

Epidemiology of tick-borne encephalitis in Switzerland, 2005 to 2011

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We provide an update on the epidemiology and disease characteristics of tick-borne encephalitis (TBE) in Switzerland. Data were collected through the mandatory notification system of the Federal Office of Public Health. Between 2005 and 2011, a total of 1,055 TBE cases were reported, with a peak of 244 cases in 2006. The average yearly incidence was 2.0/100,000 inhabitants nationwide, with the highest regional value (7.8/100,000) in eastern Switzerland. Incidence by age peaked in 60–69 year-old patients, males predominated in all age groups. Most patients suffered from meningoencephalitis (n=567) or meningitis (n=246), seven of 1,055 patients (0.7%) died. Of 617 patients who were 40 years and older, 442 (72%) suffered from a severe course of illness, compared to 196 (51%) of 384 patients younger than 40 years. Most patients were not immunised against TBE, and in 33 of 1,055 patients (3%), vaccine failure was found possible. Ongoing surveillance of TBE and intensified efforts in promoting TBE vaccination for the population at risk will be needed in light of its considerable morbidity.

Introduction

Tick-borne encephalitis (TBE) is an acute infection involving the central nervous system (CNS) with potentially serious outcome. It is caused by the TBE virus (TBEV), which belongs to the Flavivirus family. Transmission of TBEV to humans occurs by bites of infected ticks, in Europe mainly *Ixodes ricinus*. After an incubation period of four to 28 days (usually seven to 14 days), the clinical presentation of TBE usually starts with one to seven days of influenza-like illness (ILI), followed by an afebrile and mostly asymptomatic interval [1]. A few days later, CNS manifestations such as meningitis, meningoencephalitis or encephalomyelitis may occur in approximately one third of patients [2]. The case fatality rate is less than 2%, whereas permanent sequelae such as cognitive or neuropsychiatric complaints, balance disorders, headaches, dysphasia, hearing defects, and spinal paralysis are reported in up to 46% of patients [3].

In Switzerland, TBE occurs in specified endemic areas and is a notifiable disease. The average national incidence of TBE in Switzerland between 1984 and 2004 was 1.4/100,000/year, with values reaching up to 7.9 in endemic cantons (highest values: Thurgau 7.9, Schaffhausen 4.3, Zurich 2.7, and Aargau 2.2) [4]. Age distribution of patients revealed two peaks, i.e. in six to 14 year-old children and in 60 to 69 year-old adults. Children younger than six years were rarely affected [4].

Effective vaccines are available to prevent TBE, but no curative treatment exists [2,5]. In Switzerland, TBE vaccination coverage with at least one dose in 2007 was 17% for the whole country, with no difference between males and females [6]. The highest coverage was 25% in the 13 to 19 year-olds; In endemic regions, coverage varied between 28 and 47% [personal communication A Zacharias, 14 March 2014]. In the period 2010 to 2012, vaccination coverage in 16 year-old adolescents in endemic regions ranged from 42 to 71% for one and 39 to 64% for three doses [7]. While coverage with the first dose of TBE vaccine indicates the population with an initiated immunisation series, optimal protection requires a complete primary series with three vaccine doses, followed by regular booster doses.

The aim of this study was to provide an update on the epidemiology and disease characteristics of TBE in Switzerland for the years 2005 to 2011 in light of a notable increase in reported cases in recent years [8].

Methods

Data source and collection

TBE has been a notifiable disease in Switzerland since 1984. Laboratories have to report to the Federal Office of Public Health (FOPH) and the cantonal medical officer (CMO) one or more of the following test results: i) positive test for anti-TBEV IgM serum antibodies, ii) anti-TBEV IgG serum antibody seroconversion, iii) a ≥ 4 -fold rise in anti-TBEV IgG serum antibodies in paired serum specimens, and iv) successful TBEV genome

TABLE 1

Classification of reported tick-borne encephalitis cases, Switzerland, 2005–2011

Case classification	Laboratory criteria		Clinical criteria
Not a case	Positive IgM serology		No ILI and no neurological symptoms
Possible case	a)	Positive IgM serology	ILI or non-specific neurological signs and symptoms
	b)	Positive IgM + positive IgG serology ^a	Any
Probable case	a)	Positive IgM serology	Meningitis, meningoencephalitis, encephalomyelitis or pareses
	b)	Positive IgM + positive IgG serology ^a	ILI or non-specific neurological signs and symptoms
Confirmed case	a)	Positive IgM + positive IgG serology ^a	Meningitis, meningoencephalitis, encephalomyelitis or pareses
	b)	TBE-RNA detection by PCR	Meningitis, meningoencephalitis, encephalomyelitis or pareses

ILI: influenza-like illness; TBE: tick-borne encephalitis.

