衞生防護中心
Centre for Health Protection

Scientific Committee on Vector-borne Diseases

Prevention of Tick-borne Encephalitis in Hong Kong

Purpose

Tick-borne encephalitis (TBE) is a serious illness with an average of 8,755 cases reported annually in Europe and Russia in the last two decades (1). It is also endemic in areas outside Europe such as China and Japan. This paper provides an overview of tick-borne encephalitis, the global situation, assesses the potential risk to Hong Kong and recommends preventive and control measures against this disease.

The Causative Agent (2,3)

2. Tick-borne encephalitis virus (TBEV) belongs to the genus flavivirus in the family ***Flaviviridae.*** Flaviviruses are enveloped viruses with a diameter of 40 to 50 nm, containing a positive-stranded RNA genome of about 11,000 bases. The TBEV genome codes in one open reading frame which is subsequently cleaved into three structural and seven non-structural proteins. The viral genome RNA is itself infectious and produces viral particles when introduced into susceptible cells. The TBEV bears similar homology with other viruses in this genus, including dengue virus, yellow fever virus, Japanese encephalitis virus and West Nile virus.

3. There are three subtypes of TBEV: the European, Siberian and Far Eastern, which are carried by different vectors. The European subtype, carried by *Ixodes ricinus*, can be found throughout Europe and Russia (4). *Ixodes persulcatus* is the vector for the Siberian and Far Eastern subtypes and can be found in an area extending from eastern Europe to China and Japan (5,6).

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Ecology of Tick-borne Encephalitis

The Vector and Host

4. *Ixodes ricinus* and *Ixodes persuculatus* are the two commonest vectors responsible for TBEV transmission. *Ixodes ricinus* is the principal vector for the European subtype of TBEV which is widespread in central and western Europe, while *Ixodes persuculatus* is responsible for the Far Eastern and Siberian subtypes. Other vectors include *Ixodes ovatus, Ixodes nipponensis, Haemaphysalis concinna, Haemaphysalis longicornis and Dermacentor silvarum* could be found in southwest China, Taiwan, Japan and South Korea. These are suspected to be vectors transmitting TBE in different Asian countries (7-10). The main hosts of TBEV are small rodent species, while other species such as roe deer, goats, sheep, cows and birds may also carry the virus (11).

Transmission Cycle

5. The TBEV is transmitted to human by a bite from an infected tick. Human is regarded as a dead-end host and has minimal potential of transmitting the virus to non-infected ticks due to the low level of virus in blood during the viraemic phase (12). Humans can also be infected by ingesting unpasteurized milk and milk products from infected animals. Rare cases of transmission due to slaughtering of likely infected goats, blood transfusion and breast feeding has also been reported (13,14). No human to human transmission has been described (15).

6. Among ticks, the virus could be transmitted sexually, transovarially, transtadially (through the stages of larvae, nymph and adult) and during co-feeding with a non-infected tick on the same host (6,16). A tick feeds only once during each stage of their development before proceeding to the next stage. Therefore, a seasonal pattern of TBE incidence corresponds to periods of tick activity. Most cases occur between March and November, with two peaks during June to July and September to October.

Clinical Presentation and Management

7. The clinical symptoms of tick-borne encephalitis usually occur after a median of 8 days following the bite of a tick (17). However, the two main subtypes of TBEV cause clinical diseases with different features and mortality rates.

8. The European subtype (also known as Central European encephalitis virus) shows a biphasic course in the majority of patients (18,19). In the first phase, which usually lasts for 5 days, common symptoms include fever, fatigue, general malaise, headache and body pain. Blood tests would

reveal leucopenia, thrombocytopenia and slightly raised serum transaminases. This is followed by an asymptomatic period of 7 days before the second phase. In the second phase, clinical symptoms range from mild meningitis to severe encephalitis which is indistinguishable from other forms of acute viral meningoencephalitis. Cerebrospinal fluid would show moderate pleocytosis and non-specific changes could be seen on both magnetic resonance imaging and electroencephalogram. The case fatality rate of this subtype of infection is approximately 1 to 2 % (20).

