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Review

Emerging zoonotic encephalitis viruses: Lessons from Southeast Asia and Oceania

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The last decade of the 20th Century saw the introduction of an unprecedented number of encephalitic viruses emerge or spread in the Southeast Asian and Western Pacific regions (Mackenzie *et al*, 2001; Solomon, 2003a). Most of these viruses are zoonotic, either being arthropod-borne viruses or bat-borne viruses. Thus Japanese encephalitis virus (JEV), a mosquito-borne flavivirus, has spread through the Indonesian archipelago to Papua New Guinea (PNG) and to the islands of the Torres Strait of northern Australia, to Pakistan, and to new areas in the Indian subcontinent; a strain of tick-borne encephalitis virus (TBEV) was described for the first time in Hokkaido, Japan; and a novel mosquito-borne alphavirus, Me Tri virus, was described from Vietnam. Three novel bat-borne viruses emerged in Australia and Malaysia; two, Hendra and Nipah viruses, represent the first examples of a new genus in the family *Paramyxoviridae*, the genus *Henipaviruses*, and the third, Australian bat lyssavirus (ABLV) is new lyssavirus closely related to classical rabies virus. These viruses will form the body of this brief review. *Journal of NeuroVirology* (2005) **11,** 434–440.

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Arthropod-borne viruses

Flaviviruses

Japanese encephalitis virus: JEV is the major mosquito-borne encephalitis flavivirus in eastern, southeastern, and southern Asia (Umenai *et al*, 1985; Burke and Leake, 1988; Vaughn and Hoke, 1992; Endy and Nisalak, 2002; Solomon 2003b). It is a member of the JE serological complex of flaviviruses, which comprises eight antigenically related virus species and two strains or subtypes (Heinz *et al*, 2000; Mackenzie *et al*, 2002a); JEV virus itself, Murray Valley encephalitis (MVEV), West Nile (WNV), St Louis encephalitis, Koutango, Usutu (USUV), Yaounde, and Cacipacore viruses as the species, and Kunjin (KUNV) and Alfuy (ALFV) viruses as subtypes of WNV and MVEV, respectively. The JE complex is one of the most important *Flavivirus* groups on a global scale, with members endemic to all continents except the Antarctic. They cause diseases ranging from febrile illness, with or without a rash and with or without myalgia, to a meningoencephalitis with significant mortality, although most infections are subclinical or inapparent (Mackenzie *et al*, 2002a; Solomon and Vaughn, 2002). All members of the group are believed to have natural maintenance cycles alternating between birds and mosquitoes, and in many cases, ardeid (herons) birds and culicine mosquitoes. Some members of the JE complex have demonstrated an ability to readily spread and colonize new areas. Thus WNV has recently spread from the Middle East to North America, Usutu has spread from Africa to central Europe, and JEV has spread into southeastern Pakistan in about 1993 (Igarashi *et al*, 1994), into Haryana (Prasad *et al*, 1993) and Kerala (Dhanda *et al*, 1997) states in northwestern and southwestern India, respectively, and into the eastern Indonesian archipelago, New Guinea (Johansen *et al*, 2000), and the Torres Strait of northern Australia (Hanna *et al*, 1996; Mackenzie *et al*, 1997; Hanna *et al*, 1999; Mackenzie *et al*, 2002b).

JEV was first observed in the Australasian zoogeographic region in 1995 when it was responsible for three cases of encephalitis on Badu, an island in the