^a or anti-TBE IgG serum antibody seroconversion or ≥ 4 -fold rise in anti-TBE IgG serum antibodies.

amplification. The CMO is then obliged to ask for additional information from the patient's physician, such as clinical presentation, disease progression, TBE vaccination history and tick bite within four weeks before onset of illness, in a standardised reporting form and submit this to the FOPH [9]. All data for this study have been provided by the FOPH in compliance with Swiss data protection laws.

Data inclusion and surveillance definitions

Patients were excluded from further analysis if they were classified as 'not a case' on the basis of laboratory results and documented clinical characteristics, whereas possible, probable and confirmed cases were included for further analysis (Table 1). The reason to include possible, probable and confirmed cases into

the analysis was to monitor TBE infection rather than only the disease, and to compare time trends with the past data from 1984–2004 [4]. Patients resident in the neighbouring Principality of Liechtenstein (FL) were excluded.

Analysis

The data set for analysis comprises possible, probable and confirmed cases according to the definitions given in Table 1. All analysis of data was done using Microsoft Excel 2008 and SPSS (version 20.0, SPSS, Inc., Chicago, United States) software. Analysis included cross tables and incidence estimations. No statistical inference was done because surveillance data are not a random sample.

FIGURE 1

Annual incidence of tick-borne encephalitis in Switzerland, 1984 to 2011 (n=2,421)

