



Report of the 20th annual meeting of the International Scientific Working Group on Tick-Borne Encephalitis (ISW-TBE)

ISW-TBE: 20 years of commitment and still challenges ahead



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ABSTRACT

The 20th Meeting of the International Scientific Working Group on Tick-Borne Encephalitis (ISW-TBE) – a group of neurologists, general practitioners, clinicians, travel physicians, virologists, pediatricians, ecologists, and epidemiologists – was held under the theme “*ISW-TBE: 20 years of commitment & still challenges ahead*”. On the occasion of the 20th anniversary of the ISW-TBE several key topics in TBE were extensively discussed, among them current epidemiological developments and investigations, expansion of risk areas, clinical aspects and cases, traveling and mobility, and latest news on TBE vaccination.

The main goals that have been achieved by the ISW-TBE so far are, among others, an increased awareness in endemic and non-endemic countries, an increase of vaccination rates in various countries, getting TBE acknowledged and established as a travel-related risk, and building contact with the European Centre for Disease Prevention and Control.

1. Introduction

It has now been 20 years since the International Scientific Working Group on Tick-Borne Encephalitis (ISW-TBE) kicked off its first official meeting in 1998. Since then, scientists – including neurologists, general practitioners, clinicians, travel physicians, virologists, pediatricians, ecologists, and epidemiologists – from more than 30 different European countries have convened annually to exchange results of up-to-date research, identify obstacles to increase TBE vaccination rates, and shape feasible strategies to overcome them. In all these years, the main aims of the ISW-TBE have been (i) promoting national and international scientific, medical and regulatory collaboration on TBE, (ii) stimulating and co-ordinating applied and basic research, (iii) contributing to training and educational programs in the field, (iv) providing high-quality information and promoting its appropriate distribution, (v) promoting and aligning international standards of epidemiological surveillance, and (vi) defining and promoting proposals to harmonize national and international policies on prevention. The main goals that have been achieved by the ISW-TBE so far are, among others, an increased awareness of TBE in endemic and non-endemic countries, an increase of TBE vaccination rates in various countries, getting TBE acknowledged as a travel-related risk, and building contact with the European Centre for Disease Prevention and Control (ECDC).

By publishing annual conference reports since 2004, the ISW-TBE has kept the scientific community informed about current developments in the field (Kunze et al., 2004; Kunze et al., 2005; Kunze and ISW-TBE, 2006, 2007, 2008, 2009, 2010, 2011, 2012, 2013, 2014, 2015, 2016, 2017).

On the occasion of the 20th anniversary, this year's conference was titled ‘*ISW-TBE: 20 years of commitment & still challenges ahead*’. The scientific agenda was divided into seven sessions: ‘Introduction: ISW-TBE: 20 years of commitment & still challenges ahead’, ‘Virology’, ‘Epidemiology and Environmental Factors’, including a Poster Walk,

‘Clinical aspects’, ‘New Findings’, and ‘Vaccines & Vaccination’. Selected subjects of the presentations during the conference are further described in this report. Furthermore, on the occasion of the anniversary, a new website was launched (www.iswtbe.com).

Keynote lecture: Retrospective on TBE in Austria (presentation by I. Mutz)

The first report on TBE in Europe dates back to 1931 when the Austrian physician H. Schneider described a ‘*meningitis serosa epidemica*’ of unknown etiology (Schneider, 1931). The disease regularly occurred in spring and early summer in the district of Neunkirchen, a wooded area south of Vienna. In the Far Eastern Soviet Union, the disease was described for the first time in 1934, and in 1937 the virus was isolated and tick transmission demonstrated (Zilber, 1939).

In Austria, the first virus isolation dates back to 1954 when a team headed by Dutch virologists elucidated the cause of the epidemic disease in the provinces Styria and Carinthia. In 1957, the Austrian virologists Moritsch and Krausler reported the isolation of the virus detected in the Neunkirchen area (Moritsch and Krausler, 1957). Since 1967, TBE has been looked for as the possible cause of disease in patients suffering from inflammatory disorders of the central nervous system. This approach revealed the extent of the problem and the necessity to initiate preventive measures.