9. The Far Eastern subtype usually shows a more prolonged and severe clinical course. The disease is monophasic with an abrupt onset of fever, headache, flushing of the face and neck, conjunctival injection, somnolence, vomiting, dizziness and myalgia. These are followed by encephalitic syndromes with severe pain in the arms and legs, back, hyperesthesia, asymmetrical paresis of cranial nerves, tremor, ataxia, sensory disturbances and unconsciousness. Permanent paresis occurs in 5 to 30% of cases and the case fatality rate ranges from 5 to 40% (20,21).

10. A chronic form of tick-borne encephalitis has been reported to be associated with the Siberian subtype of TBEV (22). There are two forms: a Parkinson's-like disease with progressive muscle atrophy, mental deterioration and even death and another form associated with hyperkinesias and epileptoid syndrome.

11. Currently, there is no specific anti-viral treatment available for tick-borne encephalitis and only supportive treatments are given to patients. However, there is an effective vaccine available which became the mainstay for prevention of the disease.

Laboratory Diagnosis (4,14)

12. Definitive diagnosis of tick-borne encephalitis can be demonstrated by:

(a) isolation of virus by viral culture; or
(b) detection of viral antigen in serum; or
(c) detection of viral genome in serum or cerebrospinal fluid (CSF); or
(d) serology tests.

13. Viral antigen could be detected by enzyme immunoassays, but these are not routinely commercially available. Viral RNA could be detected in serum and CSF by reverse-transcriptase-polymerase chain reaction (RT-PCR)(23,24). Together with virus isolation, these can only be used during the first phase of disease. However, for virus isolation, there is a concern on laboratory safety, as the hazardous nature of the viral agents requires handling of live viruses in biosafety level 4 facilities.

14. During the non-viraemic second phase, the detection of both TBEV-specific IgM and IgG in serum by enzyme-linked immuno-sorbent assays is confirmatory. The antibodies could also be detected in CSF several days later and in all cases by day 10. However, it should be noted that cross-reaction with other flavivirus infection or previous vaccination may complicate the diagnostic process. Furthermore, the reagents are not readily commercially available.

Global Epidemiology

15. TBE is endemic in temperate regions of Europe and Asia, mostly in forests and wooded areas at altitudes up to 1,400 m. The geographical belt widely spreads across large parts of eastern and central Europe, Russia, and northern parts of China and Japan (Figure 1). TBE is now endemic in regions of 27 European countries (25). Around 10,000 – 12,000 cases of TBE are reported worldwide and new risk areas are discovered every year (26). The incidence rate is higher between March and November, with peaks during early and late summer when ticks are active.