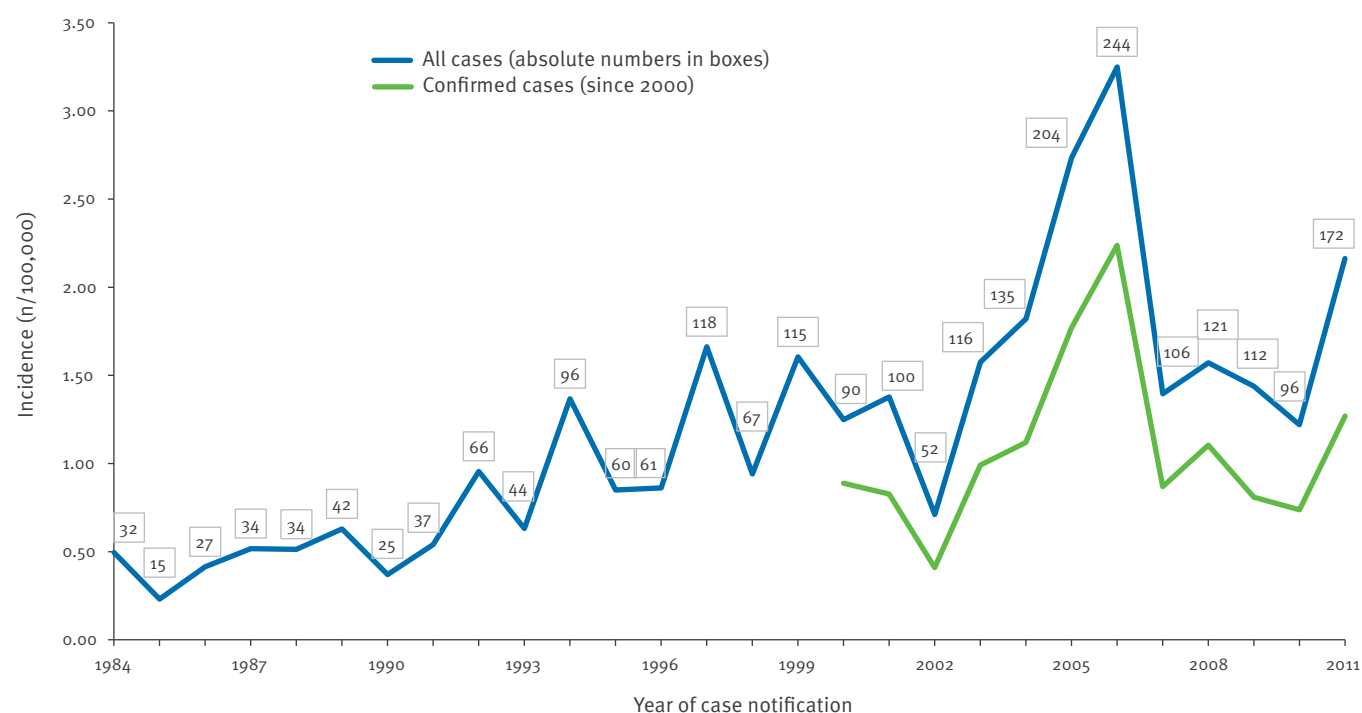


TABLE 2

Number and incidence per 100,000 inhabitants of tick-borne encephalitis cases by year and canton of residence, Switzerland, 2005 to 2011 (n=1,055)

Canton	Yearly incidence (total number)							
	2005	2006	2007	2008	2009	2010	2011	2005–2011
TG	9.8 (23)	9.3 (22)	8.0 (19)	3.7 (9)	10.2 (25)	6.4 (16)	7.5 (19)	7.8 (133)
NW	7.5 (3)	20.0 (8)	7.4 (3)	2.5 (1)	2.5 (1)	0.0 (0)	12.1 (5)	7.4 (21)
UR	2.9 (1)	11.4 (4)	8.6 (3)	8.5 (3)	0.0 (0)	2.8 (1)	0.0 (0)	4.9 (12)
AG	6.3 (36)	4.7 (27)	2.2 (13)	2.2 (13)	2.2 (13)	1.8 (11)	3.7 (23)	3.3 (136)
ZH	4.9 (62)	5.4 (69)	2.4 (32)	3.3 (44)	2.2 (30)	1.4 (19)	3.1 (43)	3.2 (299)
LU	5.3 (19)	5.3 (19)	1.7 (6)	1.6 (6)	1.6 (6)	2.4 (9)	2.4 (9)	2.9 (74)
AI	0.0 (0)	6.5 (1)	0.0 (0)	6.4 (1)	0.0 (0)	0.0 (0)	6.4 (1)	2.8 (3)
SH	5.4 (4)	4.1 (3)	0.0 (0)	2.7 (2)	2.6 (2)	2.6 (2)	1.3 (1)	2.7 (14)
BE	1.6 (15)	4.2 (40)	0.6 (6)	2.1 (20)	1.7 (17)	1.3 (13)	2.2 (22)	2.0 (133)
SG	2.6 (12)	1.1 (5)	1.5 (7)	1.7 (8)	1.5 (7)	1.7 (8)	3.3 (16)	1.9 (63)
OW	6.0 (2)	3.0 (1)	0.0 (0)	2.9 (1)	0.0 (0)	0.0 (0)	0.0 (0)	1.7 (4)
GR	3.2 (6)	2.7 (5)	1.6 (3)	1.1 (2)	1.6 (3)	0.5 (1)	1.0 (2)	1.7 (22)
AR	1.9 (1)	1.9 (1)	0.0 (0)	0.0 (0)	3.8 (2)	0.0 (0)	3.8 (2)	1.6 (6)
FR	1.2 (3)	3.9 (10)	1.1 (3)	0.4 (1)	1.1 (3)	1.4 (4)	2.1 (6)	1.6 (30)
GL	2.6 (1)	2.6 (1)	0.0 (0)	0.0 (0)	0.0 (0)	2.6 (1)	0.0 (0)	1.1 (3)
SO	2.0 (5)	2.4 (6)	0.4 (1)	0.0 (0)	0.0 (0)	0.4 (1)	0.8 (2)	0.9 (15)
SZ	0.7 (1)	0.0 (0)	1.4 (2)	0.0 (0)	0.0 (0)	1.4 (2)	2.0 (3)	0.8 (8)
VD	0.8 (5)	1.7 (11)	0.7 (5)	0.9 (6)	0.1 (1)	0.3 (2)	1.1 (8)	0.8 (38)
BS	0.5 (1)	2.2 (4)	0.0 (0)	0.5 (1)	0.0 (0)	0.5 (1)	1.1 (2)	0.7 (9)
JU	1.4 (1)	1.4 (1)	0.0 (0)	0.0 (0)	0.0 (0)	1.4 (1)	0.0 (0)	0.6 (3)
BL	0.8 (2)	1.1 (3)	0.7 (2)	0.0 (0)	0.4 (1)	0.7 (2)	0.4 (1)	0.6 (11)
ZG	0.9 (1)	0.0 (0)	0.0 (0)	0.9 (1)	0.9 (1)	0.0 (0)	0.9 (1)	0.5 (4)
VS	0.0 (0)	0.3 (1)	0.0 (0)	0.3 (1)	0.0 (0)	0.6 (2)	1.3 (4)	0.4 (8)
NE	0.0 (0)	1.2 (2)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	0.6 (1)	0.3 (3)
TI	0.0 (0)	0.0 (0)	0.0 (0)	0.3 (1)	0.0 (0)	0.0 (0)	0.3 (1)	0.1 (2)
GE	0.0 (0)	0.0 (0)	0.2 (1)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	0.1 (1)
CH	2.7 (204)	3.3 (244)	1.4 (106)	1.6 (121)	1.4 (112)	1.2 (96)	2.2 (172)	2.0 (1,055)

