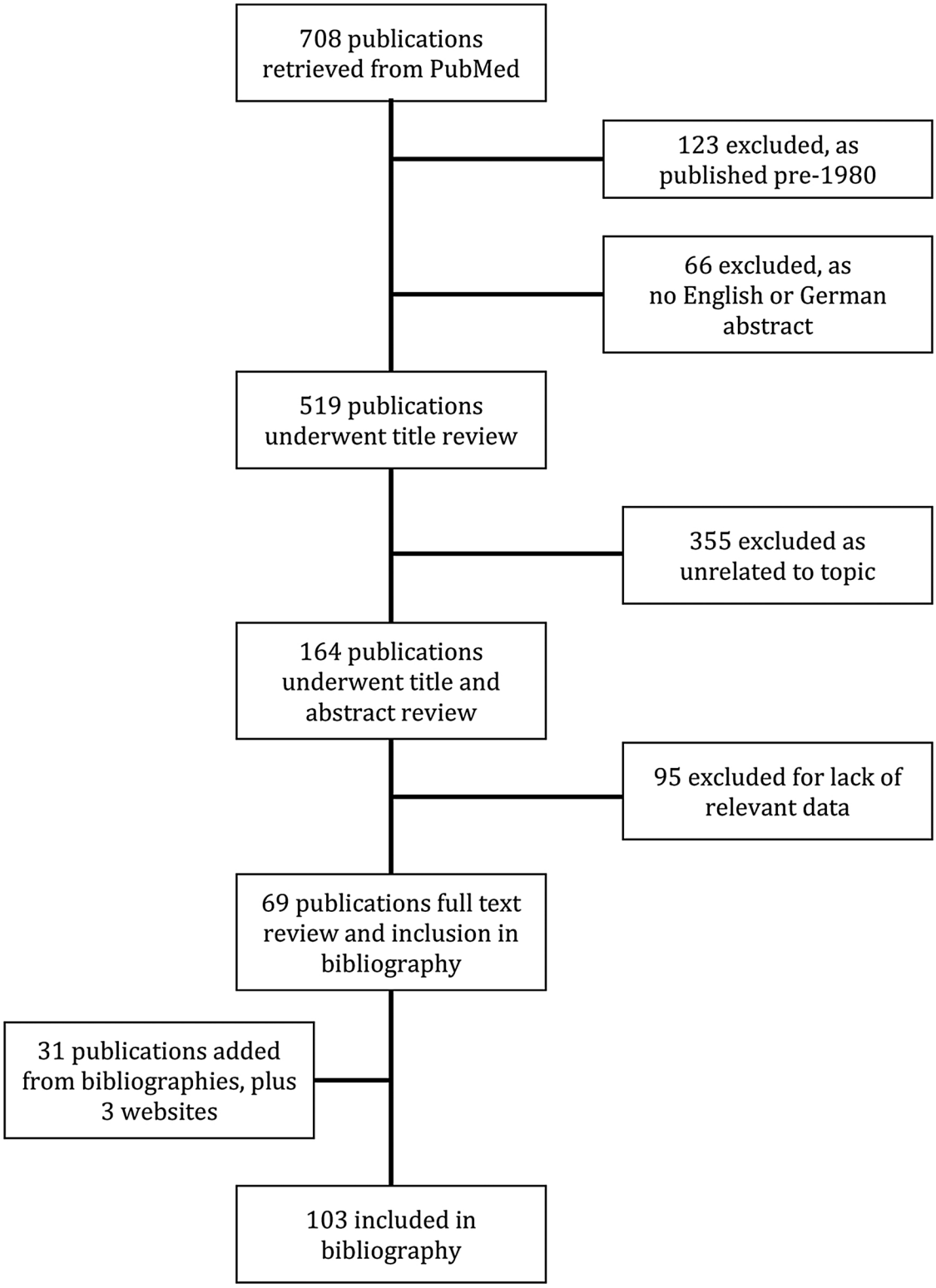

Fig. 1. Selection process for literature included for review.

additionally has been observed that the season of TBE diagnosis, which was recognized as May to October in the 1960 to 1980 period, now extends from March to November (Kriz et al., 2012; Pazdiora et al., 2012).

3.2.4. Impact of TBE vaccination

A comparative survey based on hospitals in neighboring Styria (Austria) and Slovenia clearly demonstrated how the annual incidence per 100,000 in Styria declined from 2.5 to 9.3 in the individual years 1980 to 1986 to ≤ 1 in the 1994-to-2003 period after a vaccination campaign had been implemented from 1984 (for children > 1 year). By contrast, in Slovenia, which had shown similar incidences before the Austrian vaccination program was initiated, and where only an estimated 4% were immunized, the annual incidence rose to its highest level: 22.6 per 100,000 in 1994 (Arnez and Avsic-Zupanc, 2009; Zenz et al., 2005). The annual incidence continued to exceed 15 per 100,000