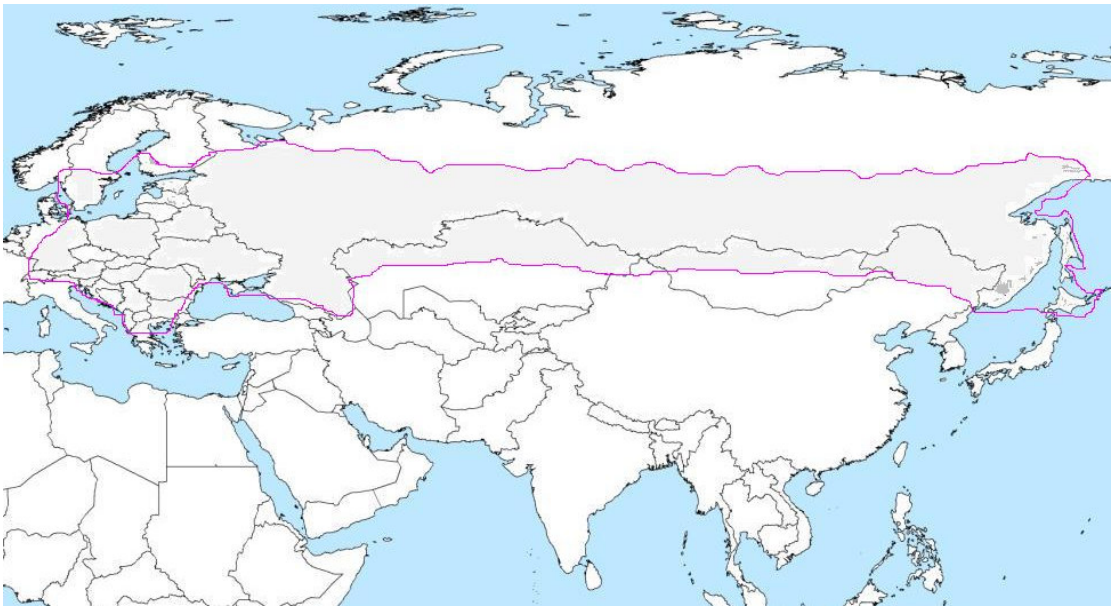

Figure 1 – Geographical border for tick-borne encephalitis endemic areas

Situation in Europe and Russia

16. In Europe, TBE endemic areas exist primarily in the central and eastern parts, the Baltic States, and Russia. New endemic foci have been found in Sweden, Germany and Norway (27). For the past decade, the incidence of TBE has increased significantly in most central and eastern European countries where TBE is endemic. TBE is a notifiable disease in 16 European countries, including Austria, the Czech Republic, Estonia, Finland, Germany, Greece, Hungary, Lativia, Lithuania, Poland, Slovak Republic, Slovenia, Sweden,

Norway, Russia and Switzerland (1). Russia by far has the highest incidence of TBE with a total of 54,526 cases reported during 1998 to 2007. Between 1990 and 2007, a total of 157,584 TBE cases were reported in 19 European countries with reliable data, resulting in an average of 8,755 cases per year (1). In 2009, preliminary data showed that there were 7,122 cases reported from 17 European countries and Russia, which was higher than the annual number reported in 2007 and 2008 (5,460 cases and 5,243 cases, respectively) (27). It has been suggested that the increase in TBE cases in these regions may be attributable to heightened international awareness and improvements in diagnosis and surveillance in certain countries (13). Moreover, the changing epidemiology may also be due to other factors such as weather and climate, changes in habitat, and increased human activity in affected areas (28-30).

Situation in Asia

17. Tick borne encephalitis virus is detected in the forested regions of China and Japan. TBE is a disease known to be endemic in the northeastern part of China. The geographical range of TBE is closely related to the distribution of its predominant tick vector ***Ixodes persulcatus,*** which is widely found in northeast China (31). There are two natural foci, namely the Northeast focus and the Xinjiang focus. The disease is reported mainly in the northeastern forest areas of Changbai Mountains in Jilin Province, Daxingan Mountain in Inner Mongolia, and Xiaoxingan Mountain in Heilongjiang Province. Moreover, TBE is intermittently reported in the forest regions in the northern slope of Tianshan Mountain and the southern slope of the Altai Mountains in Xinjiang Uygur Autonomous Region (31). Some reports of TBEV with serological evidence are also found in both western and southwestern parts of China including Tibet and Yunnan. In Yunnan, unlike northeastern China, ***Ixodes ovatus*** is a dominant tick species (51.3%) and a possible vector for TBE in the western mountainous regions (7,32).

18. The first human TBE case in China was registered in 1943. TBE is not a nationally statutory notifiable disease, except in Heilongjiang province where the regional government classified TBE as a compulsory registration disease of category B (31). In Heilongjiang, the area has been considered the most important TBE endemic region in the country, with 2,202 cases reported between 1980 and 1998. The incidence peaks every 5 to 7 years (1,33). TBE cases in China mostly occur in late April, and peak during late May and early June. This positively correlates with the seasonal peak of tick activity. Most of the people infected with TBE were forest workers, or their family members (33).