AG: Aargau; AI: Appenzel Innerrhoden; AR: Appenzel Ausserrhoden; BE: Bern; BL: Basel (county); BS: Basel (city); CH: Switzerland; FR: Fribourg; GE: Geneva; GL: Glarus; GR: Graubünden; JU: Jura; LU: Lucerne; NE: Neuchâtel; NW: Nidwalden; OW: Obwalden; SG: Saint Gallen; SH: Schaffhausen; SO: Solothurn; SZ: Schwyz; TG: Thurgau; TI: Ticino; UR: Uri; VD: Vaud; VS: Valais; ZG: Zug; ZH: Zurich.

TBE incidences were calculated based on data on the permanent resident population provided by the Federal Statistical Office [10]. Incidence rates by canton refer to the patient's place of residence, not to the presumed place of a tick bite.

Results

General characteristics

Between 2005 and 2011, 1,177 reports of TBE were notified to the FOPH. Of these, 114 (9.7%) were categorised as 'not a case' and excluded, as were the eight patients (0.7%) living in FL. Of the remaining 1,055 cases, laboratory reports were available for 1,004 (95%), and the physician reporting form with clinical and laboratory data was available for 1,008 (96%). For 47 cases, only the laboratory report was available. Complete data sets were available from 1,001 patients (95%). Of the 1,055 cases, 133 (13%) were classified as possible

cases, 249 (24%) as probable cases and 673 (64%) as confirmed cases.