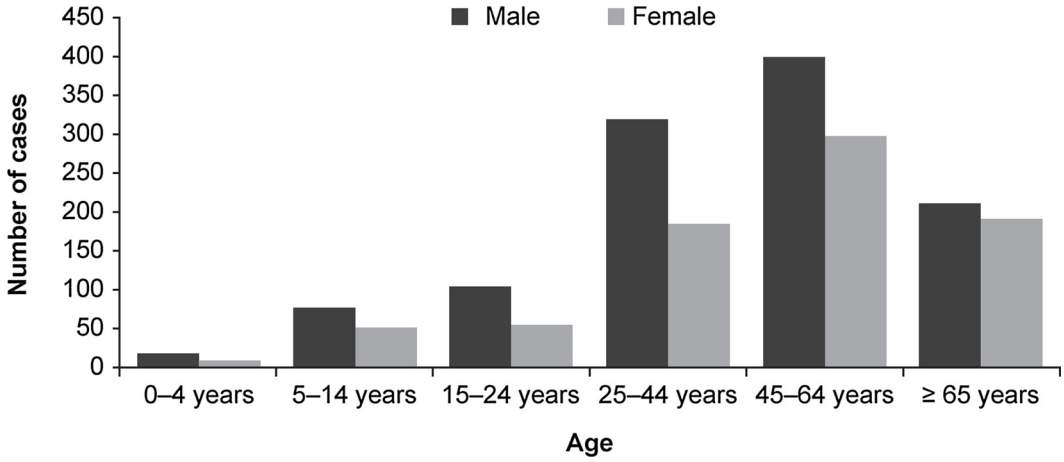

Fig. 2. Distribution of rates per 100,000 of confirmed TBE cases in EU/EEA by age and gender, 2015. (ECDC, 2018).

in 3 of 4 years between 2005 and 2008 (Arnez and Avsic-Zupanc, 2009).

Vaccine failures were mentioned mainly after incomplete series were administered, but rarely also after complete vaccination series in several of the tabulated publications (Krbkova et al., 2015; Stahelin-Massik et al., 2008; Zenz et al., 2005) and in other case reports (Andersson et al., 2010; Zlamy et al., 2016).

3.3. Clinical characteristics and course of TBE in children

Studies with data on the main characteristics and/or the outcome of TBE in pediatric populations are summarized in Table 1. Compared to adults, TBE symptoms in children are usually milder, vaguer, and nonspecific; and as young children cannot verbalize their complaints (Hansson et al., 2011; Lindquist and Vapalahti, 2008; Lindquist, 2008), ≥ 26% of infections remain unnoticed or undiagnosed. Another report described how up to 20% of pediatric TBE patients had “fever without localizing signs, no neurologic symptoms, but a biphasic course, a headache, and a reduced general condition (Meyer et al., 2010).”

Among the pediatric patients, two thirds or more had reportedly experienced a tick bite. In South Moravia, 46% among those with reported tick bites had received multiple (≤ 10) bites (Krbkova et al., 2015). The incubation period usually varied from 4 to 28 days (Günther et al., 1997; Kaiser, 2008; Roggendorf et al., 1981) with mean values of about 10 days (Kaiser, 2016); only a single study considered an incubation period of 1 to 62 days (Krbkova et al., 2015). An incubation period of 12 days in children vs 17 days in adults was not rated as significantly different (Logar et al., 2000). A few TBE patients had most likely acquired the infection by consuming unpasteurized milk (Krbkova et al., 2015).

The details on clinical data and the course of the disease are not included in Table 1, but they are recorded in detail in various reports. Phase 1 is characterized by nonspecific influenza-like symptoms (Fritsch et al., 2008) such as fever > 38 °C and headache, with meningeal signs recorded in ≥ 85% (Fritsch et al., 2008; Lesnicar et al., 2003; Logar et al., 2000). In the initial phase of TBE, meningeal signs are, as a rule, not expressed, and in the cerebrospinal fluid (CSF) white cell counts are within the normal range. The proportion of pediatric patients with fatigue, adynamia, malaise, vomiting, abdominal pain, and upper respiratory symptoms varied between 15% and 90%; arthralgia was mentioned less often (Fritsch et al., 2008; Lesnicar et al., 2003). The prodromal uncharacteristic symptoms of Phase 1 lasted just 1–6 days in one (Lesnicar et al., 2003), but ≤ 14 days in other studies (Fritsch et al., 2008; Krbkova et al., 2015).

All studies except a small Swedish one have recorded a biphasic course in the vast majority of patients. One report indicated that this was less often observed in preschool children (Hansson et al., 2011), while another documented a biphasic course in 90% of children vs 77% of adults ($P = 0.33$) (Logar et al., 2000). The duration of the interval was described as 2 to 25 days with medians ranging from 6 to 14 days (Fritsch et al., 2008; Krbkova et al., 2015; Lesnicar et al., 2003; Logar et al., 2000).

