

Japanese encephalitis

K. Morita*, T. Nabeshima & C.C. Buerano

Department of Virology, Institute of Tropical Medicine, Nagasaki University, 1-12-4 Sakamoto, Nagasaki City, Nagasaki, 852-8523, Japan

*Corresponding author: moritak@nagasaki-u.ac.jp

Summary

Japanese encephalitis (JE) is an inflammation of the central nervous system in humans and animals, specifically horses and cattle. The disease, which can sometimes be fatal, is caused by the flavivirus Japanese encephalitis virus (JEV), of which there are five genotypes (genotypes 1, 2, 3, 4 and 5). The transmission cycle of the virus involves pigs and wild birds as virus amplifiers and mosquitoes as vectors for transferring the virus between amplifying hosts and to dead-end hosts, i.e. humans, horses and cattle. In horses and cattle the disease is usually asymptomatic, but when clinical signs do occur they include fever, decreased appetite, frothing at the mouth, rigidity of the legs and recumbency, and neurological signs, such as convulsive fits, circling, marked depression and disordered consciousness. In pigs, it can cause abortion and stillbirths. At present, the virus is detected in a wide area covering eastern and southern Asia, Indonesia, northern Australia, Papua New Guinea and Pakistan. JEV RNA has also been detected in Italy, first in dead birds in 1997 and 2000 and then in mosquitoes in 2010. Genotype shift, i.e. a change of genotype from genotype 3 to genotype 1, has occurred in some countries, namely Japan, South Korea, Chinese Taipei and Vietnam. Laboratory methods are available for confirming the causative agent of the disease. There are control measures to prevent or minimise infection and, among them, vaccination is one of the most important and one which should be adopted in endemic and epidemic areas.

Keywords

Amplifier – Cattle – Clinical sign – *Culex tritaeniorhynchus* – Diagnosis – Genotype shift – Horse – Japanese encephalitis virus – Pig – Wild bird.

Introduction

Japanese encephalitis (JE), a mosquito-borne zoonosis occurring in many Asian countries, is an inflammation of the central nervous system of humans and various animals, principally horses and cattle. The disease is caused by the Japanese encephalitis virus (JEV). In humans, about 68,000 clinical cases occur every year, with a fatality rate as high as 30% and a high incidence of sequelae in those who recover (1). In pigs, which are amplifiers of the virus, infection due to JEV has an effect on reproduction. In Japan, enzootic encephalitis was seen in a large number of horses in the 1940s, but the number of cases gradually decreased after the introduction of vaccination in 1948. With the exception of a fatal case in an unvaccinated horse in 2003, no new cases have been reported since 1985 (2, 3). Other countries in which cases of encephalitis in horses have been recorded include Chinese Taipei, India, China, Singapore and Malaysia (4, 5, 6, 7). A few cases of JEV infection in cattle have been recorded in Japan (8, 9, 10, 11, 12).

For JEV, the main concern in the horse and cattle industries, and for human health, is protection from infection. For the pig industry, a bigger problem than infection itself is the culling of pigs and the banning of pig exports to control the spread of the disease during a human epidemic outbreak. Reproductive losses are also a concern for the pig industry.

This paper reviews the historical and current knowledge of the aetiological agent, provides an understanding of the epidemiology and modes of transmission of the disease, describes the clinical signs of the animals infected, presents the methods of diagnosis, and discusses the control measures (including vaccination) being adopted.

Aetiological agent

Japanese encephalitis virus, a member of the genus *Flavivirus* in the family *Flaviviridae*, belongs to a JE serocomplex consisting of eight species of viruses and two subtype

viruses (13). To this serocomplex belong Murray Valley encephalitis virus, West Nile virus and St Louis encephalitis virus, all of which can cause neuroinvasive disease (14).

Japanese encephalitis virus, an enveloped virus of about 50 nm in diameter, has a non-segmented, single-stranded, positive-sense RNA genome of about 11 kb in length (Fig. 1). The genome has one long open reading frame (ORF) that encodes a single polyprotein and is flanked by 5' and 3' non-coding regions. The polyprotein is cleaved co- and post-translationally into three structural proteins and seven non-structural proteins by cellular and viral proteases. The three structural proteins encoded in the 5' one-third of the ORF are the capsid (C), precursor to membrane (prM), and envelope (E) proteins. The prM is further processed into pr and M proteins. The seven non-structural proteins encoded in the remaining 3' two-thirds are NS1, NS2A, NS2B, NS3, NS4A, NS4B and NS5 (15, 16). These non-structural proteins, which provide the replicative, morphogenetic and polyprotein processing functions of the virus during infection and replication, are potential antiviral targets (17). Based on the nucleotide sequence of genomic RNA, JEV is classified into five major genotypes (Table I) (18, 19, 20, 21).