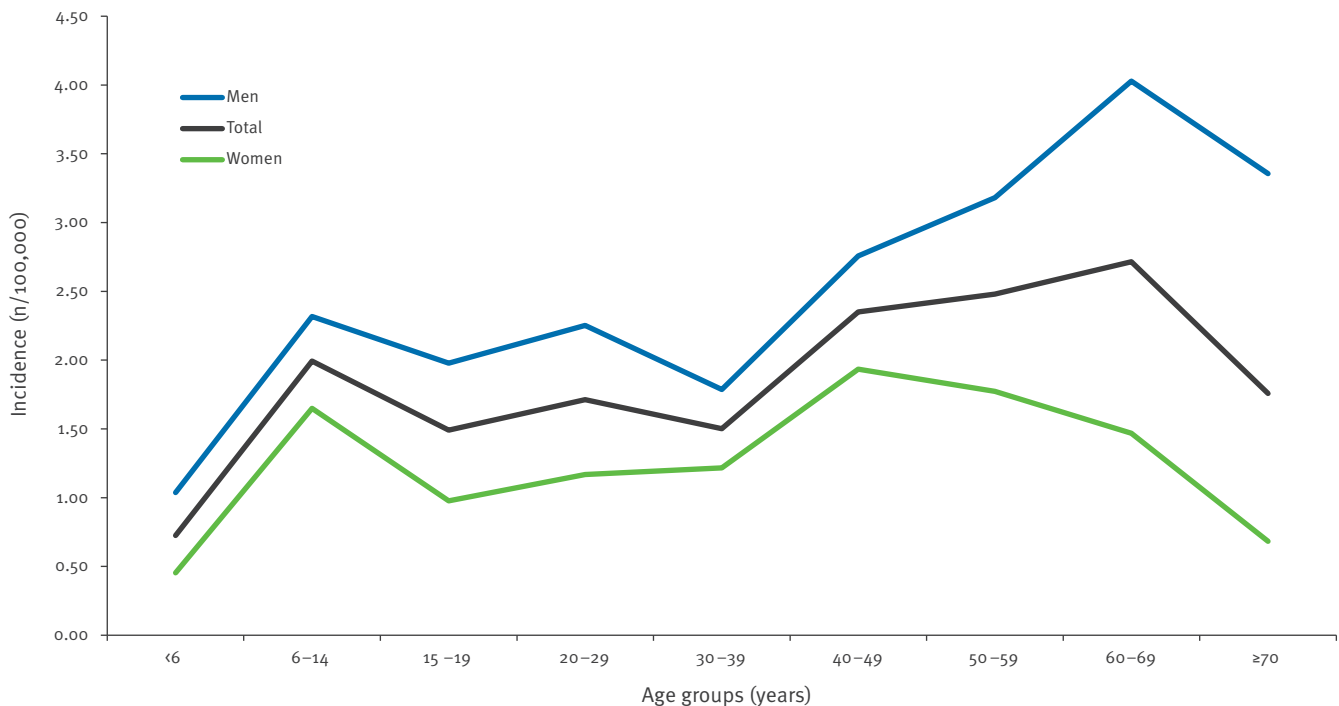
Epidemiological findings

There were two peaks of reported TBE cases (combining possible, probable and confirmed cases as defined in Table 1) during the study period: one during the years 2005 (n=204) and 2006 (n=244) and one in 2011 (n=172). From 2007 to 2010, the number of cases was relatively stable with an average of 109 cases per year.

The yearly national incidence rates (n cases/100,000 inhabitants) in Switzerland fluctuated within a range of 1.2 (2010) and 3.3 (2006), leading to an average yearly incidence of 2.0 for the whole study period, with the highest average value of 7.8 in the canton of Thurgau in eastern Switzerland (Figure 1, Table 2). When the incidence of reported TBE cases since initiation of surveillance in 1984 is considered (Figure 1), an increasing

FIGURE 2

Incidence of tick-borne encephalitis by age and sex, Switzerland, 2005 to 2011 (n=1,053)



trend of yearly incidences can be seen. Each of the 26 Swiss cantons reported at least one patient with TBEV infection during the study period. Nonetheless, case numbers fluctuated considerably from year to year, with only nine cantons notifying at least one patient every year.

Incidence was consistently higher in men in all age groups (Figure 2). Further, incidence was low in children under the age of six years, constant at equal levels for age groups between six and 39 years, and reached highest values between 40 and 69 years of age.

Most cases of TBE with known date of manifestation (n=884) occurred between April and September, peaking in June (n=221; 25%) and July (n=228; 26%). From October to March, only few cases with TBE were reported: three (0.3% of total) in January, one (0.1%) in February, eight (0.9%) in March and 10 (1.1%) in December. Comparison of different age groups showed no substantial variability with regards to TBE seasonality (data not shown).

In 478 (45%) of 1,055 patients, a history of tick bite(s) within four weeks before onset of illness was reported, whereas 147 patients (14%) could not remember any tick bite. In 430 patients (41%) the history of tick bite was unknown. Sixty-seven (6.4%) patients experienced tick bites outside their cantons of residence, 50 (4.7%) in Switzerland and 17 (1.6%) in a foreign country. Almost half of the patients (n=502; 48%) were either bitten in the canton of their residence or had permanently stayed in the canton of their residence during