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Torres Strait of northern Australia (Hanna *et al*, 1996; Ritchie *et al*, 1997). This was a jump of about 3000 km from Bali, the nearest known location with clinical Japanese encephalitis. Subsequent studies revealed that JEV had probably reached the Torres Strait by island hopping, probably undetected in mosquito-bird and mosquito-pig cycles, through the eastern Indonesian archipelago to Irian Jaya and Papua New Guinea (PNG) (Mackenzie *et al*, 2002b). In support of this hypothesis, JEV had been isolated from mosquitoes collected on Lombok (Olson *et al*, 1985) and Flores (JG Olson, unpublished results) Islands in 1978 to 1979 and 1981, respectively; antibodies to JEV were found in human sera collected between 1989 and 1995 from Western Province in PNG (Johansen *et al*, 1997); clinical cases of Japanese encephalitis were reported in Irian Jaya (Spicer, 1997) and PNG (J Oakley, S Flew, CA Johansen, RA Hall, D Phillips, JS Mackenzie, unpublished results) in 1997 to 1998; and JEV was isolated from mosquitoes in Western Province, PNG, in 1997 to 1998 (Johansen *et al*, 2000). JEV activity continued to occur in the Torres Strait in 1996, 1997, and 1998, with seroconversions in sentinel pigs, a further human case in 1998 on Badu, and, for the first time, in Cape York on the Australian mainland (Hanna *et al*, 1999), but no activity was detected in 1999. JEV appeared again in the Torres Strait each wet season between 2000 and 2004, with virus again detected on Cape York in 2004 (Pyke *et al*, 2001; van den Hurk *et al*, 2001a; GA Smith, SA Ritchie, AT Pyke, PW Daniels, unpublished observations).

Genomic sequence studies showed that JEV isolates from the Torres Strait in 1995 belonged to genotype 2 (Chen *et al*, 1990, 1992) and were closest genetically to strains isolated in Java 15 to 18 years previously. Interestingly, and of considerable concern, a second genotype of JEV was detected in the Torres Strait in 2000 belonging to genotype 1 (Pyke *et al*, 2001), and from 2000 onwards, this new genotype appears to have replaced the earlier genotype 2 viruses. Even more worrying, a new mosquito vector, *Culex gelidus*, a major Asian vector of JEV was detected in the Torres Strait and northern Australia, and yielded the initial genotype 1 JEV isolate (van den Hurk *et al*, 2001a). It is uncertain how this genotype reached the Torres Strait, but it further demonstrated the ability of the virus to move and reemerge over long distances.

Thus JEV appears to readily move into new areas and become established, as it has in eastern Indonesia and PNG and probably in the Torres Strait, and as its close relative, WNV has done in North America. Consequently, there is a very real concern that JEV will become established in northern mainland Australia, given its occasional forays into Cape York, and the presence of competent mosquito vectors and susceptible vertebrate hosts (Mackenzie *et al*, 2002b).

Tick-borne encephalitis virus: The first case of encephalitis in Japan due to TBEV occurred in a farming area in southern Hokkaido in 1993, although serological studies of domestic animals had suggested its presence earlier (Takashima *et al*, 1997). Virus was subsequently isolated from the sera of sentinel dogs (Takashima *et al*, 1997, from *Ixodes ovatus* ticks (Takeda *et al*, 1998), and from wild rodents (*Apodemus speciosus* and *Clethrionomys rufocanus*) (Takeda *et al*, 1999). Molecular phylogenetic studies of isolates have shown that they are closely related to the Far-Eastern subtype of TBEV, and that they appear to have diverged from strains from in eastern Russia (Khabarovsk) between 260 and 430 years ago (Hayasaka *et al*, 1999).

Alphaviruses

Me Tri virus: A novel *Alphavirus*, Me Tri virus, was isolated from *Culex tritaeniorynchus* mosquitoes collected in Vietnam in 1971 (Ha *et al*, 1995). It was associated with encephalitis in children. Serological surveys indicated a relatively wide distribution in both humans and livestock (cattle, horses, pigs, as well as monkeys). Me Tri virus was shown to be most closely related to Semliki Forest virus (Ha *et al*, 1995). Although other members of the Semliki Forest antigenic complex occur widely in Asia (Chikungunya, Sagiyama, Getah, Bebaru) and Oceania (Ross River virus, Getah), plaque-reduction neutralization tests appeared to clearly distinguish these other viruses from Me Tri virus. Semliki Forest virus is most commonly associated with Africa, but it has been reported from far-eastern Russia, although not elsewhere in Asia. These other viruses also generally cause febrile illness with rash rather than encephalitis, although Semliki Forest virus has been associated with a encephalitis in a laboratory-acquired infection (Ha *et al*, 1995; Williams *et al*, 1979). Most cases of arboviral encephalitis in Vietnam and other Southeast Asian nations tend to be caused by JEV or occasionally dengue, and it might be that cases due to Me Tri virus are not diagnosed due to lack of knowledge or lack of reagents. It might be expected that similar viruses would occur elsewhere in the region.