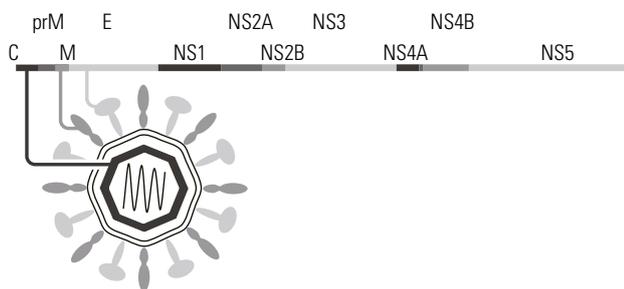


Fig. 1
Schematic representation of the genome and structure of a Japanese encephalitis virus particle

The lines connect specific parts of the genome with the specific virus protein structures which they encode

Table I
Distribution of Japanese encephalitis genotypes around the world

Genotype	Country
Genotype 1	People's Republic of China, Vietnam, South Korea, Northern Thailand, Cambodia, Japan, Australia, India, Chinese Taipei
Genotype 2	Southern Thailand, Malaysia, Indonesia, Northern Australia, Papua New Guinea
Genotype 3	Indonesia, Malaysia, Nepal, Sri Lanka, India, Indochinese Peninsula, Philippines, Chinese Taipei, South Korea, People's Republic of China, Vietnam, Japan
Genotype 4	Indonesia (isolated only during 1980 and 1981)
Genotype 5	Malaysia, Tibet (China), South Korea

It is thought that the virus originated in Southeast Asia. It seems likely that the current five genotypes of JEV emerged around the Indonesia/Malaysia region, because all the genotypes, including the most divergent and rare genotypes 4 and 5, are distributed in this region. Genotype 4 was isolated in Indonesia in 1980 and 1981 (22). Genotype 5 was isolated in Malaysia in 1952 from a patient who came from Muar in the south of the country (18, 23, 24, 25). It re-emerged in China in 2009 (26) and in South Korea in 2010 (27).

Genotypes 1, 2 and 3 spread out of the Indonesia/Malaysia region across a wide area of Asia and Oceania, and their distribution has been changing dynamically. At present, genotype 2 is distributed in Thailand, Indonesia, Papua New Guinea and Malaysia (18, 28). It is also present in Australia, where it was introduced in 1995 (29, 30).