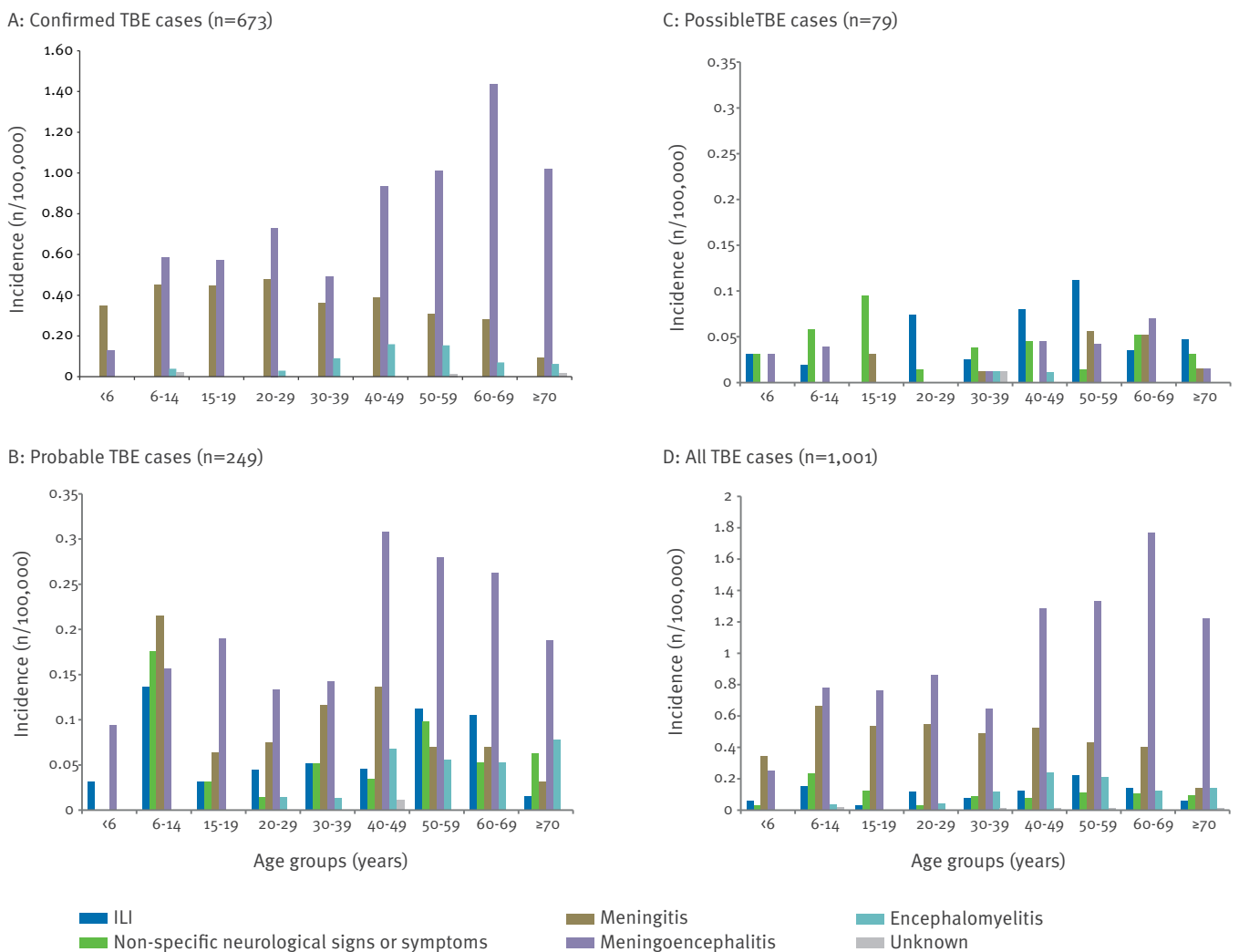
the maximal incubation period, i.e. up to four weeks before onset of illness.

Clinical findings

Meningoencephalitis was the most frequent manifestation in probable and confirmed TBE cases and overall (Figure 3). A clinical diagnosis was available in 1,001 of 1,008 cases (99%) with physician report. The official TBE notification form requires reporting physicians to specify the patient's CNS manifestations as one of five clinical diagnoses: 'meningitis', 'meningoencephalitis', 'encephalomyelitis', 'radiculitis' and 'others' where free text can be entered [9]. Due to the difficulties in exact clinical differentiation and according to international literature [1,2,11], we combined encephalomyelitis and radiculitis in one category for the purposes of our analysis. Furthermore, patients presenting with headache, vertigo, paraesthesia, myoclonia and similar manifestations as reported under 'others' were categorised together as 'non-specific neurological signs and symptoms'. Five patients received the diagnosis 'paresis' without indication of other neurological symptoms (i.e. no meningitis, meningoencephalitis or radiculitis): three had a paresis of the facial nerve, one had an unspecified cranial nerve paresis and one had a paresis of unknown localisation. The total number of patients with paresis (combined with other neurological manifestations) is unknown. Of 617 patients of at least 40 years of age, 442 (72%) suffered from a severe course of illness, i.e. with meningoencephalitis, encephalomyelitis or pareses, compared with 196 (51%) of 384 patients under the age of 40 years (Figure

FIGURE 3

Incidence of clinical findings in cases of tick-borne encephalitis, by age, Switzerland, 2005 to 2011 (n=1,001)*



ILI: influenza-like illness; TBE: tick-borne encephalitis

3). There was no year-by-year variability in proportions of diagnoses from 2005 to 2011 (data not shown).