The second phase occurs in 5%–30% of the children who developed the initial uncharacteristic phase of illness; it starts with a recurrence of fever. The data in Table 1 clearly show that in a pediatric population of TBE patients, meningitis is the most frequent symptom; meningoencephalitis occurs less often, and meningoencephalomyelitis is only rarely diagnosed. Only in Switzerland, the rates of meningitis and meningoencephalitis were equivalent in a pediatric population (Zimmermann and Koch, 2005). Signs of encephalitis lasting for 1–6 days generally included tremor (mainly tongue, face); less frequent symptoms included somnolence, vertigo, ataxia, behavioral changes, seizures, and paresis of cranial nerves or limbs (Fritsch et al., 2008; Krbkova et al., 2015; Lesnicar et al., 2003). A clear tendency for a more severe course with increasing age was repeatedly mentioned (Kaiser, 2008; Lesnicar et al., 2003; Rakar, 1993; Stahelin-Massik et al., 2008; Tomažič et al., 1996).

Data on duration of the hospitalization varied greatly across studies, and the proportion of patients admitted to intensive care ranged from 0% (Lesnicar et al., 2003) to 22% (Krbkova et al., 2015).

3.4. Outcome of TBE

3.4.1. Pediatric population

The ECDC 2014/2015 data provided by TESSy are inconclusive with respect to the clinical outcome. While some countries reported an unknown outcome in all patients, few reported complications, particularly sequelae.

Based on the reviewed reports, up to half of the children complained about headache and/or fatigue for ≤ 6 months, but these were not rated as sequelae (Krbkova et al., 2015). Other groups reported far lower rates of such complaints (Cizman et al., 1999; Rakar, 1993).

All early studies had concluded that permanent neurologic sequelae were rare. Two Slovenian studies reported rates of 10% overall, 4% for severe outcome (Rakar, 1993) and 2% (Cizman et al., 1999), respectively; in the latter it was noted that these children were at least 11 years old (Cizman et al., 1999). Two Austrian studies and one Swiss study each reported 2% of pediatric patients having neurologic sequelae (Fritsch et al., 2008; Stahelin-Massik et al., 2008; Zenz et al., 2005). In a German survey, a rate of 6% was recorded (Kaiser, 2006). As shown in the synoptic Table 1, rates of neurologic sequelae vary between 0% and 10%, many were irreversible. The 17-day-old neonate with TBE remained severely impaired at 1 year of age (Jones et al., 2007; Stahelin-Massik et al., 2008).

Table 1
Summary of Epidemiologic and Clinical Characteristics from Pediatric TBE Studies.

First Author	Published	Data Collection	Region	N	Age Range, y	Male, %	Tick bite, %	Biphasic, %	MENING, %	MENENC, %	MEENMY, %	Permanent sequelae, n (%)	Remarks
Rakar	1993	1978-1992	Slovenia	146	≤ 15	N/A	N/A	N/A	69	31	0	15 (10%; 4% severe)	Follow-up after 6 months
Tomazic	1996	1994	Slovenia	77	4-15	74	N/A	N/A	53	46	1	N/A	Limited data on children
Cizman	1999	1993-1998	Ljubljana, Slovenia	133	≤ 15	N/A	N/A	N/A	49	48	3	3 (2%), neurologic	7 with severe course, all boys
Kaiser	1999	1994-1998	SW Germany	77	≤ 14 (71% ≤ 10)	N/A	N/A	N/A	64	36	0	N/A	
Logar	2000	Jun-Aug 1997	Ljubljana, Slovenia	20	3-14	70	75	90	N/A	N/A	N/A	N/A	
Lesnicar	2003	1959-2000	Celje, Slovenia	371	1-15 (8% < 6)	63	48	67	63	37	0	0	
Zenz	2005	1980-2003	Styria, Austria	139	≤ 16	N/A	N/A	N/A	N/A	N/A	N/A	3 (2%), neurologic	1 patient with 3 doses of vaccine. Study demonstrates success of vaccination campaign in Styria
		1980-2003	Slovenia	783	≤ 16	N/A	N/A	N/A	N/A	N/A	N/A	N/A	
Schmolck	2005	N/A	Freiburg, Germany	19*	5-13	68	most	100	32	68	0	0 neurologic sequelae, but EEG slower, cognitive impairment	* + 19 controls; Follow-up 6 mo to 11 (mean 3) y after hospitalization
Zimmermann	2005	1984-2004	Switzerland	18	< 6	N/A	N/A	N/A	28	28	6	N/A	
				88	6-14	N/A	N/A	N/A	33	33	3	N/A	
Kaiser	2006	1994-2003	Western Germany	124	≤ 16	57	62	72	64	35	1	1 neurologic sequelae, 5 cognitive (Schmolck)	
Fritsch	2008	1981-2005	Styria, Austria	116	3 mo-15 (9% ≤ 3)	N/A	N/A	65	79	21	0	2 (2%), neurologic	1 patient with persistent hemiparesis had received 2 1/2 doses of vaccine
Stähelin	2008	2000-2004	Switzerland	55	6 wk-15 (16% ≤ 5)	69	76	N/A	67	29	4	1 (2%), neurologic	36% with symptoms at discharge
Pazdiora	2012	1960-2007	W Bohemia, Czechia	410	0-19	63	59	N/A	N/A	N/A	N/A	N/A	1 death (15 y/o M)
Sundin	2012	2009	Stockholm, Sweden	10	3-17	N/A	70	20	N/A	N/A	N/A	N/A	
Engman	2012	F/U to Sundin	Stockholm, Sweden	8	4-18	38	N/A	N/A	N/A	N/A	N/A	25% cognitive by FtFQ, 88% subjective or parental complaints	Follow-up (F/U) 12-18 mo after TBE diagnosis
Fowler	2013	2004-08, F/U	Stockholm, Sweden	55	3-17	61	53	73	N/A	N/A	N/A	69% ≥3 symptoms in RPQ, 39% problems basing on BRIEF-Test	Follow-up (F/U) 2-7 y after TBE with CNS involvement
Krbkova	2015	1993-2012	Brno, Czechia	153	2-18 y / 37% ≤ 9	58	74	58	85	14	1, enceph	19 (11%), cognitive 6-12 mo after discharge	34% with multiple tick bites (max 10)

