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Report of the 19th Annual Meeting of the International Scientific Working Group on Tick-Borne Encephalitis (ISW-TBE) – TBE in a changing world

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ABSTRACT

The 19th meeting of the International Scientific Working Group on Tick-Borne Encephalitis (ISW-TBE) – a group of neurologists, general practitioners, clinicians, travel physicians, virologists, pediatricians and epidemiologists–was held under the title *"TBE in a changing world"*. Key topics within virology, current epidemiological developments and investigations, expansion of risk areas, clinical aspects and cases, traveling and mobility, vaccination rates, and latest news on vaccination were presented and extensively discussed. Over the past four decades, TBE has become a growing public health challenge in Europe and parts of Asia. It may be considered a complex eco-epidemiological system, characterized by an intricate interplay between the virus, ticks and tick hosts on the one hand and human exposure strongly influenced by socioeconomic conditions on the other hand. Although the facts are simple – vaccination is the best prevention – the socioeconomic conditions keep changing, and with them the ability or willingness of people to get vaccinated.

1. Introduction

It has now been 19 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 physicans, virologists, pediatricians, ecologists and epidemiologists–from more than 30 different European countries have convened annually to exchange the results of up-to-date research, identify obstacles to increasing vaccination rates, and shape feasible strategies to overcome them. In all these years, the main aims of the ISW-TBE have been promoting national and international scientific, medical and regulatory collaboration on TBE, stimulating and co-ordinating applied and basic research, contributing to training and educational programs in the field, providing high-quality information and promoting its appropriate distribution, promoting and aligning international standards on epidemiological surveillance, and defining and promoting proposals to harmonize national and international policies on prevention. Main goals that have been achieved by the ISW-TBE are, among others, an increased awareness of TBE 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 (ECDC).

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

Hence, this year's conference was titled '*TBE in a changing world*'. The conference agenda was divided into seven sessions over one and a half days: 'TBE in a changing world', 'Virology', "Epidemiology and Environmental Factors" (including a Poster Walk), 'Clinical aspects', 'New Findings' and 'Vaccines & Vaccination'. Selected subjects of the presentations and discussions during the conference are described in this report.

2. Session 1: keynote lecture

2.1. Living in a changing world – which role do vaccinations play? (Presentation by N. Barrett)

Vaccines against infectious diseases have been one of the major success stories in medical history. Vaccination has saved millions of lives over the last 50 years.

In the need for better vaccines the existing vaccines must be improved, the number of necessary shots reduced and vaccine delivery enhanced (nasal, oral, transdermal). The principles and the rationale of active and passive immunisation can be utilised in a range of non-infectious disease targets. As human life expectancy substantially increases, vaccination can make contributions to healthy aging with respect to oncology, neurodegenerative or metabolic diseases. There is still need for new prophylactic vaccines against a range of significant infectious diseases such as Respiratory syncytial virus, Group A Streptococcus or bacterial diarrheal diseases.

Therapeutic vaccines will be an important development in the campaign to treat and cure chronic infectious diseases such as HIV (human immunodeficiency virus) and HBV (hepatitis B virus). Passive immunisation (hyperimmune globulin, monoclonal antibodies) may be an important prophylactic and therapeutic approach for nosocomial infections and selected emerging viral diseases. The development of novel immunological interventions (adjuvants, cell therapies, check-point inhibitors, etc.), in combination with standard therapies, may open the door to a new era of cancer treatment. A multitude of innovative combination therapies are being developed to overcome immune tolerance to tumor-associated antigens

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and generate synergistic immune response in the form of effector T cells following vaccination; these combinations have the potential to make vaccines a highly potent therapeutic option for a multitude of cancer targets.

Financing the availability of even the already existing vaccines will be a continuous major challenge in our rapidly changing developed world and even more in the developing countries.

3. Session 2: virology

3.1. Zika and Chikungunya today! New emerging flavi-and alphaviruses tomorrow? (Presentation by O. Kistner)

More than 100 Alphavirus and Flavivirus species have been described over the last hundred years. Out of about 35 alphaviruses at least 10 can be pathogenic for humans, e.g. Chikungunya virus, Eastern/Venezuelan/Western equine encephalitis virus, Mayaro-virus, O'Nyong-Nyong-virus, Ross-River-virus and Sindbis-virus. Among more than 70 described flaiviviruses at least 40 are pathogenic for humans, e.g. tick-borne encephalitis virus (TBEV), Powassan virus, Kyasanur Forest disease virus (Monkey Fever), Murray Valley encephalitis virus, West Nile virus, Usutu virus, Yellow fever virus and Zika virus.