In 1971, the Austrian virologist C. Kunz, together with J. Keppie from the Microbiological Research Establishment in Porton Down (England) developed the first vaccine against TBE (Club Carriere, 2006). The seed virus for vaccine preparation (termed Neudörfel) was isolated from a tick in Austria. The third passage of this virus in suckling mice was used and plaque-cloned in specific pathogen-free chick embryo. After inactivation by formaldehyde 1:2000, the final product contained human albumin as a stabilizer, aluminum-hydroxide as adjuvants, and thiomersal as a preservative. Immuno AG (founded 1960, sold to Baxter 1996) took over the vaccine production in 1975, and one year later the vaccine was registered in Austria (FSME-Immun®). The

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Table 1
TBE epidemiology – summary of poster presentations.

Country	Overall trend	No. clinical cases 2017	No. clinical cases 2016	Incidence (cases/year/100,000)	Highly endemic areas	Vaccination coverage (%)
Slovakia	Highly endemic country; increase in the last 10 years; alimentary transmission as a major risk factor	75 (among them 15 alimentary cases; 2 family outbreaks); 2006-2017: 32 alimentary outbreaks	174 (among them 79 alimentary cases)	1.38 (2017) 3.21 (2016)	Northern & central regions	Increase from 0.01% (2016, adults) to 6.5% (2017), calculated from sold vaccines
Poland	90% of cases in 2 provinces in the northeast	267	283	0.4 overall; 13.5 Podlaskie region (2016)	Northeastern provinces	?
Germany	Increase of risk areas within or nearby southern endemic regions	485	348	0 < 2.1 (52 risk areas) up to < 642 (52) up to 48.37 (52)	Bavaria, Baden-Württemberg; South Hesse, south-eastern Thuringia	School children 2012–16: 39 high, 31 other, 12 non risk areas
Czech Republic	Highly endemic country; 350-1000 cases/yr.	687	565	5-year interval 2013–17 ^a 6.1 overall (2017), Southern Bohemia 18.6, Highland 14.3, NEW: Pardubice region 9.7	Southern Bohemia	23 (2009); 16.1 in the Pilsen region; significant differences in age groups
Austria	50-100 cases/yr; (approx. 16% of the prevacc. era); risk areas spreading to alpine regions in the west	116	89	0.45 overall, 5 in unvaccinated people	Southern Styria, southern Carinthia, Lower Austria, Tyrol	82 (2017) with at least one shot

^a Robert Koch Institut: FSME: Risikogebiete in Deutschland. Epidemiologisches Bulletin 17: 161–176, 2018.

second European TBE vaccine, Encepur®, now with GlaxoSmithKline (GSK), has been available since 1991.

The recommendation of TBE immunization for persons > 6 years was implemented in Austria in 1981 and extended to persons > 1 year three years later. Since 1981, an annual mass vaccination program has been implemented with extensive social marketing measures. Thereupon, the TBE vaccination rate increased to more than 80% in the population and the number of hospitalized cases fell from several hundred to 50 to 100 per year (Kunz, 2003).

2. Session 1: ISW TBE–20 years of commitment & still challenges ahead

2.1. TBE within the Austrian armed forces (presentation by S. Sperandio)

Ticks and tick-borne diseases pose a risk to military personnel. The Austrian military has gained much experience with the disease and TBE vaccination over the years. TBE vaccination has been offered to all active soldiers, the current vaccination rate is almost 100%. Up to 70% of the conscripts are getting their first shot when marching in. Additional preventive measures include impregnation of the battle dress uniform and the boots. After combat a body check has to be undertaken by the soldiers. Since 1995, only two TBE cases occurred among the military personnel (both soldiers had refused vaccination before).

3. Session 2: virology

3.1. TBE virus in ticks other than *Ixodes ricinus* (presentation by L. Chitimia-Dobler)

The hard ticks *Ixodes ricinus*, *I. persulcatus*, *Dermacentor reticulatus* and *Haemaphysalis concinna* are known vectors of the TBE virus (TBEV) in Europe. Recently, TBEV was also detected in the newly described tick species *I. inopinatus*, which expanded its range from the Mediterranean to the north (Chitimia-Dobler et al., 2018). Both, *I. ricinus* and *I. inopinatus* collected from TBE natural foci in Central Europe show several morphological anomalies (Chitimia-Dobler et al., 2017). A study with monthly tick collections (nymphs and adult ticks) by flagging in three known TBEV foci in Germany (Haselmühl, Heselbach, and Immenstetten) was undertaken with the aim of tick identification, investigation of the seasonal activity of *I. inopinatus* vs *I. ricinus* and testing the ticks for TBEV and *Rickettsia*.