Zoonotic viruses

Henipaviruses

Hendra virus: Two new closely related viruses have emerged in Australia and Southeast Asia during the past decade, Hendra (HeV) and Nipah (NiV) viruses, being the first members of a new genus, *Henipavirus*, in the family *Paramyxoviridae*. The animal reservoirs for both viruses appear to be fruit bats of the genus *Pteropus* (order *Chiroptera*, suborder *Megachiroptera*). HeV, formerly named equine morbillivirus, was responsible for an outbreak of severe respiratory disease in horses and humans in Brisbane, Australia, in 1994 in which 14 of 21 infected horses and one of two human infections died (Murray *et al*, 1995; Selvey *et al*, 1995). A second human infection with

HeV was recognized a year later as a fatal case of encephalitis (O'Sullivan *et al*, 1997). The patient had acquired the virus about 14 months previously after assisting in the necropsy of two dead horses, both of which were later found to have died from HeV infection (Hooper *et al*, 1996; Rogers *et al*, 1996), and had presented initially with a mild meningitic illness but subsequently recovered. Thus it is believed he had a latent infection which reactivated a year post infection.

Ecological studies have clearly shown that Pteropid fruit bats (flying foxes) are the reservoir hosts of HeV (Young *et al*, 1996): as with many established host-parasite relationships, infection in the bats appears to be asymptomatic. The virus was first isolated from the uterine fluid and fetal tissues of a euthanased pregnant flying fox (Halpin *et al*, 2000), and shown to be indistinguishable from the equine and human isolates. At least some of all four members of the genus found in Australia (the black flying fox, *Pteropus alecto*; the grey-headed flying fox, *P. poliocephalus*; the little red flying fox, *P. scapulatus*; and the spectacled flying fox, *P. conspicillatus*) have been shown to be seropositive. Indeed approximately 47% of flying foxes sampled over their full geographic range have been found to have antibodies to Hendra virus, although variation in prevalence was found between species (Field *et al*, 2001). Interestingly, the three human infections were all acquired from infected horses, not from contact with flying foxes, and despite the often close relationship between flying foxes and bat carers (volunteers who care for sick or orphaned flying foxes), there have been no instances of transmission from flying foxes to humans (Selvey *et al*, 1996; Mackenzie and Field, 2004).

There are many questions still to be answered in the ecology and biology of HeV (Mackenzie and Field, 2004). These include the apparent association between HeV and pregnancy, the very low transmissibility from infected horses, and the host range of the virus with respect to other domestic species.

Nipah virus: NiV first came to light as the causative agent of a major outbreak of disease in pigs and humans in Peninsula Malaysia between September 1998 and April 1999, which resulted in 265 human cases with 106 fatalities, and the eventual culling of about 1.1 million pigs (Chua *et al*, 1999, 2000a). The outbreak began as sporadic cases of encephalitis among pig farmers, and was initially thought to be caused by JEV. The epidemic then spread to an intensive pig-rearing area in the State of Negri Sembilan where it reached a peak in March 1999. Almost all clinical cases were associated with people in close contact with pigs, either through farming, or through transport or slaughter of pigs. The outbreak also spread to abattoir workers in Singapore (Paton *et al*, 1999) in pigs sent for slaughter. NiV was isolated from the brain tissue of a fatal human case and found to be closely related to HeV (Chua *et al*, 1999, 2000a), and was thus the second member of this new *Hantavirus* genus. There was no evidence of human-to-human transmission.

NiV infection caused a severe rapidly progressive encephalitic syndrome in most patients, although some also had significant pulmonary symptoms (Chua *et al*, 1999; Lee *et al*, 1999; Goh *et al*, 2000). In fatal cases, death was probably due to severe brain-stem involvement (Goh *et al*, 2000), and there was a significant association between presence of the virus in the cerebrospinal fluid (CSF) and mortality (Chua *et al*, 2000b). Interestingly, when followed up 24 months later, 7.5% of patients who had survived acute encephalitis had recurrent neurological disease or relapsed encephalitis, and of those who did not have encephalitis initially, 3.4% subsequently developed late onset encephalitis after an average interval of 8.4 months (Tan *et al*, 2002).