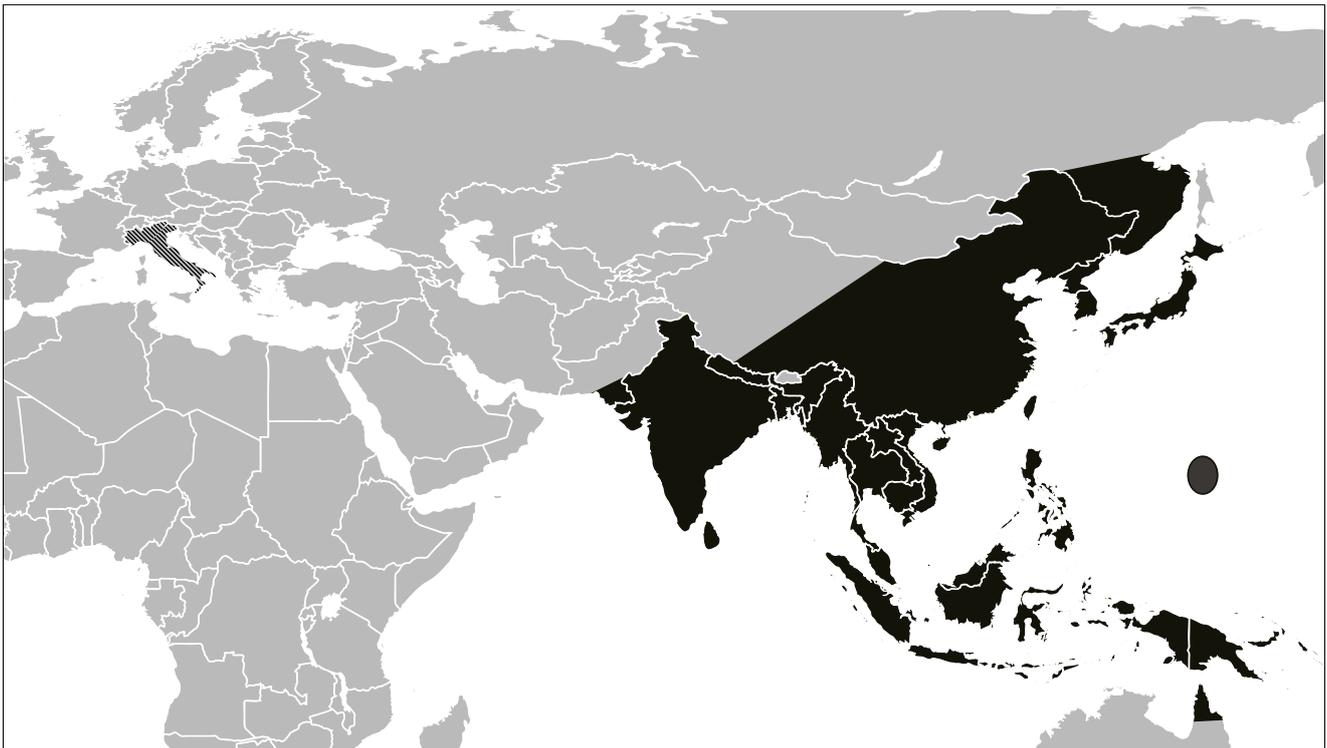
Genotype 3 is distributed in tropical and temperate zones of Asia, and strains of this genotype have been isolated from Indonesia, Malaysia, Nepal, Sri Lanka, India, the Indochinese peninsula, the Philippines, Chinese Taipei, South Korea, China, Vietnam and Japan (18, 31). It continues to be the dominant genotype in many of these countries, but in some of them, genotype 1 has become more prominent.

Until the 1980s, as far as is known, genotype 1 was distributed only in the Indochinese peninsula and Yunnan province of China. In the 1990s it spread to Vietnam, South Korea and Japan, where it supplanted genotype 3 as the dominant genotype. This replacement phenomenon is called 'genotype shift' (20, 32, 33). In 2000, genotype 1 was introduced into the Australian region. Genotype 3 was circulating in China, India and Chinese Taipei during this time, but in Chinese Taipei in 2008, a shift to genotype 1 occurred (34). It was reported that wind-blown mosquitoes were captured on a ship in the East China Sea and Pacific Ocean (35, 36, 37), which implies that wind-blown mosquitoes could carry JEV across oceans and that they could be the facilitators of genotype shift.

It was thought that JEV was distributed only in Asia and Oceania, but in 1997 and 2000, viral RNA of JEV was detected in dead birds in Tuscany in northern Italy, and in 2010 it was detected in mosquitoes in a neighbouring region (Fig. 2) (38, 39). Sequences of the viral RNA showed 99–100% similarity to the NS5 or E protein-coding region of JEV genotype 3. However, additional evidence is required to show whether JEV has been transmitted in this country.

Epidemiology and transmission

In Japan, epidemics of encephalitis in the summer season have been recorded for many years. An epidemic occurred

**Fig. 2****Distribution of Japanese encephalitis virus (JEV) around the world**

Areas in which JEV has been detected are in black. The area marked with black and grey stripes is Italy, where JEV RNA showing 99–100% similarity to NS5 or E protein-coding regions of JEV genotype 3 has been detected (in dead birds in 1997 and 2000, and in mosquitoes in 2010 [38, 39])

in Kyoto prefecture as far back as 1871, and it is regarded as the first description of JE (40). In 1934, Hayashi reported his discovery that the disease was caused by a viral pathogen (41). He inoculated filtered human cadaveric cerebral fluid into monkey brains, and demonstrated the transmission of encephalitis in monkeys. In addition, Mitamura *et al.* reported in 1937 that they were able to experimentally transmit JEV from mosquitoes to mice, confirming that JEV was transmitted by mosquitoes (42).