19. More recently, TBE cases have been identified in Japan. In 1993, a case of TBE was reported in Oshima, the southern part of Hokkaido. Since 1992, the TBE virus has been isolated from the sera of dogs, rodents and horses collected in the area (8). In Mongolia, some endemic areas are located in the

north of the country. TBEV causes approximately 20 cases every year, and 75 cases have been reported from 2005 to 2008 since the disease was registered at national level in 2001 (34). In South Korea, the TBE virus was isolated only recently in ticks and mice, and human TBE cases have not yet been reported so far (1).

Situation in Hong Kong and other regions

20. Outside Europe and Asia, tick-borne encephalitis is rarely reported. For example, in the United States, there are only few sporadic reports on TBE cases from travellers visiting TBE endemic areas (35). In Hong Kong, TBE is not a statutory notifiable disease. No human cases of TBE have ever been reported to the Department of Health so far.

Prevention and Control of TBE in Endemic Countries

21. In some endemic countries, TBE is not a statutory notifiable disease and surveillance data are still incomplete. Prevention strategies for TBE in endemic areas mainly focus on pre-exposure immunisation and avoidance of tick bites. In different endemic areas, the risk for infection after a single tick bite varies between 1:200 and 1:1000 (26).

22. The International Scientific Working Group on Tick-borne Encephalitis (ISW-TBE), a group comprised of internationally recognized scientific experts from TBE endemic countries, has been set up since 1998 to promote national and international exchange on the prevention and control of TBE and promote international awareness of TBE. The ISW-TBE recommended TBE vaccination in most endemic countries. Austria is by far the only European country to have a routine vaccination program and a surveillance system that has been in place for 30 years. Before the TBE vaccination campaign was introduced in 1981, Austria had the highest recorded morbidity of TBE in Europe, with up to 700 hospitalized cases annually (36). The increase in vaccination coverage since 1981 has resulted in a steady decline in the incidence. The vaccination coverage of the Austrian population has also increased from 6% in 1980 to 86% in 2001 (36). In other countries without routine vaccination programs, such as the Czech Republic and Germany, the incidence rates remained high and increased over time (37,38).

23. Two TBE vaccines are currently licensed and available in Europe, namely Encepur® and FSME-IMMUN®. Both are inactivated vaccines and provide safe and reliable protection against TBE infection. The recommended primary vaccination series consists of three doses with an interval of 1 to 3 months between the first two doses, and third dose given between 5 and 12 months after the second dose. For a rapid schedule, the second dose can be given 2 weeks after the first. The protection is up to 97% after initial two doses. Reactions following vaccination are usually mild and transient, such as

headache, muscle pain and nausea (39).

24. The vaccines are now widely used in over 25 European countries (38). In Mainland China, a licensed purified and inactivated vaccine derived from the Senzheng strain in 2001 is currently available for protection of those at risk. People with frequent exposure to forested areas such as forest workers are advised to receive vaccination in TBE endemic areas in the Mainland (7,31).

TBE vaccination in non-endemic countries

25. For unvaccinated travellers to endemic areas, the estimated risk for contracting TBE during tick transmission season is approximately 1 case per 10,000 person-months (40). This estimated risk varies with the degree of unprotected outdoor exposure in forested areas. The World Health Organization recommends TBE vaccines for at-risk travellers only, and booster doses are required to maintain immunity and should be given every 3 years if there is continuing risk (41).

26. In non-endemic countries outside Europe such as Canada, FSME-IMMUN® is registered and available for travellers visiting TBE high-risk areas (42). In the United States, where TBE vaccines are not licensed or available, travellers who are at high risk of exposure, e.g. working or camping in the forested areas for an extended period of time, may get vaccinated in Europe or Canada (43).