Of the 1,055 patients with TBE, 789 (75%) were hospitalised, 193 (18%) were reportedly treated as outpatients, and for 73 (6.9%) patients, the respective information was missing. Precise dates of admission to and discharge from hospital were available for 666 (84%) of the 789 hospitalised patients. The mean duration of hospitalisation was 9.0 days (interquartile range (IQR): 5–11 days). Duration of hospitalisation increased with the age of the patient in a linear pattern, from a mean of 5.0 days (IQR: 3–7 days) in children up to the age of 14 years to a maximum mean of 14.6 days (IQR: 9–18 days) in those 70 years and older.

Nine (0.9%) of 1,055 patients died in timely association with TBE. For seven of them, the course of the TBE illness was fatal, whereas the remaining two deaths

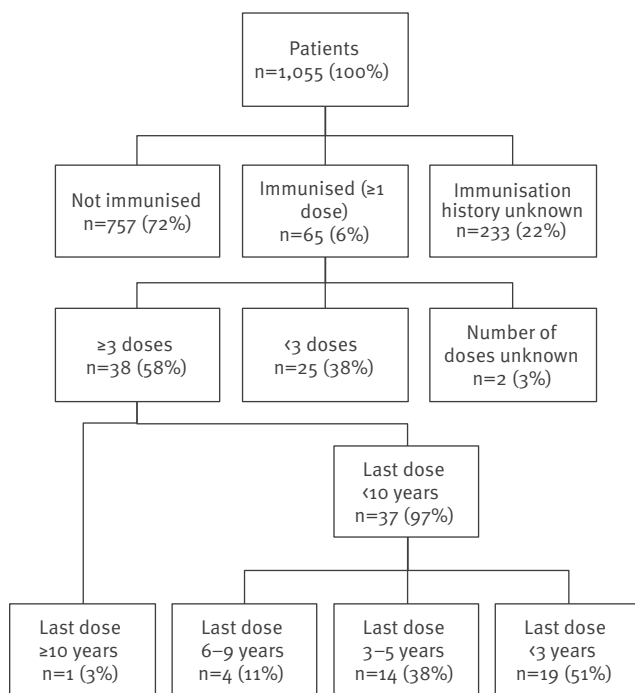
were most likely unrelated to TBE: one patient died after abdominal surgery and another after a bicycle accident. Of the seven patients with fatal TBE, five had a diagnosis of meningoencephalitis and two had a diagnosis of encephalomyelitis. The age range of these seven patients was 15 to 87 years (median: 81 years), three were female (age: 15–38 years), four were male (age: 81–87 years).

Tick-borne encephalitis immunisation history

Sixty-five (7.9%) of 822 patients with known immunisation status had a history of at least one dose of TBE vaccine administered at least four weeks before onset of disease, and 38 (4.6%) patients had received a complete primary vaccination series with at least three doses (Figure 4). In 19 of these 38 patients, the last dose was administered less than three years before disease onset. In five patients (three confirmed, one probable and one possible case), the last dose had

FIGURE 4

Vaccination history in patients with reported tick-borne encephalitis in Switzerland, 2005 to 2011 (n=1,055)



been administered more than five years before TBE disease; it is therefore possible that the disease in these five patients could have been prevented with a booster dose, as indicated in the package insert approved by Swissmedic [12,13]. As the coverage of vaccinated people in Switzerland is not known, it is not possible to calculate whether these rare cases are in the limits of expected vaccine failures. Of the remaining 33 patients (4.0%) with possible vaccine failure (i.e. who had received at least three doses of vaccine and the last dose within five years before disease onset), 19 patients (2.3% of 822) were classified as confirmed, three (0.4%) as probable and 11 (1.3%) as possible cases.

The median age of patients with completed vaccination series with at least three doses (n= 38) was 53 years (IQR: 37–65.5 years), that of unimmunised patients (n=757) was 46 years (IQR: 27–59 years). The frequency of hospitalisation in patients with at least three doses of TBE vaccine was lower (26 of 38, 68%) than that of unimmunised patients (592 of 757, 78%).

Discussion

Between 2005 and 2011, a total of 1,055 TBE cases fulfilling the case definition and living in Switzerland were reported to the FOPH, with a peak of 244 cases in 2006. When compared to the previous surveillance period, 1984 to 2004 [4], the average annual incidence increased from 1.4 to 2.0 in this current study. This could be due to an increase in endemic areas, in the tick population, or in human exposure through

increased outdoor activities, or a combination of these factors. Similar trends have been observed in several other TBE-endemic countries in Europe [14]. Alternatively, increased awareness of TBE may have led to increased reporting.