The serological surveillance carried out by Mitamura *et al.* in Japan in the 1930s showed that various mammals, such as horses, pigs, goats, rabbits and sheep, had antibody reactions against JEV. They were also able to isolate JEV from the Eurasian tree sparrow (*Passer montanus*) (43). In 1937, Kii *et al.* isolated a viral pathogen from encephalitic horse brain, and it was found to be serologically identical to human JEV (44). Several years later, Yamamoto *et al.* and Shimizu *et al.* reported clinically apparent JEV infection in cattle and the isolation of the virus (8, 9).

Scherer *et al.* isolated JEV from the serum of black-crowned night herons (*Nycticorax nycticorax*), little egrets (*Egretta garzetta*) and plumed egrets (*Ardea plumifera*) in Japan (45, 46). They also collected mosquitoes in the Kanto

region in Japan, and JEV was isolated mainly from *Culex tritaeniorhynchus*, rarely from *Cx. pipiens*, and not at all from the other mosquito species of the genera *Culex* and *Aedes* (47). *Culex tritaeniorhynchus* and *Cx. pipiens* were different in their selection of blood meal hosts: *Cx. tritaeniorhynchus* were more strongly attracted by pig bait than by birds, and *Cx. pipiens* were more strongly attracted by the black-crowned night heron than by pigs (48). In a survey carried out in the area of Sagiyama in Tokyo prefecture in 1956 and 1957, 98–100% of pigs became seropositive to JEV (49). The high incidence of seropositive pigs, and data that showed that viraemia lasted for four days (50), suggested that pigs and *Cx. tritaeniorhynchus* play an important role in the JEV infection cycle. The same survey demonstrated that wild rodents were rarely infected by JEV (51). In 1964, Konno *et al.* examined pigs in Miyagi prefecture at a time when there was an outbreak of JEV in humans and found that 100% of the pigs were seropositive (52).

It was these pioneering works that first determined the transmission cycle of JEV (Fig. 3) and established that JE was a mosquito-borne zoonosis whose pathogen, JEV, was mainly transmitted by *Cx. tritaeniorhynchus*. It was these studies that demonstrated that, although the virus can infect a wide range of vertebrate host animals, the major