The low rates described above are sharply contradicted by more recent publications, which, instead of accounting only for neurologic sequelae, assessed cognitive signs in follow-up examinations performed from 6 months to > 10 years after the initial diagnosis. In a first case-control study conducted in Germany, 19 children with a history of TBE were thoroughly compared to 19 matched controls. While none had severe neurologic or neuropsychologic sequelae, some 3 years later (range 0.5 to 11), 11 (58%) children had nonspecific slowing in the EEG background activity; one had focal abnormalities. The children also had a higher incidence of impaired attention, concentration (26%) and psychomotor speed. On 4 of 10 subsystems of the Touwen neurologic examination (sensorimotor apparatus, posture, gross motor function, quality of motility), these children had lower scores. One developed depression shortly after the acute phase of illness (Mauritz et al., 2004; Schmolck et al., 2005). EEG abnormalities were noted in 58% (Schmolck et al., 2005), and MRI imaging was abnormal for an undetermined duration of time according to an 11-patient study (von Stulpnagel et al., 2016). In another 11 pediatric patients, MRI abnormalities with diffuse neuronal damage were demonstrated, but there was no follow-up (Ullman et al., 2016).

Based on a previously published Swedish study (Sundin et al., 2012), a follow-up was performed 12–18 months after diagnosis in 8 children with TBE, 12 with neuroborreliosis, and 15 pediatric controls with other CNS infections. The Five-to-Fifteen-Questionnaires (FtFQ, 181 items) and a semi-structured interview were used, including questions related to convalescence and developmental history. Malaise, fatigue, irritability, and recurrent headache were reported significantly more often in the TBE group vs those with neuroborreliosis or other diagnoses. The screening for cognitive dysfunction by FtFQ revealed significantly more difficulties, as well as a prolonged period of convalescence and greater number of sick days in the TBE group. In 5 of the 8 TBE children (62%) there were psychosocial consequences, but that was also the case in 83% of those with a history of neuroborreliosis, and in 33% of the controls. Rates for behavioral changes, attention problems, fatigue, headache, hyperactivity, irritability and cognitive aberrancy were all highest in the TBE group in this small survey. Two of the children apparently had neurodevelopmental disabilities before the acute TBE infection. Among the six without preexisting problems, all had subjective and parental complaints and/or FtFQ difficulties (Engman et al., 2012).

Another cohort of Swedish children aged 3–17 years with pleocytosis in the CSF and established TBE virus infection were evaluated 2–7 (mean 4) years later using the Rivermead Post-Concussion Symptoms Questionnaire (RPQ, n = 42) and the Behavior Rating Inventory of Executive Functioning (BRIEF) for parents and teachers (n = 32 and 22, respectively). Based on the RPQ 29 children (69%) reported ≥ 3 symptoms, most frequently headache, memory impairment, fatigue, irritability, and impaired concentration. Persistent nausea and photosensitivity were associated with moderate-to-severe TBE. In the BRIEF, a score of clinical significance was found in 11 of 28 (39%) of the children. Additionally, both children with mild and severe TBE demonstrated slightly substandard performance with respect to general cognitive ability (Wechsler Intelligence Scale for Children [WISC]). The authors concluded that two thirds of these patients experienced long-term residual problems, but a few of them already had these problems prior to TBE infection (Fowler et al., 2013).

Various neuropsychologic tests, including the WISC, were used at Brno University Hospital to assess persisting impairment in 170 Czech children age 6–12 months after the acute phase of TBE. Cognitive problems were detected in 12% of the 153 hospitalized patients vs none in 17 pediatric outpatients with the abortive form of TBE; worsening of school grades was recorded in 6%. Similar to other studies, neurologic sequelae were persistent in only 5 (3%) of those patients (Krbkova et al., 2015).