Still, the presented data on TBE in Switzerland are probably underestimates because of missed diagnoses and possible underreporting. If the physician does not suspect TBE, a laboratory test for TBE will not be ordered and therefore the diagnosis will be missed. This is particularly possible assuming that meningitis or ILI are the leading clinical features. In agreement with this assumption, fewer cases of TBE meningitis than cases of TBE meningoencephalitis are reported in Switzerland, which is in contrast to reports from other European countries with endemic TBE [1,11].

In comparison to other TBE-endemic countries in Europe, the incidence in Switzerland (range 1.2–3.3/100,000) is low. Especially in eastern Europe, much higher yearly incidences were reported for the period 2005 to 2009, such as those from the Czech Republic (range: 5.3–10.0/100,000), Estonia (range: 6.7–13.3/100,000), Latvia (range: 6.2–14.6/100,000) or Slovenia (range: 9.9–18.6/100,000) [14]. In contrast, the nationwide average incidence in Germany in 2005 to 2011 (range: 0.3–0.7/100,000) was lower than in Switzerland, but values in the endemic regions of southern Germany, e.g. Baden-Württemberg (range: 0.9–2.6/100,000) and Bavaria (range: 0.8–1.7/100,000) were comparable to those of neighbouring Switzerland [15]. Until the national mass vaccination campaign was started in 1981, Austria was the country with the highest recorded TBE morbidity in Europe, with incidences ranging from 3.9 to 9.0 per 100,000 in the period from 1972 to 1982 [16,17]. Not surprisingly, reported incidence rates in the non-immunised Austrian population are still in this range, whereas they dropped to about 1 per 100,000 (range for 2005–2011: 0.6–1.3) in the total population due to a vaccination coverage of at least 85% which was achieved during the past decade [17-19].

Epidemiological data from different countries should be compared with caution, as there are different reporting standards, varying case definitions and classifications as well as differences in vaccination coverage. In an effort to improve data comparability in the future, the European Commission proposed an institutional case definition for EU Member States in August 2012 [20]. In contrast to our current case classification, the new classification only differentiates between probable and confirmed cases, but does not define possible cases. Furthermore, only manifestations of CNS inflammation such as meningitis, meningoencephalitis, encephalomyelitis and encephaloradiculitis are accepted clinical TBE criteria, whereas ILI or non-specific neurological signs and symptoms do not qualify a case. Still, 81% (673 confirmed and 182 probable cases, Figure 3, panels A and B) of our 1,055 cases fulfilled the new EU case

definitions. It is of importance that not only disease is monitored, but also infection, because infection is a much more sensitive indicator than disease with respect to the epidemiology.

TBE is a disease that occurs in local endemic regions, therefore population-based incidence rates have to be interpreted cautiously [21]. Because history of tick bite was reported by less than half of the patients in this study, we decided to determine incidence rates based on the patients' cantons of residence. Local incidence rates can be much higher than the reported national average of 2 per 100,000 inhabitants; they can also be higher than incidences by canton because endemic foci do not match with political borders.

Despite convincing evidence of the vaccine's effectiveness and safety [22], TBE vaccination coverage in endemic regions of Switzerland is in the range of approximately 25–50% and therefore still low [7]. In our study population, most of the patients were not immunised against TBEV or their immunisation history was unknown (n=990; 94%). Assuming a 99% effectiveness of complete vaccination [5], TBE could have been prevented in 1,041 of the 1,055 patients. Nevertheless, 3.1% of the patients were completely immunised (at least three doses, last dose within five years before disease) and have to be regarded as cases of apparent vaccine failure. Considering that no curative treatment of TBE exists and that there is high long-term morbidity [1], more effort should be made to increase TBE vaccination coverage in risk groups.

In conclusion, ongoing surveillance of TBE and intensified efforts in promoting TBE vaccination for the population at risk will be needed in light of the increasing incidence and its considerable morbidity.

*Author's correction:

On request of the authors, subtitles in Figure 3 as well as the graph in Figure 3A were corrected on 7 April 2014.

Conflict of interest

None declared.

Authors' contributions

HpZ has collected the TBE data. MS, HpZ and UH have analysed the data. MS wrote the first draft of the manuscript. All other authors have contributed to further versions of the manuscript and approved the final version before submission.

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