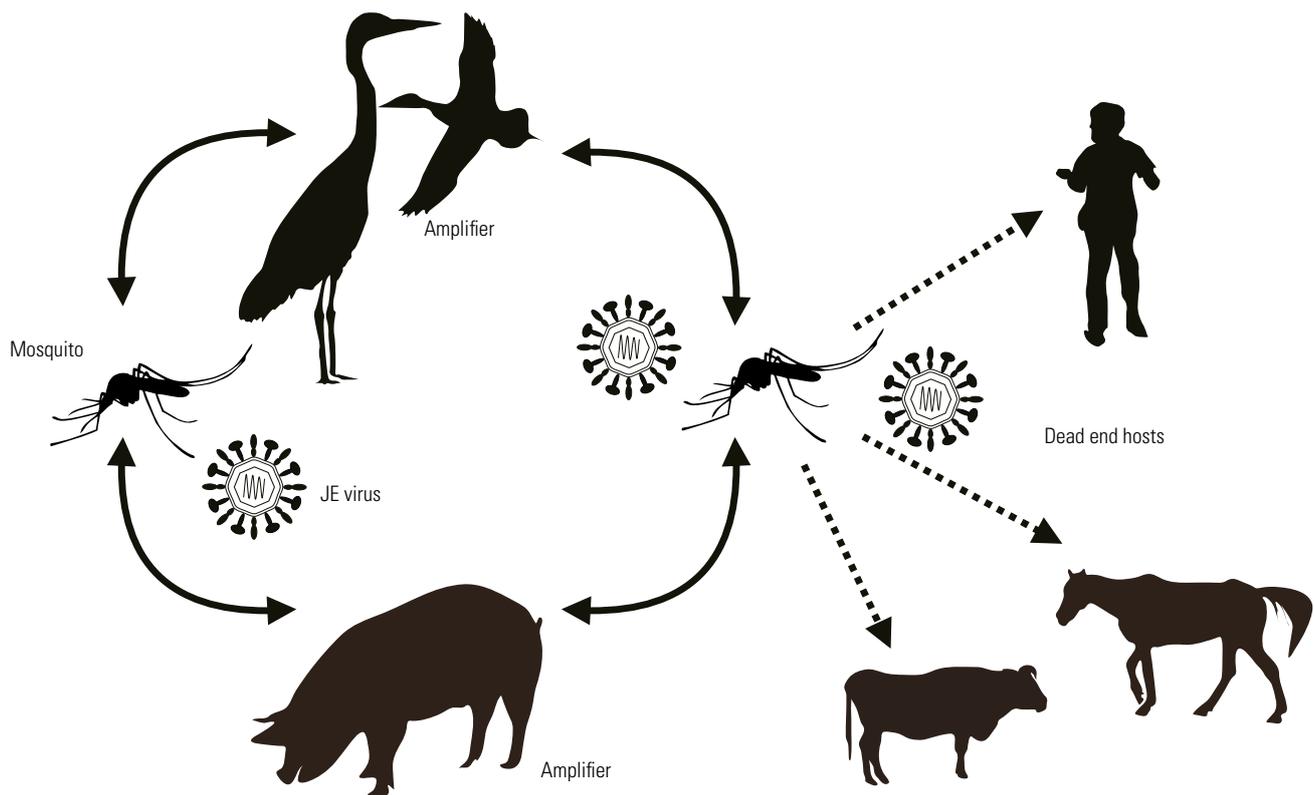


Fig. 3
Transmission cycle of Japanese encephalitis virus between amplifiers (pigs and wild birds) and mosquito vectors (especially *Culex tritaeniorhynchus*), including the infection of dead-end hosts (humans, horses, cattle)

reservoirs and amplifiers of JEV are wild birds and pigs; they also showed that the infection in humans, horses and cattle was mostly inapparent, but sometimes caused severe encephalitis.

Animals in temperate countries such as Japan contract the disease during late summer and early autumn (53). But in Japan, it has been shown that JEV can be isolated during non-epidemic seasons as well, implying that the virus can settle and overwinter. For example, in 1985, outbreaks of swine abortion occurred on Hokkaido island in June (a non-JE epidemic season), and a strain of JEV was isolated from a stillborn pig (54). In December 2008 and May 2009, JEV was isolated from wild boars in Japan (55). In addition, phylogeographic analysis suggests that some populations of JEV have been settling in this country (20, 33).

Culex mosquitoes overwinter as imagos in Japan, except in the south-west islands. Wada *et al.* collected female mosquitoes coming out of hibernation in Nagasaki prefecture in March of 1970, 1973 and 1974 and found that all of them were nulliparous, indicating that they had not had a blood meal before hibernation (56). Hence, it

was concluded that overwintering mosquitoes in Japan are seldom infected with JEV, and that their contribution to the overwintering of the virus is negligible. To date, despite many studies, it is not yet known in which animals JEV overwinters in temperate zones.

Clinical signs

Infection with JEV is mostly subclinical in horses, cattle and pigs. If horses or cattle do manifest clinical signs, the animal will recover if the illness is mild, but will die if the case is severe. In horses, clinical signs include low appetite, fever, hypersensitivity of the head and neck, marked depression, photophobia, muscular tremor, uncoordination of the four limbs, ataxia with extended hind legs, circling, pedalling, paralysis and recumbency (3, 5, 7). The animal manifesting severe neurological disorder dies within two weeks of the onset of illness (3, 5, 6, 7).

Clinical signs for cattle include decreased appetite, fever, frothing at the mouth, groaning, grinding of teeth, circling, convulsive fits, disordered consciousness, depression,

rigidity of the legs, inability to stand upright and recumbency (9, 10, 11, 12). The animal dies a day after the onset of clinical signs. In some other cases, if the animal is still alive after four days, it is euthanised.

Pigs do not show clinical signs similar to those of cattle and horses. In sows, clinical signs include abortion and stillbirths (54). Experimental infection of piglets (three weeks old) results in the development of fever, which may last three to four days, depression and slight tremor of the hindlimbs (57, 58). JE infection in boars causes aspermia and disruptions to spermatogenesis (59, 60).

Pathological features

Some of the histopathological findings in infected horses include: focal and perivascular accumulation of lymphocytes and petechial haemorrhages in sections of the brain, widespread congestion of blood vessels, along with swelling of endothelial cells in the cerebral hemispheres, multi-focal areas of neuronal swelling, degeneration, necrosis and glial cell proliferation (5, 7).