I. inopinatus was found to be active from March to October, and the seasonal activity depends on the field structure. TBEV, *Rickettsia helvetica*, and *R. monacensis* were detected in *I. inopinatus*. However, open questions remain, e.g. does *I. inopinatus* play a role in the natural TBEV transmission cycle or is there a change in the TBEV characteristics.

With being active from September to May unfed adult *D. reticulatus* showed a seasonal activity different from that of *I. ricinus*. TBEV was isolated from 12 adult ticks (total number collected: 1534).

Especially in Eastern Europe and in Russia (and also in the former Soviet Union), *H. concinna* has been in focus of research as a vector of TBEV. However, a complete distribution map for the relict tick *H. concinna* was missing until now. This gap was overcome by the publication of Rubel et al. (2018), who presented a detailed map for the entire Eurasian distribution range of *H. concinna* based on georeferenced locations.

4. Session 3: epidemiology & environmental factors

4.1. A new hot spot for TBE: a marked increase in France 2016/2017 (presentation by A. Velay)

Since 1968, about 10 TBE cases have been reported in France each year, mainly from the Alsace region (northeastern France). The

epidemiology and clinical findings among the TBE-confirmed cases were described in a prospective study over a four-year period (from January 2013 to December 2016). A total number of 54 confirmed TBE cases was reported, 4 in 2013, 10 in 2014, and 11 in 2015. In 2016, a threefold increase with 29 confirmed cases - in contrast to a mean of 8 cases during the 3 previous years - was observed. This unusually high number of cases caused a warning by the Regional Health Agency. The seasonal distribution of the recorded cases was similar to those in other European studies (Velay et al., 2018). In 2017, 17 confirmed cases were registered (preliminary results), 8 of which were imported cases (from Germany, Siberia, and Romania) vs. only one imported case in 2016. This number seems to confirm the tendency for increase.

5. Session 4: poster session walk & TBE epidemiology overview

5.1. Poster walk: epidemiological update Europe

The following countries presented an epidemiological update by a poster presentation: Austria, Czech Republic, Germany, Poland, and Slovakia (Table 1). The number of TBE cases in these countries was altogether 1645 in 2017, which is a considerable increase in comparison to 1307 cases in 2016 and 833 in 2015. However, such annual fluctuations are well-known for TBE. In Germany, 348 cases were reported in 2016 and 485 cases in 2017. Also 10 new risk areas were defined (altogether 156 defined counties now).

5.2. Project OSWALD – a novel approach for mapping the tick-borne encephalitis risk

To move away from case-based risk estimation to an exposure-based approach, a model for the description of the vector–virus–host interaction and its spatio-temporal change by means of mathematical equations will be developed. The model will be applied to identify the relevant factors for emerging TBEV-infected ticks and human TBE cases, to predict areas with increased density of TBEV-infected ticks, and to evaluate different models for forecasting human TBE cases in Germany. First results comprise the modelling of the seasonal cycles of the TBE vector *I. ricinus* with time-lagged and interval-averaged predictors (Brugger et al., 2017) as well as the seasonal forecast of *I. ricinus* nymphal density. An independent verification of the tick densities predicted for 2017 and 2018 shows the high reliability of the forecasts (Brugger et al., 2018).

6. Session 5: clinical aspects

6.1. Diagnosis, management and prevention of tick-borne encephalitis: a consensus review of the European Academy of Neurology (EAN) (presentation by E. Schmutzhard)

Providing recommendations on the prevention, diagnosis, and management of TBE, based on evidence or consensus decisions by the Task force (even when evidence-based data were not available), were the main objectives of a recent consensus review by the European Academy of Neurology (EAN). For this systematic evaluation, the relevant literature from 1970 to 2015 was searched for. The most important recommendations given in this consensus are the following (Tabá et al., 2017):

- Vaccination against TBE is recommended for all age groups > 1 year in highly endemic areas (i.e. with ≥ 5 cases/100 000/year), but also for individuals at risk in areas with a lower incidence.
- Travelers to TBEV-endemic areas should be vaccinated if their visits

will include extensive outdoor activities.