Transmission of NiV between pigs was primarily via the respiratory route, and the primary means of spread between farms and regions was through the movement of infected pigs. The clinical disease in pigs resulted in lesions in either or both the brain and lungs (Hooper *et al*, 2001). As with HeV, the principal reservoir hosts of NiV are believed to be Pteropid fruit bats from serological studies (Johara *et al*, 2001), and the virus was recovered from the urine of an island flying fox (*Pteropus Hypomelanus*) on Tioman Island (Chua *et al*, 2002). The mechanism by which the virus was transmitted from the fruit bats to pigs remains unknown, although various hypotheses have been suggested, such as pigs consuming fruit contaminated with virus from bat saliva, consuming infected bat carcasses, or consuming after-birth or birthing fluids from bats.

The establishment of a new *Henipavirus* genus to accommodate HeV and NiV indicate that the two viruses differ from other members of the family *Paramyxoviridae* in a number of ways, including the genome organization and length, the coding pattern of the P gene, sequence and size of intragenic regions, and biologically, the site of replication and its affect on virus transmission (Hooper *et al*, 2001; Eaton *et al*, 2004). It would be surprising if there were not more viruses in the *Henipavirus* genus, given that there are about 60 species within the *Pteropus* genus of flying foxes with a broad, overlapping distribution in southern Asia, Oceania, and Indian Ocean islands (Mackenzie and Field, 2004). Indeed, antibodies to related viruses have been found in bats in PNG (Field *et al*, 2001) and Cambodia (Olson *et al*, 2002), and outbreaks of disease in Bangladesh in May 2001, January/February 2003 (ICDDR, 2003), and January to April 2004 (WHO, 2004), and in India in Uttar Pradesh (Kumar, 2003) and North Bengal (ProMED, 2001). The most recent outbreak in Bangladesh in 2004 saw 53 cases in six provinces, 35 of whom died. Nipah virus was isolated by the Centers for Disease Control and Prevention (CDC) from at least two cases, and the isolates shown to share 95% homology with

the 1999 Malaysian virus. Whether related viruses extend to the more remote *Pteropus* species on islands in the Indian Ocean is not known, but it would be extremely interesting to investigate this in more detail to better understand the evolution of these emergent viruses.

Lyssaviruses

Australian bat lyssavirus: Australian bat lyssavirus (ABLV) was first described in eastern Australia in 1996 in a black flying fox (*Pteropus alecto*) that had been euthanased after displaying abnormal behaviour. The virus was shown to be closely related antigenically to classical rabies but distinct genetically (Gould *et al*, 1998; Guyatt *et al*, 2003). Subsequent studies demonstrated that the virus occurs in all four Australian flying fox species (black flying fox : *Pteropus alecto*; grey headed flying fox: *P. poliocephalus*; little red flying fox: *P. scapulatus*; and spectacled flying fox:*P conspicillatus*), and in at least one species of insectivorous bat, the yellow-bellied sheath-tailed bat (*Saccolaimus flaviventris*).

Two human infections due to ABLV have since been recognized; both were in bat carers and both were fatal. The first case was in 1996 in a bat carer who had been scratched and perhaps bitten 5 weeks previously by a yellow-bellied sheath-tailed bat (Allworth *et al*, 1996; Hooper *et al*, 1997; Samaratunga *et al*, 1998). The patient developed progressive muscle weakness in all limbs and later a depressed conscious state, requiring ventilation. An electroencephalogram was consistent with a diffuse encephalitis. The patient exhibited progressive evidence of cerebral damage, and died (Allworth *et al*, 1996). A second case occurred in 1998 after a 27-month incubation period following a bite from a flying fox (Hanna *et al*, 2000). After a history of fever, vomiting, anorexia, pain about the left shoulder girdle, and a sore throat, the patient's condition worsened with muscle spasms, paralysis requiring ventilation, and death 17 days post onset. Thus both cases displayed an encephalitis similar to classical rabies.

Molecular studies of the ABLV isolates have shown that isolates from flying foxes can be distinguished from isolates from the sheath-tailed bats on the basis of the genomic sequences (Gould *et al*, 2002; Guyatt *et al*, 2003; Warrilow *et al*, 2002), thus forming two clades.

Murine studies have demonstrated that rabies vaccine offers protection against infection with ABLV (Hooper *et al*, 1997; Lyssavirus Expert Group 1996a, 1996b). Preexposure vaccination has been therefore been offered to bat carers and others at risk such as veterinarians, and postexposure treatment with vaccine and rabies immune globulin is offered to anyone who has been bitten or scratched by a bat.