In infected cows, histopathological examination shows nonsuppurative encephalomyelitis with perivascular cuffing, perivascular infiltration which mainly contains lymphocytes mixed with a small number of plasma cells and large mononuclear cells, the presence of actively proliferating glia cells, and neuronophagias in the cerebrum. Histological lesions can also be observed in the diencephalon, medulla oblongata and spinal cord (9, 10, 11, 12). JEV antigens are present in the cytoplasm of neurons (11, 12). Cattle are usually asymptomatic, but the presence of other diseases may compromise the immune status, thus allowing the infected animal to succumb to infection. Pathological findings in cattle include pulmonary emphysema, mild abomasal ulceration and mild nonsuppurative interstitial nephritis, slightly thickened alveolar septa in the lungs, fibrous pleuropneumonia and co-infection with organisms such as *Sarcocystis* spp. in the myocardium and *Pasteurella haemolytica* in the lungs. Co-infection with other organisms such as *Trypanosoma evansi* also occurs in horses (5).

Diagnosis

Clinical and field diagnosis

Horses and cattle having fever and showing some neurological signs, and pigs giving birth to mummified fetuses or weak piglets may be suspected of having been infected with JEV (3, 5, 7, 9, 10, 11, 12, 53, 54). In Malaysia, horses at race tracks are suspected of being infected with the virus whenever they show clinical signs, as it has been observed that illness in these animals is usually due to JEV infection (53).

Laboratory diagnosis

Laboratory confirmation of the disease includes serological tests to detect antibodies in serum or cerebrospinal fluid samples, immunohistochemical techniques to detect viral antigen in tissues, reverse-transcriptase polymerase chain reaction (RT-PCR) to detect the virus genome, and virus isolation, which is the definitive diagnosis. Some serological tests are used for surveys of JEV infection in animals having no apparent clinical signs for the purpose of surveillance (61, 62, 63).

The serological tests most commonly used are: immunoglobulin M (IgM) capture enzyme-linked immunosorbent assay (ELISA) to detect anti-JEV IgM; indirect IgG ELISA to detect anti-JEV IgG; haemagglutination inhibition (HI) test in the presence of JEV antigen to detect the presence of antibody that prevents agglutination of goose red blood cells; and neutralisation tests such as plaque reduction neutralisation tests (3, 4, 5, 12, 53, 61, 62, 63, 64). To detect recent infection, IgM capture ELISA, which needs only one serum sample, is very useful. Other serological techniques require paired sera to establish whether or not infection is present.

Viral antigen in formalin-fixed paraffin-embedded tissue sections is detected by immunohistochemical techniques which make use of anti-JEV antibody as the primary antibody and a secondary antibody labelled with an enzyme such as peroxidase which, when exposed to a substrate, allows the visualisation of the antigen (10, 11, 12).

For the detection of the virus genome, the 3' untranslated region, prM, C/prM and E gene fragments are targeted for amplification by RT-PCR (3, 4, 5, 11, 12). For virus isolation, the specimens used are serum (preferably taken up to a day after the onset of clinical signs), brain samples (preferably the cerebrum) and culture fluids from cells infected with clinical samples.

The methods for virus isolation are cell culture and inoculation of mice or mosquitoes. Samples for isolation are from brain tissues, serum, leukocyte lysate and cerebrospinal fluid (3, 4, 5, 6, 10, 11, 12). For isolation in cell culture, primate cells (Vero and porcine cells) or mosquito cells (C6/36 cells) are used and virus is detected in infected cell culture fluids by RT-PCR and by a virus neutralisation test using anti-JEV antiserum. For isolation through mouse inoculation, suckling, weanling or young mice are infected intracranially or intraperitoneally with the homogenate or supernatant of the clinical sample. Successful isolation is confirmed by RT-PCR using the mouse brain or by inoculating the infected mouse brain into another mouse. The hyperimmune serum from this mouse is used for the HI test with JEV antigen. In mosquito isolation, brain samples are inoculated intrathoracically in mosquitoes, the heads

of which are squashed so that the presence of flavivirus antigen can be detected by the immunofluorescence assay technique with the use of polyclonal antiserum against JEV (65).