According to two studies, no single prognostic marker in the acute phase correlated with long-term outcome; mild TBE was not indicative of a better prognosis with respect to persistent cognitive problems (Fowler et al., 2013; Schmolck et al., 2005).

As shown in Table 1, a fatal outcome was reported for a 15-year-old male with TBE in West Bohemia (Pazdiora et al., 2012). A 15-year-old girl died of TBE in Switzerland after a tick bite that occurred between the first and second TBE vaccine dose (Brauchli et al., 2008). A fatality in an unknown location was recorded for a 12-year-old child (Lindquist, 2008). A fourth fatal case was recorded earlier in Klagenfurt in an 11-year-old boy who was in the initial phase of the disease and underwent an appendectomy (Hellwig et al., 1983). A fifth fatality was reported for a boy who died shortly before his sixth birthday (Hellwig et al., 1983).

3.4.2. Outcome in adult populations for comparison

Among the 11 TBE-related fatalities in the ECDC 2014/2015 data provided by TESSy, all were in adults ranging in age from 28 to 87 years (7 were ≥ 64). Few original publications included both children and adults, as well as their outcomes. All showed that adults had a far greater risk of severe course and neurologic sequelae (Haglund et al., 1996; Kaiser, 2000; Lesnicar et al., 2003; Logar et al., 2000; Tomažič et al., 1996). Some 7 years (range 1 to 13) after the acute phase, ≤ 63% of adults showed residual symptoms, with severe daily impairment reported in 14% (Karelis et al., 2012). Cognitive impairment in adults has been reported at a rate of 55% (Gustaw-Rothenberg, 2008). The most recent study evaluated patients for a post-encephalitic syndrome, which is defined as ≥ 2 subjective symptoms emerging or worsening since onset of TBE (with no other medical explanation) and/or ≥ 1 objective neurologic sign. The syndrome was reported in 42% (95% CI: 36%–47%) of patients 6 months after the acute phase, and in 33% (95% CI: 28%–37%) 12 months thereafter. This proportion remained unchanged 2 to 7 years after TBE, but the proportion of severe post-encephalitis symptoms decreased (Bogovic et al., 2018).

3.4.3. Comparison of vaccination recommendations against TBE in children

Basing on personal communications from national experts (see acknowledgements) and as shown in Table 2, there are broad variations relating to recommendations even among countries with substantial endemicity.

In Estonia, Lithuania, and Sweden, TBE vaccination is not (or not widely) recommended in their respective national immunization programs. In Estonia, TBE immunization is only recommended and reimbursed for those individuals with occupational exposure. In contrast to the official Lithuanian authorities, professional societies support and recommend this preventive measure for all permanent inhabitants of the country. In other countries, including Poland, it is recommended only for persons with high risk of exposure (e.g., children and adolescents in youth camps); for others, vaccination is just to be considered.

In countries recommending TBE immunization in children, the strategy with respect to the place of residence varies. In Austria, all children are to be protected, irrespective of whether they live in an endemic area. The same applies to Czechia and Latvia where the entire countries are rated as endemic. Germany, Slovenia, and Switzerland recommend TBE immunization only for those residing in or temporarily visiting areas of endemicity. In Sweden, recommendations for vaccination are issued by affected counties.

The lower age limit for vaccination differs, but in most countries, it is 12 months, following the label of licensed vaccines. In some high-risk federal provinces of Austria, there previously was a lower age limit of 6 months; that off-label application has also been advocated for “special situations” in a consensus report (Kunze et al., 2004). However, that practice has been associated with reduced immunogenicity after the second dose, particularly when mothers had been immunized (Demicheli et al., 2009; Eder and Kollaritsch, 2003). Some pediatricians continue with this off-label protocol; however, they are advised to warn the parents of the infant accordingly (Ministerium Frauen Gesundheit, 2017). In Germany, the Ständige Impfkommission (Standing Vaccination Commission) draws attention to the fact that, after the application

Table 2
Recommendations by National Authorities for TBE Immunization in Children in Selected European Countries.

Country	Recommended Lower Age Limit, y	Regions in Country (Individual Risk Assessment)	Remarks
Austria	1	Entire country	Off-label vaccination often practiced at age of 7 months; immunogenicity may be reduced
Czechia	(1)	Entire country	No statement by the National Committee on vaccination, but semiofficial recommendation by the Czech Vaccinology Society with note: higher occurrence of fever in children younger than 2 years-of-age after the vaccination
Estonia	(1)	Entire country (Individual risk assessment)	Not included in the National Immunization Schedule. For groups at occupational risk, TBE vaccination is reimbursed
Germany	3	Risk areas	Vaccination from 1 year if substantial exposure. Indication for 1-3 years old children to be carefully evaluated in view of higher rate of adverse events to vaccine as compared to age > 3 years
Latvia	1	Residence in endemic territory	Note: whole country is endemic
Lithuania	(1)	(All permanent inhabitants of the country)	TBE vaccination not included in the National Immunization Program, but recommended by various medical societies
Poland	(No age limit)	Areas with high prevalence of TBE	Particularly for children/adolescents participating in youth camps
Slovenia	Recommended 1; in future 3 (then reimbursed)	Most of Slovenia is endemic; living in or traveling to endemic area	Mandatory and reimbursed in occupational exposure, otherwise recommended
Slovakia	(1 per package insert; if parents ask, then after age 2)	(Residents in endemic areas where incidence > 5/100000, incl. children)	Officially recommended only for those professionally exposed
Sweden	(1)	Risk area (map) > 1-2 weeks outdoor April to November	TBE immunization not included in the National Immunization Schedule. Recommendations on homepage of county.
Switzerland	6	Residence or temporary stay in endemic region	In children below the age of 6 years the vaccination is in general not indicated as serious illness in this age group is rare