As with the Henipaviruses, similar viruses might be expected to occur elsewhere in Asian bats, and indeed serological evidence has been reported from six different bat species in the Philippines (Arguin *et al,*. 2002), four of which were species in the *Microchiroptera* (*Taphozous melanopogan*, *Miniopterus schreibersi*, *Philetor brachyopterus*, and *Scotophilus kuhlii*) and two in the *Megachiroptera* (*Pteropus hypomelanus* and *Rousettus amplexicaudatus*).

Concluding comments

This brief review has been restricted to emerging zoonotic viruses causing neurological disease in Southeast Asia and Oceania. Emerging zoonotic viruses are, of course, not confined to the Oceania and Southeast Asian regions, they also occur in other parts of the world. There are many examples; West Nile virus is an example of a known virus spreading into a new geographic region, North America, and Alkhurma virus is an example of a novel, previously unknown virus emerging to cause severe encephalitis in Saudi Arabia (Zaki, 1997; Charrel *et al*, 2001). Two nonzoonotic viruses have also recently been associated as aetiological agents of newly recognized encephalitic syndromes in Southeast Asia. They are enterovirus 71 (Mackenzie *et al*, 2001; McMinn 2002) and the dengue viruses (e.g., Solomon *et al*, 2000); the former is the etiological agent of a common childhood exanthem, hand-foot-and-mouth disease, but has been the cause of some major epidemics in Asia with significant mortality due to encephalitis, and the latter is globally one of the most important tropical and subtropical febrile diseases and an occasional cause of a life-threatening hemorrhagic fever. Although rarely al zoonotic virus in sylvan areas, the vast majority of cases are due to human-to-human transmission via *Aedes aegypti* mosquitoes. The role of dengue in neurological disease has been controversial, but recent data have indicated that dengue encephalitis does occur and may be more common than initially recognized. In addition, as it often occurs in areas with endemic JEV, dengue may be missed as a cause of neurological illness.

A number of other arthropod-transmitted and bat-borne viruses occur in Southeast Asia and Oceania (Karabatsos 1985; Mackenzie, 2000; Mackenzie *et al*, 1994, 2001). Some of these arthropod-transmitted viruses are also spreading into new areas or reappearing after a number of years of absence, but as febrile diseases with rash and/or polyarthritis, not neurological illness. Thus, in the Southeast Asian area, Chikungunya virus has been reappearing in a number of countries after several years of absence, and in Oceania, Ross River virus, the most common arbovirus causing human disease in Australia and a major cause of polyarthritis, spread to many island nations in Oceania in 1979 to 1980 (reviewed in Mackenzie *et al*, 1994, 2001) and threatens to do so again if transported by a viraemic traveller. Of the fruit bat-borne viruses, two closely related novel members of the *Rubulavirus* genus in the family *Paramyxoviridae* have been recently described.

The first was Menangle virus in 1997, which was isolated from stillborn piglets at a commercial piggery in New South Wales (Philbey *et al*, 1998), and the second in 2000 was Tioman virus, an apparently asymptomatic virus infection of flying foxes in Malaysia (Chua *et al*, 2001). Menangle virus caused stillbirths with deformities in the piglets, which included severe degeneration of the brain and spinal cord and skeletal abnormalities (Philbey *et al*, 1998), and an influenza-like illness in humans (Chant *et al*, 1998).

Finally, it is interesting to note that about 75% of emerging or novel viral diseases are zoonoses. That they emerge and spread is almost always due to human activities—be those activities land clearing or deforestation, increased irrigated agriculture, the building of dams for water impoundment, increased urbanization, or other activities that alter our ecosystem. It is also almost certain that further novel diseases will continue to appear from animal reservoirs, as severe acute respiratory syndrome (SARS) did in 2003. This could lead to increasing pressure on the management of wildlife (e.g, Field *et al*, 2004), and thus the more information on the generation and spread of novel zoonotic diseases, the greater might be the opportunities for early recognition and control. It also reinforces the need to respect wildlife and their habitats—often the first casualty of our need to cope with an increasing population and a consumer-driven lifestyle.

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