Control

Measures to prevent and control JEV infection include vaccination of humans and animals, vector control, prevention of contact with the vector and introduction of changes in the local environment, e.g. adopting new agricultural practices (66, 67).

Vaccination

In the absence of drugs to treat JEV infection, vaccination is the most effective preventive method for both humans and animals. In Japan, vaccination of horses started in 1948 and since then a proportion of the horse population has been vaccinated annually (68), leading to a marked decrease in the number of cases, such that, with the exception of a fatal case in an unvaccinated horse in 2003, no cases have been reported since 1985 (2, 3). Vaccination of racehorses is either required or recommended in several countries, e.g. Singapore, Malaysia, China (Hong Kong and Macau), Australia, Japan and the United Arab Emirates (69, 70, 71, 72, 73). Vaccination of pigs has been reported in Japan, Nepal, Chinese Taipei and South Korea (66, 74, 75).

Currently, there are several types of vaccines for horses and pigs, but none for cattle (75, 76, 77) (Table II). The vaccines are either inactivated or live. The JEV genotype 3 strains used for preparing these vaccines are Nakayama, Beijing, BMIII, AT or Anyang. The vaccines are either monovalent,

containing JEV components only, or polyvalent, containing other viral (porcine parvovirus, Getah virus or influenza virus) or bacterial components. JEV genotype 1 has become the dominant genotype in some countries and there was a reduction in neutralising antibody titre against genotype 1 in pigs immunised with a live attenuated genotype 3 virus; consequently, there has been an attempt to produce an inactivated vaccine for pigs that incorporates a genotype 1 JEV strain and it has shown promising results (75).

Vector control

Vectors can be controlled by using insecticides in rice fields (against mosquito larvae or adults), implementing malathion fogging, growing larvivorous fish in rice paddies and using cake powder made from the plant neem as a larvicide (78, 79, 80, 81). As an emergency measure to break the transmission cycle during a local outbreak, aircraft can be used to spread larvicidal granules or ultra-low volume insecticides over large areas of rice fields (82, 83). However, widescale use of insecticides, which is not considered suitable as a long-term approach, poses a threat to human health, raises environmental issues, and is costly when used during widespread outbreaks (66, 67).

Prevention of contact with the vector

Methods of preventing or minimising exposure of susceptible animals to the mosquito vector are: the use of screened housing or purpose-built buildings, use of insecticide-treated mosquito nets not only for humans but also for pigs, and application of residual insecticides on housing and equipment. However, these are only short-term solutions, unlike vaccination, which gives long-term protection (66, 67, 84, 85).

Table II

Japanese encephalitis vaccines available in Japan and South Korea

Unless otherwise indicated, all vaccines were produced in Japan

Type	Virus strain	Culture method	For use in
Inactivated JE	Nakayama	Chicken embryos	Horses, pigs
Inactivated JE	Beijing	NI*	Horses, pigs
Inactivated JE	BMIII	MPK-IIIaCl cells	Horses, pigs
Inactivated JE/Getah	BMIII	MPK-IIIaCl cells	Horses
Inactivated influenza (H7N7)/JE/tetanus	Beijing	Vero cells	Horses
Inactivated influenza (H3N8)/JE/tetanus	Beijing	Vero cells	Horses
Inactivated influenza/JE/tetanus	BMIII	MPK-IIIaCl cells	Horses
Live JE	AT	Hamster kidney cells	Pigs
Live JE	M	HmLu-1- KB cell, HmLu-1 cells	Pigs
Live Parvo/JE	M	Porcine kidney cells	Pigs
Live Parvo/JE/Getah	M	HmLu-1 cells	Pigs
Live JE**	Anyang	NI*	Pigs

JE: Japanese encephalitis

* Not indicated

** Produced in South Korea

Introduction of changes in the environment

Japan, Chinese Taipei and South Korea have experienced JE outbreaks in the past, but there has been a decline in JE incidence (67, 86). This has been partly attributed to the adoption of some changes in the local environment, e.g. locating pig-rearing facilities in farms far away from human habitats, and changes in agricultural practices, e.g. enhanced mechanisation or improved irrigation methods,

such as the system of alternating wet and dry irrigation to minimise mosquito breeding sites. Keeping cattle in the same areas as pigs is another strategy that can be adopted, because mosquitoes have a preference for feeding on cattle, which diverts them away from pigs and humans (78).