No reimbursement in most countries; parentheses indicate recommendation only by professional societies.

of TBE vaccine in the 1- to 2-year-olds, fever > 38 °C occurs in 15% of patients vs 5% in 3- to 11-year-old children. Therefore, they rather recommend immunization at age ≥ 3 years, unless there are particular concerns about exposure (Robert Koch Institut, 2017). To note, in the 1- or 2-year-old patients who were vaccinated, there was no fever > 40 °C, and the rates were lower after the second dose (Galgani et al., 2017; Pavlova et al., 2003; Weinzettel et al., 2007). Also, the Czech Vaccinology Society mentions in their general recommendation on TBE vaccination: “However, there is a higher occurrence of fever in children younger than 2 years of age after the vaccination” (Czech Vaccinology Society, 2016). Apparently, Slovenia plans to raise the lower age limit at which TBE vaccination is recommended from 1 to 3 years and then to reimburse patients for this preventive measure. In Sweden the lower age limit had previously dropped from 6 to 3 years of age, and now stands at 1 year as a result of the Swedish studies having demonstrated cognitive sequelae. Some in Sweden opposed early TBE vaccination (Skogman et al., 2004a,b), while others there and in Germany recommend the pros and cons be weighed for each individual patient regarding immunization before age 3 years (Anon., 2016; Froding and Hjertqvist, 2013). Traditionally, Switzerland is the only country generally recommending TBE vaccination at age 6 years, unless there is a high risk of exposure.

4. Discussion

TBE infections can occur at any age. So far there have been only a few anecdotal reports about TBE in infants before the first birthday (Fritsch et al., 2008; Grubbauer et al., 1992; Iff et al., 2005; Jones et al., 2007; Kosina et al., 2008; Leistner and Dahlem, 2011; Stahelin-Massik et al., 2008), but the 5 cases reported to the ECDC in just a two-year period (1 each from Austria, Germany, Poland, Slovakia, and Sweden) indicate that the majority of such cases may remain unpublished and that TBE in infants is not exceedingly rare.

There is uncontested evidence from studies that the incidence is lower in younger vs older children (Table 1) or in children vs adults. The same trend is illustrated by recent ECDC data in Fig. 2. These rates may be biased as a consequence of vaccination programs targeting particularly adults. In studies from Estonia, Germany, Slovenia, and Sweden, all of which included TBE patients of all age groups, the proportion of children aged ≤ 14 years varied between 10% and 16% (Epstein and Kutsar, 2009; Grgic-Vitek and Klavs, 2011; Holmgren and Forsgren, 1990; Kaiser, 2002; Tomažič et al., 1996). The question remains whether the lower rates of TBE in children are associated with lower exposure or to a reduced risk of developing manifest disease (Arnez and Avsic-Zupanc, 2009; Lindquist, 2014; Ruzek et al., 2010). Because infants and toddlers are unable to verbalize their symptoms, which often are unspecific, they more frequently remain undiagnosed for TBE (Engman et al., 2012; Hansson et al., 2011). It is probable that a combination of all of the above is at the root of those lower rates. It has been suggested that, particularly in young children living in TBE-endemic areas, TBE should be suspected in any unexplained, uncharacteristic, acute CNS-related symptoms, and TBE-related serologic investigation should be requested (Sundin et al., 2012).

In children and adolescents, meningitis is the predominant form of the infection (Table 1). Therefore, a milder course is more common; meningoencephalitis or the most severe meningoencephalomyelitis are more often seen in adults (Hombach et al., 2017; Kaiser, 2006; Stahelin-Massik et al., 2008; Zimmermann and Koch, 2005).

In all reviewed studies that compare the outcomes in different age groups with respect to neurologic sequelae, the prognosis is said to be markedly better in children than in adults (Haglund et al., 1996; Kaiser, 2000; Lesnicar et al., 2003; Logar et al., 2000; Tomažič et al., 1996). As shown in Table 1, the proportion of pediatric patients with neurologic sequelae varied between 0% and 10%; in several surveys and in an analytic review on 1000 cases a rate of 2%–3% was mentioned (Arnez and Avsic-Zupanc, 2009; Kaiser, 2006). Few fatalities were reported in children; none below the age of 10 years.