- Post-exposure prophylaxis after a tick bite is not recommended.
- A case of TBE is defined by the presence of clinical signs of meningitis, meningoencephalitis, or meningoencephalomyelitis with cerebrospinal fluid (CSF) pleocytosis ($> 5 \times 10^6$ cells/l) and the presence of specific TBEV serum immunoglobulin M (IgM) and IgG antibodies, by the presence of CSF IgM antibodies, or TBEV IgG seroconversion.
- A positive polymerase chain reaction in the blood is diagnostic in the first viremic phase, but it is not sensitive in the second phase of TBE with clinical manifestations of CNS inflammation.
- Lumbar puncture should be performed in all patients with suspected CNS infection unless there are contraindications.
- Imaging of the brain and spinal cord has a low sensitivity and a low specificity, but it can be useful for differential diagnosis.
- No effective antiviral or immunomodulating therapy is available for TBE; therefore the treatment is symptomatic. Patients with a potentially life-threatening meningoencephalitis or meningoencephalomyelitis should be admitted to an intensive care unit. In the case of brain edema, analgesication should be deepened. Osmotherapy and application of corticosteroids are not routinely recommended. If intracranial pressure is increased, therapeutic hypothermia or decompressive craniectomy might be considered. Seizures should be treated as any other symptomatic epileptic seizures.

7. Session 6: new findings

7.1. TBE in a naturally infected sheep (presentation by B. Böhm)

In veterinary medicine, sporadic TBE cases in wild and domestic animals have been reported. However, a vast number of wild and domestic animals have tested positive for TBEV antibodies. The probably first report of a natural TBEV infection with clinical manifestation in a sheep in Europe was presented (Böhm et al., 2017). The 5-month-old lamb became infected most likely on the pasture, however, the cause of the clinical manifestation in the lamb remains unclear. The animal suffered from ataxia, torticollis, tremor, nystagmus, salivation, and finally somnolence with inappetence and recumbency. The histopathology of the brain showed mild to moderate necrotising, lymphohistiocytic, and granulocytic meningoencephalitis with degeneration and necrosis of neurons, neuronophagic nodules and gliosis, but no cytoplasmatic or intranuclear inclusion bodies, no scrapie- or listeriosis-associated histopathological lesions. Pronounced neuronophagia and numerous glial nodules indicate a protracted course of disease, which might explain the negative outcome of the immunohistochemistry since a rapid virus clearance is typical for TBEV in humans and animals.

Sheep or goat flocks, especially those that are used for the production of raw milk or raw milk products and live on pastures with possible tick contact, should be tested for TBEV, because these can be the source of transmission of so-called alimentary TBE to humans (Böhm et al., 2017). In sheep with neurological symptoms, TBEV infection should be considered, especially in TBE risk areas.

7.2. National and international leisure time and travel habits (presentation by S. Mayrhofer)

The world's most visited region is Europe with more than 616 million international tourist arrivals in 2016 (+2% vs. 2015; UNWTO (World Tourism Organization), 2017). About 126 million arrivals were registered in Central/Eastern Europe (increase of 4%). Many destinations enjoyed strong results, including Slovakia (+17%), Bulgaria (+16%), Romania and Lithuania (both +11%), Poland and Czech

Republic, both with an increase of 4%. All those countries have highly TBEV-endemic areas. More than half (53%) of the international tourists report as main travel purpose leisure time, recreation, and holidays (UNWTO (World Tourism Organization), 2017). 31% of travelers (EU-28) reported to spend some time in nature (in the mountains, at lakes etc.), and 12% do sports (Flash Eurobarometer, 2016), activities related to an increased TBE infection risk. International tourist arrivals worldwide are expected to increase by 3.3% per year from 2010 to 2030 to reach 1.8 billion by 2030 (UNWTO (World Tourism Organization), 2011). Arrivals in emerging destinations are expected to increase at twice the rate of those with advanced economy (+4.4% vs. +2.2% a year).

