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Review article

Japanese encephalitis virus infection, diagnosis and control in domestic animals

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ABSTRACT

Japanese encephalitis virus (JEV) is a significant cause of neurological disease in humans throughout Asia causing an estimated 70,000 human cases each year with approximately 10,000 fatalities. The virus contains a positive sense RNA genome within a host-derived membrane and is classified within the family *Flaviviridae*. Like many flaviviruses, it is transmitted by mosquitoes, particularly those of the genus *Culex* in a natural cycle involving birds and some livestock species. Spill-over into domestic animals results in a spectrum of disease ranging from asymptomatic infection in some species to acute neurological signs in others. The impact of JEV infection is particularly apparent in pigs. Although infection in adult swine does not result in symptomatic disease, it is considered a significant reproductive problem causing abortion, still-birth and birth defects. Infected piglets can display fatal neurological disease. Equines are also infected, resulting in non-specific signs including pyrexia, but occasionally leading to overt neurological disease that in extreme cases can lead to death. Veterinary vaccination is available for both pigs and horses. This review of JEV disease in livestock considers the current diagnostic techniques available for detection of the virus. Options for disease control and prevention within the veterinary sector are discussed. Such measures are critical in breaking the link to zoonotic transmission into the human population where humans are dead-end hosts.

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1. Introduction

The earliest reports of what is now referred to as Japanese encephalitis virus (JEV) occurred following outbreaks of “summer encephalitis” in Japan during the 19th century. The virus was first isolated and passaged in mice and monkeys in the early 1930s. At

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this time it was shown to be related, but distinct, to viruses causing encephalitis in humans in North America and sheep in the UK (Webster, 1938). The virus is now known to be endemic in a large area of Asia (Fig. 1) with cases being reported from Japan, China, India, the Philippines and Pakistan (Erlanger et al., 2009). There have been no autochthonous cases of JEV in Africa, Europe or the Americas. JEV is the leading cause of human encephalitis in eastern and southern Asia, and currently numerous genotypic forms are recorded in Asia (reviewed by Jeffries and Walker, 2015).

JEV is classified within the family *Flaviviridae*, genus *Flavivirus*. It consists of a positive-sense single-stranded ribonucleic acid (RNA) genome approximately ten kilobases in length. Being of positive sense, the genome acts directly as messenger RNA encoding a single open reading frame. This is translated to generate a polyprotein that is proteolytically cleaved to form the viral structural and non-structural proteins (reviewed in Yun and Lee, 2014). These properties are shared by all members of the genus flavivirus along with the adaptation for efficient transmission by arthropod vectors. In the case of JEV, transmission is by mosquitoes, a factor that may currently limit the distribution of this virus through the availability of competent vectors. In tropical and sub-tropical regions of Asia, the virus is transmitted primarily by *Culex* species, particularly *Culex tritaeniorhynchus* (Hammon et al., 1948). This species feeds on birds (ornithophilia) and so the natural ecological cycle involves virus circulation between mosquitoes and avian species. However, *Cx. tritaeniorhynchus* has also been described as feeding on mammals, or mammalophilia, (Mitchell et al., 1973; Guo et al., 2014) acting as a "bridge vector" leading to the infection of livestock and humans.

Disease prevention in humans and livestock can be achieved through sanitary measures and vaccination. Prevention of mosquito feeding through mesh screening of animal housing, particularly at peak vector activity periods at dawn and dusk, effectively breaks the transmission cycle although may not be practical in large buildings. Vector suppression can also be considered as a control measure. Human vaccines for JEV, based on inactivated preparations of the virus, have been available since the 1930s and are used internationally (Zanin et al., 2003). All vaccine preparations are able to protect against all known isolates of JEV. Cross-neutralization of other flaviviruses has been observed in vaccinated individuals (Mansfield et al., 2011). Veterinary vaccines are commercially available in Asia for both swine and horses (Nah et al., 2015) with swine vaccination being considered a major preventative measure to reduce the impact of infection in some areas (Igarashi, 2002). No antiviral prophylaxis is available for treatment of disease (Baharuddin et al., 2014). Diagnosis of JEV can be achieved through serological testing or detection of the virus during the viraemic phase. However, detecting the virus is challenging due to the short period during which infected animals are viraemic and serological detection of JEV specific immunoglobulin (IgM and IgG) offers the most effective means of confirming infection. Serological surveillance also reveals the presence of virus in particular regions in the absence of overt disease (Yang et al., 2007).