These are low proportions compared to adults, in whom 26%–46% were reported as having an incomplete recovery. This term usually was usually associated with focal neurologic sequelae (e.g., hemiparesis, persistent cranial or spinal nerve paralysis, hearing loss); however, some included cognitive impairment as well (Haglund and Günther, 2003; Kaiser, 1999; Lindquist, 2014). Follow-up rates of spinal nerve paralysis were recorded in 6% of adults in two studies; ataxia and tremor were reported in 10%–15% (Günther et al., 1997; Lindquist and Vapalahti, 2008; Mickiene et al., 2002; Tomažič et al., 1996). One year

after the acute phase of TBE infection, 8% of adult patients still required adjustment of daily activities because of severe disabilities. With a mean follow-up of 4 years, 28% of adults had moderate-to-severe sequelae (Lindquist and Vapalahti, 2008; Mickiene et al., 2002). In the reviewed literature, all experts agreed that TBE is generally more severe in adults vs children, with a worse prognosis with respect to neurologic sequelae; several suggested very recently that severity escalates with the patient's age (Hombach et al., 2017; Kaiser, 2016; Logar et al., 2006).

More recently several groups started to perform follow-up studies in children that included cognitive assessment. A battery of questionnaires and semi-structured interviews was used; EEG was also reassessed. Based on two small and two larger surveys (Engman et al., 2012; Fowler et al., 2013; Krbkova et al., 2015; Schmolck et al., 2005), cognitive problems were recorded in 12% to 69%. Up to two thirds of the children reported problems, mainly headache, fatigue, and cognitive issues. Parents reported persistent attention and concentration deficits since the infection in 26%. Teachers also reported impairments in their students: in two children with cognitive sequelae, declining school grades were recorded; one child developed depression (Fowler et al., 2013; Krbkova et al., 2015; Schmolck et al., 2005). EEG and MRI abnormalities are frequently observed, but usually there was no follow-up to determine their persistence (Schmolck et al., 2005; Ullman et al., 2016; von Stulpnagel et al., 2016). There was no correlation between age at onset of illness (range 3 to 17 years) and severity of symptoms at follow-up (Fowler et al., 2013). This contradicts an earlier statement from a survey of 124 children that found all children with persistent damage were > 6 years old (Kaiser, 2006). Cognitive problems in children and adolescents subsequent to acute TBE cause consequences for the families and the society (Engman et al., 2012; Sundin et al., 2012).

Some earlier studies concluded that TBE in childhood is a disease with a relatively mild clinical course and favorable outcome (Lesnicar et al., 2003). This must now be contradicted, and one must question whether the assumption that "prognosis of the majority of children with an episode of TBE appears to be good" (Rostasy, 2012) is still justified. Even if some of the studies on cognitive impairment summarized above were small, and even if a variety of widely different tools were used for the long-term assessment, it is no longer appropriate to claim that TBE in children is usually innocuous, in view of the fact that a substantial proportion of patients who suffer cognitive problems for many years thereafter. A fundamental contradiction is demonstrated by two quotes: "TBE in children has a benign course with minimal sequelae" (Krbkova et al., 2015) vs TBE "is not benign in children" (Schmolck et al., 2005). As a consequence, it should be no surprise that TBE vaccine recommendations vary widely. As Lindquist stated: "…there is no clear consensus about when TBE vaccination should be recommended or not, and if recommended, at what age primary immunization should be initiated in childhood" (Lindquist, 2014). This lack of consensus is particularly salient with regard to national health authorities who would have to cover the costs of immunization programs; there is a tendency to reject a proposed health initiative if there is discordance among experts.

Reduction of risk (Reduction of exposure to tick bites) theoretically is the first line of defense, but the options for tick avoidance at best have a limited effect (Bogovic and Strle, 2015). Repellents offer no more than moderate effectiveness (Buchel et al., 2015; Kosina et al., 2008; Kunze et al., 2004; Staub et al., 2002). While battle-dress uniforms impregnated with permethrin reduced the tick-bite incidence by 98% (Faulde et al., 2015), clothing covering so much of the body is impractical for leisure activities. For a variety of reasons, only a limited proportion of those exposed are compliant with restrictive recommendations, which also include careful examination of the body and removal of ticks as soon as possible after exposure (Beaujean et al., 2013); however, there is no evidence that such rapid intervention reduces the risk of infection, as the TBE virus is almost immediately transmitted after the skin is broken by the infected tick (Kaiser, 2016). Additionally, even if only 1% or fewer of all TBE cases are associated with unpasteurized milk or dairy products, this consumption must be avoided (Hudopisk et al., 2012).