Encéphalite japonaise

K. Morita, T. Nabeshima & C.C. Buerano

Résumé

L'encéphalite japonaise est une maladie inflammatoire ayant pour tropisme le système nerveux central ; elle affecte l'homme ainsi que les animaux, spécifiquement les chevaux et les bovins. La maladie, dont l'issue est parfois fatale, est causée par un flavivirus qui compte cinq génotypes (catalogués de 1 à 5). Les porcins et l'avifaune participent au cycle de transmission du virus de l'encéphalite japonaise en tant qu'amplificateurs tandis que les moustiques jouent le rôle de vecteurs en transportant le virus des hôtes amplificateurs aux hôtes définitifs, à savoir les personnes, les chevaux et les bovins. Chez les chevaux et les bovins, la maladie se présente généralement sous forme asymptomatique ; en cas de maladie clinique, les manifestations en sont une fièvre, une perte d'appétit, une salivation excessive, une rigidité des membres et une prostration ainsi que des signes neurologiques tels que des crises convulsives, une démarche en cercle, un abattement marqué et des altérations de l'état de conscience. Chez les porcins, la maladie cause des avortements et des mortalités. Actuellement, l'aire de distribution du virus est très vaste puisqu'elle couvre l'Asie de l'Est et du Sud, l'Indonésie, le nord de l'Australie, la Papouasie-Nouvelle-Guinée et le Pakistan. L'ARN du virus de l'encéphalite japonaise a également été détecté en Italie, tout d'abord chez des oiseaux morts en 1997 et en 2000 puis chez des moustiques en 2010. Un remplacement de génotype (c'est-à-dire le passage du génotype 3 au génotype 1) a été observé dans certains pays, à savoir au Japon, en Corée du Sud, au Taipei chinois et au Vietnam. Des méthodes de laboratoire ont été mises au point pour confirmer la détection de l'agent causal. L'infection peut être atténuée ou prévenue au moyen de méthodes de contrôle appropriées ; la vaccination est la plus intéressante de ces méthodes et celle qu'il convient d'appliquer dans les régions endémiques ou en cas d'épidémie.

Mots-clés

Avifaune – Bovin – Cheval – *Culex tritaeniorhynchus* – Diagnostic – Hôte amplificateur – Porc – Remplacement de génotypes – Signe clinique – Virus de l'encéphalite japonaise.

Encefalitis japonesa

K. Morita, T. Nabeshima & C.C. Buerano

Resumen

La encefalitis japonesa es una inflamación del sistema nervioso central que afecta a personas y animales, concretamente caballos y ganado vacuno. El virus causante de la enfermedad, que a veces resulta letal, es un flavivirus del que existen cinco genotipos (catalogados del 1 al 5). En su ciclo de transmisión participan como amplificadores los porcinos y las aves salvajes, mientras que los mosquitos ejercen de vectores que transfieren el virus del hospedador amplificador al hospedador final, esto es, el ser humano, el caballo o el ganado vacuno. En caballos y bovinos la enfermedad suele ser asintomática, pero cuando se manifiesta clínicamente lo hace con signos como fiebre, inapetencia, salivación excesiva, rigidez de los miembros y postración, así como signos neurológicos como convulsiones, andares circulares, marcado abatimiento y desorientación. En el cerdo puede causar aborto y mortinatalidad. Actualmente se viene observando la presencia del virus en una vasta zona que abarca el este y el sur de Asia, Indonesia, el norte de Australia, Papua Nueva Guinea y Pakistán. También se ha detectado su ARN en Italia, primero en aves muertas (en 1997 y 2000) y después (en 2010) también en mosquitos. En algunos países, a saber, el Japón, Corea del Sur, Taipei Chino y Vietnam, se ha observado un cambio genotípico, esto es, el paso del genotipo 3 al genotipo 1. Existen métodos de laboratorio para confirmar la presencia del agente causal. También hay medidas de lucha que sirven para prevenir o reducir a niveles mínimos la infección. Una de las más importantes, que conviene aplicar en toda zona endémica o epidémica, es la vacunación.

Palabras clave

Amplificador – Ave salvaje – Caballo – Cambio genotípico – Cerdo – *Culex tritaeniorhynchus* – Diagnóstico – Ganado vacuno – Signo clínico – Virus de la encefalitis japonesa.



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