8. Session 7: vaccines & vaccination

8.1. TBE vaccination in risk groups (presentation by U. Wiedermann)

Some sub-groups of people have been observed to respond poorly to vaccines, putting them at an increased risk for vaccine-preventable diseases (Painter et al., 2015), e.g. patients with allergies or obesity. A recent study with (i) allergic patients (allergic group), (ii) allergic patients receiving maintenance doses of specific immunotherapy (SIT; SIT group), and (iii) non-allergic controls who had received TBE booster vaccine showed that levels and kinetics of neutralizing TBE-specific antibodies (reflecting protection) were not significantly different among the three groups (Garner-Spitzer et al., 2018). The allergic group showed Th2 polarization pre-booster as indicated by increased TBE-specific IgG1 and elevated mitogen-induced IL5 production. Alum-adjuvanted TBE vaccine led to Th2-biased immune responses in the controls, but not to further enhancement of Th2 polarization in the allergic and SIT group. Furthermore, in the SIT group the cellular parameters reflected the induction of immunomodulation due to increased regulatory T cells, elevated baseline IL10, and lack of TBE-specific IL5. Importantly, these cellular regulatory responses did not limit the ability to mount sufficient TBE-specific antibodies after the booster.

TBE booster vaccinations were immunogenic and safe in both the allergic and the SIT group and contributed to balanced immune responses. All allergic patients, even when undergoing SIT, should be vaccinated without hesitation and at regular intervals according to standard recommendations (Garner-Spitzer et al., 2018).

9. Conclusion

After 20 years of work and commitment of the ISW-TBE, substantial progress has been achieved. However, TBE is still underdiagnosed and/or underprevented in several European countries, which are confronted with increasing numbers of TBE cases.

Despite the fact that highly effective vaccines are available, this most effective way of prevention is still underused in the majority of the countries with TBE, even in highly endemic areas. The ISW-TBE recommends vaccination to everyone living in or traveling to TBEV-endemic areas and getting exposed to ticks there.

Hence, the work of the ISW-TBE will be continued. There is a clear need for keen awareness, comprehensive surveillance, and improvement of diagnostics, and also for international cooperation to look beyond natural foci and national borders. Increasing the problem awareness also outside TBE-endemic regions in the future is one of the major challenges for the ISW-TBE, especially while living in a changing world with all its serious issues.

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Ursula Kunze*, the ISW-TBE¹,
Institute for Social Medicine, Center for Public Health, Medical University of Vienna, Kinderspitalgasse 15, A-1090, Vienna, Austria
E-mail address: ursula.kunze@meduniwien.ac.at

* Corresponding author.

¹ Horst Aspöck, Daniela Bartkova, Dietmar Beier, Zusana Belchova, Petra Bogovic, Brigitte Böhm, Livia Borsoi, Katharina Brugger, Roswitha Bruhns, Lidia Chitimia-Dobler, Renata Ciupek, Thomas Csank, Daniel Desgrandchamps, Andrey Dmitrovskiy, Gerhard Dobler, Silvius Frimmel, Sara Gredmark Russ, Martin Haditsch, Eva Jilkova, Olaf Kahl, Jana Kerlik, Peter Kimmig, Kersti Kink, Benno Kohlmeier, Lenka Krbkova, Thomas Krech, Suvi Kuivanen, Michael Kunze, Tomas Laskus, Lev Levanov, Leide Liepina, Ute Mackenstedt, Rasti Madar, Sonia Mayrhofer, Tomas Molcányi, Masyar Monazahian, Ingomar Mutz, Rainer Oehme, Martin Pfeffer, Eva Maria Pöllabauer, Lidija Prtenar Prislov, Daiva Radizsauskiene, Franz Rubel, Norbert Satz, Polona Savic, Erich Schmutzhard, Zoran Simonovic, Sylvia Sperandio, Gerold Stanek, Robert Steffen, Franc Strle, Jochen Süß, Malin Veje, Aurelie Velay, Janna Vogelgesang, Sanja Vuzem, Melanie Walter, Ursula Wiedermann-Schmidt, Joanna Zajkowska, Kai Zilmer, Werner Zenz, Milda Zygutiene