JEV is primarily known as a human pathogen with an estimated 70,000 cases a year (Campbell et al., 2011). There is now a large body of evidence that this virus infects livestock leading to disease and death (Rosen, 1986). The continued burden on both human and

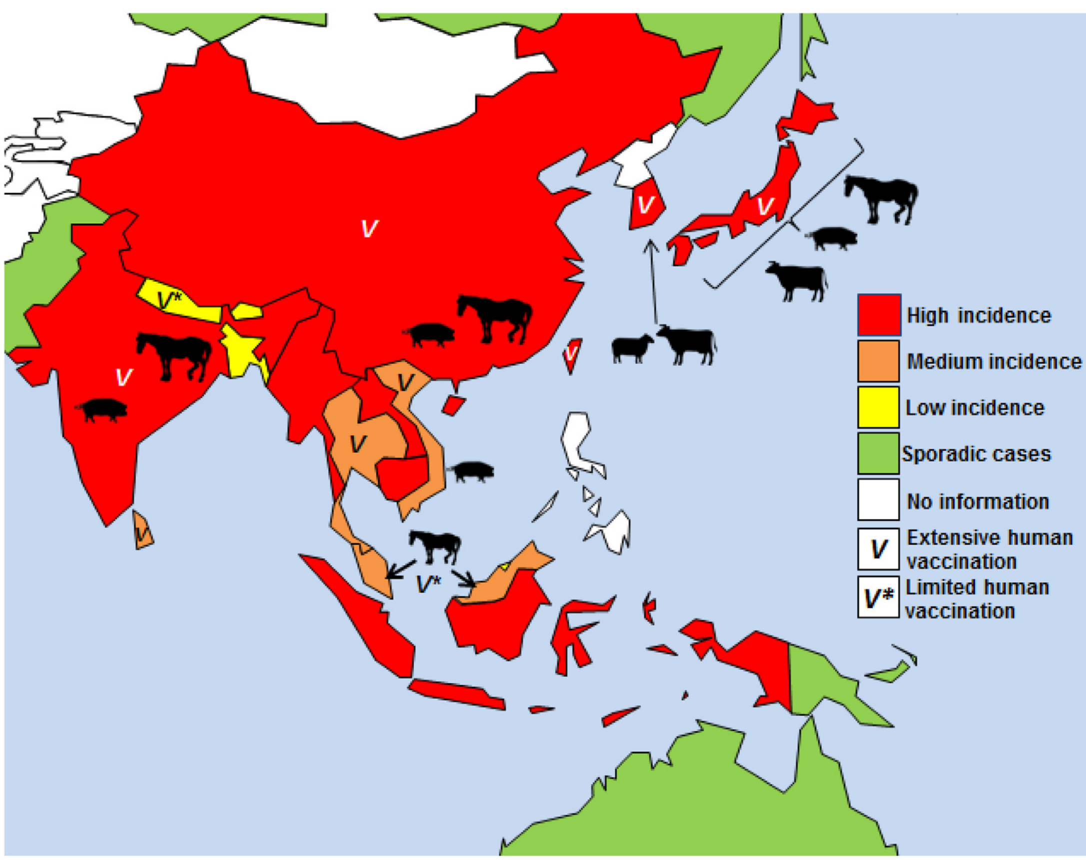

Fig. 1. The impact of JEV on human and animal populations across South East Asia. Countries are coloured according to epidemiological data presented by Campbell et al., 2011 and references therein. Shading corresponds to the reported incidence of human disease but occasionally, due to the lack of reporting of JEV in endemic regions shading may reflect reporting within a comparatively small area in country. Cases of livestock infection are denoted by images of pigs, horses, large or small ruminants. Human vaccination is also shown according to whether extensive campaigns have been carried out or limited campaigns of human vaccination have been instigated in the face of local epidemics (Campbell et al., 2011).