Journal of BTHA, Volume XII, 2008

Tick-borne Encephalitis (TBE) in East Asia

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Abstract

Currently data available about the epidemiology of TBE in East Asia is limited. TBE appears to be endemic in several regions of East Asia. Risk assessment for travellers and the need to become protected by vaccination is hampered by the limited data about TBE in these areas. It has been shown that vaccination with TBE antigens derived from Western subtype of TBE virus induces cross-reactive immune response to Siberian and the Far-Eastern subtypes of TBE virus.**1-3** Unequivocally, travellers to the Russian part of East Asia should become vaccinated, but vaccination can also be recommended for travellers to northern parts of Mongolia and to the northern and north-eastern parts of China.

The epidemiology of TBE virus, transmitted by ticks, is well described for Europe. The northernmost occurrence in Europe is in the region of Kokkola (Finland), which is only 300 km south of the polar circle. The Western restriction is in the Alsace and the West Alps of France. The TBE virus also is endemic south of the Alps and infections have been reported from the Latium, a region in Central Italy. During the last 10 years, the number of reported cases has been increased in Central Europe (e.g. Germany, Czech Republic), the Baltic countries and the European part of Russia. Although there is no uniform case definition for TBE in Europe and notification is not mandatory in every European country, the epidemiology of TBE virus and the appearance of new foci is well reported in the national and international literature**4,5** and by national reference centres.

The European TBE virus subtype generally produces a biphasic febrile illness starting with fever lasting 2-7 days and followed by an afebrile and relatively asymptomatic period, lasting 2-10 days. In approximately 30 % of patients infected, the second phase of disease develops and this phase represents symptoms and signs of meningitis or meningoencephalitis.**6** Compared to Europe, less data are available on TBE epidemiology in Asia, except that most of TBE cases occur east of the Ural in Siberia and Far Eastern Russia (about 10,000 cases annually.**6** This geographic differentiation into Siberia and Far Eastern Russia is also used for the classification of two subtypes of the TBE virus based on molecular characteristics, the Siberian and the Far Eastern subtypes in addition to the European subtype.**6** The European TBE virus subtype mostly is transmitted by the tick *Ixodes ricinus,* while the Siberian and the Far Eastern subtypes are generally transmitted by *I. persulcatus* (and also by other tick species e.g. *I. ovatus*).

Until recently, the knowledge about TBE virus in Asia was very limited with the exception of Russia. This review is aimed to summarise the epidemiology of the TBE virus in East Asia, to evaluate the risk for travellers to acquire TBE and to possibly become protected by vaccination.

Japan

The first case of TBE has been reported from the southern part of Hokkaido in 1993 and occurred in a farmer's wife.**7** Epidemiological investigations revealed that infections have happened in human individuals, cows, goats and dogs in closer

surroundings to this index case,**8** indicating that the south of the island is an endemic area for TBE virus. Sequencing of various Japanese TBE virus isolates revealed a high homology to isolates from Far Eastern Russia (Far Eastern subtype).**9** It was concluded that the main vector is *I. ovatus*.**10** Molecular epidemiology studies indicate that the TBE virus is at least endemic in Japan since 1300 B.C. E. and multiple exchanges must have occurred between Far Eastern Russia and Japan.**11** This is in agreement with the finding that ticks of the genus *Ixodes* have been found on migratory birds.

Mongolia

In 2003, an epidemiological survey was carried out in two northern provinces of Mongolia to analyse the seroprevalence of pathogens transmitted by ticks. Among adults in the provinces Selenge and Bulgan, a TBE prevalence of 5.1 % and 1.0 % was measured respectively.**12** Positive results in ELISA were confirmed by neutralization assay. TBE virus strains have yet not been isolated in Mongolia.

China

Knowledge on TBE epidemiology in China was limited until recently, because most of the reports are in Chinese and have not been published in international journals. A recent published review article delivers insight into the epidemiology of the TBE virus in various regions of China.**13** Seroepidemiological investigations in humans and animals revealed that TBE virus is endemic in the northeast of China (provinces Heilongjiang and Jilin), in the north (Inner Mongolia) and in the north-west (Province Xinjiang). In addition, human TBE cases have been reported since the 1940ies from north-eastern regions of China. In 1952, incidence rates were notified of 3.2 per 100,000 inhabitants from the province Heilongjiang. Several TBE virus strains have been isolated from ticks and from ill humans and molecular analyses of the genome showed a high similarity to strains from Far Eastern Russia. The molecular characterisation of Chinese TBE virus isolates is confirmed by the high mortality rate of 25 %, which is a typical feature of the Far Eastern subtype.**4** *I. Persulcatus* is supposed to be the main vector in China.

Seroepidemiological studies in humans indicate a high infection rate in the region of Linzhi in the south of Tibet. A high rate of seropositive serum samples from mammals and humans is also reported in region of higher altitude in the province of Yunnan in the south-western part of China. However, several of these studies may have been carried out with diagnostics not unequivocally discriminating with antibodies to other flaviviruses like Japanese encephalitis virus, which are known to cross-react. Thus, as long as molecular characterized viral clones are not available, these two regions should be regarded as possible TBE endemic regions.**13**

South Korea

No TBE case has been reported yet from South Korea. Admittedly, the number of patients with encephalitis by unknown agents is increasing each year. This has prompted scientists to determine the possible presence of TBE virus in Korea. TBE virus could be isolated from ticks and field mice collected in northern regions of South Korea. Possibly, the ticks *Haemaphysalis longicornis* and *I. nipponensis* are the main vectors in South Korea. Molecular analyses revealed Korean TBE virus isolates belonging to the European subtype.**14**

Conclusion

The current knowledge on TBE in East Asia is still incomplete. There is no compulsory registration of disease, no uniform case definition and no valid identification and registration of cases in East Asia, probably causing underestimation of the medical importance. With increasing intercontinental travel to areas of endemicity, the risk for tourists of acquiring TBE will increase. Serodiagnosis for TBE is hampered in some of East Asian regions by the presence of other flaviviruses, e.g. Japanese encephalitis virus due to cross-reactivity among antibodies directed to the viral envelope glycoproteins. **4** Thus, exact diagnosis needs the access to neutralisation assays and/or PCR-based genomic analyses. Table 1 and Figure 1 outline our current knowledge on TBE in East Asia. Travellers to countries with marked zones in grey should consider TBE vaccination – depending on which region they travel to and on their outside-activities.

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Declaration of interests
The author is an employee of Novartis Vaccines, producing TBE vaccines.

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Table 1
Countries in East Asia with investigations in TBE

Spectrum of data available on TBE/TBE virus	Russia	Mongolia	China	Korea	Japan
TBE virus isolated	Yes	No	From some regions	Yes	Yes
Genome sequences available	Yes	No	Yes	Yrs	Yes
Human cases reported	Yes	No	From some regions	No	From Hokkaido
Human serology data available:					
Neutralisation test	Yes	Limited	No	No	Limited
ELISA	Yes	Limited	Limited	No	Limited
Animal serology data available	Yes	No	Yes	No	Limited

Figure 1
Geographic section of East Asia

Countries, in which TBE virus has been identified, are marked in grey (Russia, Mongolia, China, South Korea). Regions of these countries where TBE endemicity has been proven, are hatched (Hokkaido, northern parts of South Korea, Mongolia and China). The Chinese provinces Tibet and Yunnan, which are probable TBE endemic areas are dotted.