Prevention of Tick-borne Encephalitis in Hong Kong

Preventive measures for travellers

27. No local case of tick-borne encephalitis has been reported in Hong Kong. but travellers visiting infested rural areas of endemic countries may acquire the infection. During their stay in an endemic area, travellers should avoid tick bites by wearing long-sleeved clothes and trousers. They should apply DEET containing insect repellent on exposed body parts and permethrin containing insecticide spray onto clothes. If ticks are found to be attached to the body, they should be removed as soon as possible by using a pair of tweezers or tick remover to grasp the tick near the head region as close to the skin as possible and care must be taken not to squeeze the contents of the stomach into the site of the bite. In addition, travellers should avoid consumption of raw dairy products in endemic areas (39). Moreover, vaccines against TBE, although not currently available in Hong Kong, can be obtained for high risk travellers on named-patient basis and the first two doses should be administered before departure. Travellers are advised to seek health advice from medical practitioner or the Travel Health Centres of the Department of Health before departure to endemic areas.

Disease Diagnosis and Investigation

28. The Public Health Laboratory Services Branch of the Centre for Health Protection provides laboratory diagnostic capacity for the investigation of communicable diseases in Hong Kong. Should a suspected case of tick-borne encephalitis arise, blood or cerebrospinal fluid obtained as soon as possible after onset of infection could be sent to the Branch for flavivirus polymerase chain reaction (PCR) and DNA sequencing for a definitive diagnosis.

29. Upon receipt of report of tick-borne encephalitis, the Centre for Health Protection will collaborate with the Food and Environmental Hygiene Department (FEHD) to carry out prompt epidemiological investigation and vector control measures.

Vector Surveillance and Control

30. The Pest Control Advisory Section of the FEHD is responsible for the control of pests (including rodents, mosquitoes, ticks and other arthropod pests) with medical importance. Upon notification by the Centre for Health Protection of a case of tick-borne disease, tick survey will be carried out in areas visited by the patient. Most of the ticks surveyed were from the tip of grasses and leaves as well as soil. Four genus of hard ticks (***Haemaphysalis, Hyalomma, Ixodes*** and ***Rhipicephalus***) are recorded locally by the FEHD of which ***Haemaphysalis*** and ***Rhipicephalus*** are most common. ***Haemaphysalis*** and ***Rhipicephalus*** are not known to be vectors for transmission of tick-borne encephalitis.

31. The two main species of ticks capable of transmitting tick-borne encephalitis, ***Ixodes ricinus*** and ***Ixodes persulcatus,*** were not found in Hong Kong in the past. However, ***Ixodes ovatus,*** which is suspected to be a vector transmitting TBE, has been identified once in 2003 from an individual coming from Australia. Although no serological test was done to ascertain the presence of TBEV in this vector, the possibility of identifying TBEV-carrying ***Ixodes ovatus*** in Hong Kong in the future is not negligible as TBEV-carrying ***Ixodes ovatus*** has already been found in southern China, Japan and South Korea. (7,8,10)

Public Health Education

32. Increasing awareness and improving the knowledge of the public (including physicians and travellers) on tick-borne encephalitis is of paramount importance on disease surveillance and control. Fact sheets on tick-borne diseases are available at the website of the Centre for Health Protection. Specific health advice and updated information on activities of tick-borne encephalitis around the world are disseminated through the Travel Health

Centres, travel health promotion activities, such as exhibitions and seminars on travel health, and the website of Travel Health Service of the Department of Health. In addition, the Food and Environmental Hygiene Department also provides education materials on the prevention and control of ticks in the environment.

Conclusion

33. Given the two main tick species capable of transmitting TBE are not found in Hong Kong, the risk of local transmission of TBE is low. However, on-going surveillance and effective control of ticks, laboratory capacity on prompt diagnosis and swift investigation of suspected cases remain the essential public health strategies for TBE. Physicians should also remain vigilant against possible imported cases and travellers visiting endemic areas should be reminded to take all necessary preventive measures to avoid tick bites during their stay in endemic areas.

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