Several (re-)emergences of Alphavirus and Flavivirus infections in humans have been reported in the last 20 years. In recent years, a couple of alphaviruses and flaviviruses re-emerged (e.g. Yellow fever virus), conquered new continents (e.g. West Nile virus, Zika virus, Chikungunya virus in the Americas) or increased their pathogenic potential from mild to more severe (e.g. Chikungunya virus, Murray Valley encephalitis virus, Zika virus). Furthermore, well-known alphaviruses and flaviviruses of remote regions appear to have increased their distribution (e.g. Chikungunya virus, Zika virus, Kyasanur Forest disease virus) or their human pathogenicity (e.g. Usutu virus). As a result of these developments, more diligent surveillance of human and animal alphaviruses and flaviviruses, further investigations on certain virological parameters (e.g. mutations) and ecological factors (expansion or change of vectors) and finally the development of new vaccines − including the introduction of robust and reliable production technologies − are crucial.

Despite high morbidity and substantial mortalitiy only few vaccines against these viruses have been developed so far, namely TBEV, Japanese encephalitis virus, and Yellow fever virus vaccine. Vaccines under development or for restricted use include Equine encephalitis, Dengue, West Nile, Chikungunya, and Ross River.

4. Session 3: epidemiology & environmental factors

4.1. First human case of tick-borne encephalitis acquired in the Netherlands, July 2016 (Presentation by J.de Graaf and V. Hira)

Autochthonous human TBE infection had not been reported in the Netherlands and all TBE cases in the Netherlands so far were considered imported from endemic regions. Shortly after the first report about Dutch TBEV-positive ticks by the Dutch National Institute for Public Health and Environment the first human case of TBE acquired in the Netherlands was detected (de Graaf et al., 2016). Even though the liquor was negative for anti-TBEV IgM antibodies, the high serum IgM and IgG levels in an unvaccinated patient, combined with a typical biphasic clinical course and TBEV detected in the tick collected from the patient (verified by qRT-PCR), confirmed the diagnosis of TBE.

This clinical case confirms the repeated occurrence of TBE in so-called TBEV-free regions, consequently there is a clear need of increased awareness among health care workers with respect to surveillance and diagnosis of TBE in such areas.

4.2. Alimentary transmission of TBE in Slovakia (Presentation by R. Madar)

As the consumption of unpasteurized milk and dairy products of goat, sheep and cow milk is very popular in Slovakia, outbreaks of alimentary aquired TBE have often occurred. The largest outbreak so far with 660 cases had happened in Rožňava, South-Eastern Slovakia, in 1951. In the past 5 years, 22 outbreaks in various parts of the country caused 148 alimentary cases. Thereby, alimentary cases are responsible for almost 23% of all TBE cases in Slovakia.

5. Session 4: postersession 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, Lithuania, Poland, Slovakia, Switzerland, and Sweden (Table 1). Altogether, with 1900 cases in 2016, a considerable increase was observed in these countries in comparison to 1258 cases in 2015. However, such annual fluctuations are well-known for TBE. The fact that 35 of 348 registered cases in Germany were reported outside of the known TBE risk areas is striking.

6. Session 5: clinical aspects

6.1. TBE MRI results and specific clinical presentation (Presentation by J. Zajkowska)

The mechanism of blood-brain barrier (BBB) breakdown during TBE, as well as TBEV entry into the brain, is still unknown. In an in vitro BBB model, the virus crossed the BBB via a transcellular pathway without compromising the integrity of the cell monolayer. These results indicate that human microvascular endothelial cells may support TBEV entry into the brain without altering BBB integrity (Palus et al., 2017).

Few autopsy reports of fatal TBE cases demonstrate that the most affected areas in the brain are the cerebral and cerebellar cortex, basal ganglia, thalamus, substantia nigra, pons, medulla oblongata, and the spinal cord (Gelpi et al., 2006). A recent pilot study revealed that glucose hypometabolism was present in 7 out of 10 TBE patients reflecting neuronal dysfunction in predilection areas of TBEV infiltration responsible for development of clinical signs and symptoms (Dietmann et al., 2016).

To combine symptoms with lesions in the brain, the provision of a magnetic resonance imaging (MRI) is not obligatory, but it may support the