Globally, six TBE vaccines are available: one licensed by EMA via the mutual recognition procedure (FSME-IMMUN [Baxter, Austria]), one licensed in 22 countries in Europe (Encepur [Novartis, Germany]), 3 licensed in Russia and some Russian-speaking countries (TBE Moscow [Chumakov Institute, Russia], Klesch-E-Vac [Russia-produced], EnceVir [Microgen, Russia]), and one licensed in China (SenTaiBao [Changchun, China]). As there is no specific treatment for TBE infection beyond supportive care, prevention is of paramount importance. Vaccines in use for children have recently been fully reviewed, and while there are differences in some respects, they appear to be safe and effective (Barrett et al., 2003; Beck et al., 2016; Bogovic and Strle, 2015; Hombach et al., 2017; Kollaritsch et al., 2012; Pöllabauer and Kollaritsch, 2017; World Health Organization, 2011; Zent et al., 2005, 2003). There are very few contraindications for TBE immunization in children. As with any vaccine, immunization should be postponed in case of acute illness, particularly if febrile. Although the vaccines are produced in chicken embryo cells, mild allergy to egg protein is not considered a contraindication (Greenhawt, 2015; World Health Organization, 2011). In addition, TBE vaccine can be used in patients with multiple sclerosis (Baumhackl et al., 2003).

As late as 2005, the possibly rhetorical question was raised as to whether a general vaccination is appropriate in children, in view of the fact that "prognosis in children is much better than in adults" (Zenz et al., 2005). However, in view of cognitive handicaps and neurodevelopmental deficits seen in ≤ 40% of the affected children (Sundin, 2017), TBE is by no means benign, and it has a long-lasting impact on patients and their families. It is essential to protect the younger generation from cognitive impairment (Fritsch et al., 2008). Of note, most researchers who conducted pediatric studies on TBE, reviewed data, or contributed to a consensus statement concluded in favor of broad vaccination recommendations (Arnez and Avsic-Zupanc, 2009; Cizman et al., 1999; Engman et al., 2012; Fritsch et al., 2008; Hellwig et al., 1983; Kosina et al., 2008; Krbkova et al., 2015; Kunze et al., 2004; Lindquist and Vapalahti, 2008; Lindquist, 2008; Mauritz et al., 2004; Pazdiora et al., 2012; Schmolck et al., 2005; Stahelin-Massik et al., 2008). They also concluded that travelers to endemic areas should obtain advice regarding immunization (Arnez and Avsic-Zupanc, 2009; Zenz et al., 2005; Steffen, 2016).

In the context with other immunizations, and in other parts of the world, it has been demonstrated that the lack of vaccination in childhood ultimately may impact educational attainment, adult earnings, and social functioning (Barnighausen et al., 2014; Bloom et al., 2012). A broad economic evaluation including all these aspects is needed. Vast differences between low (12%) and high (69%) estimates on the proportion of children with persisting problems (Engman et al., 2012; Fowler et al., 2013; Hansson et al., 2011; Krbkova et al., 2015) also illustrate that more research efforts with large long-term follow-up and a standardized protocol are urgently needed.

As shown in Table 2, Austria is the only country in Western and Central Europe with universal recommendations. In several other countries, the pre-vaccination endemicity of TBE for all age groups exceeds 5 cases per 100,000 population. The World Health Organization (WHO) recommends vaccination of all individuals age ≥ 1 year (or ≥ 3 years with the Russian-manufactured vaccines) in these regions (World Health Organization, 2011). Based on the ECDC data, this incidence of 5/100,000 was exceeded in Czechia, Estonia, Latvia, Lithuania, and Slovenia in at least one year during the 2012–2015 period (ECDC, 2018). It is no longer justified to emphasize the importance of immunization only in adults and highly exposed professionals (Grgic-Vitek and Klavs, 2011); the WHO recommendation should be applied to children as well. As shown in Table 2, professional societies support more extensive recommendations than those issued by the national

authorities, but their influence, by experience, is limited.

With respect to the ideal timing to start TBE vaccination in children, WHO does not formulate a preference, whereas the Central European Vaccination Awareness Group has a preference for 1 year at least for those living in high-risk areas (Zavadska et al., 2013). As mentioned, there are markedly increased systemic adverse events recorded in those aged 1 or 2 years even with the current vaccines (Zent et al., 2003). Thus, it is justifiable as recommended in Germany to withhold immunization until the third birthday, unless a toddler has a history of exposure to ticks; then immunization is indicated earlier. Data show increasing numbers of pediatric patients in the first three years of life. It is uncertain whether this is associated with increasing exposure, with a higher proportion developing symptomatic infection, or both. We must also keep in mind that from a public health perspective, combined immunization against measles/mumps/rubella should be prioritized in areas where parents are overall critical of immunizations and oppose “too many jabs” at age 1 year. The Swiss recommendation to start TBE immunization as a general rule at age 6 years (Bundesamt für Gesundheit, 2006; Stahelin-Massik et al., 2008) needs to be reconsidered, as it is based on tradition and not on modern evidence.

5. Conclusion

Although the clinical course of TBE infections is less serious in the pediatric population as compared to adults, and although they result in fewer neurological sequelae, the potential for long-term cognitive sequelae are of great concern. While more data from large standardized studies with long-term follow-up are needed, the existing database should already result in the decision to broadly recommend vaccination against TBE for children age 1 to 3 years in countries with high endemicity, along with the WHO recommendation for the general population.

Declaration of interest

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